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REVIEW

State-of-the-Art management of knee osteoarthritis

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Abstract

Osteoarthritis (OA) is the most common type of arthritis found in the United States' population and is also the most common disease of joints in adults throughout the world with the knee being the most frequently affected of all joints. As the United States' population ages along with the increasing trends in obesity prevalence in other parts of the world, it is expected that the burden of OA on the population, healthcare system, and overall economy will continue to increase in the future without making major improvements in managing knee OA. Numerous therapies aim to reduce symptoms of knee OA and continued research has helped to further understand the complex pathophysiology of its disease mechanism attempting to uncover new potential targets for the treatment of OA. This review article seeks to evaluate the current practices for managing knee OA and discusses emerging therapies on the horizon. These practices include non-pharmacological treatments such as providing patient education and self-management strategies, advising weight loss, strengthening programs, and addressing biomechanical issues with bracing or foot orthoses. Oral analgesics and anti-inflammatories are pharmacologicals that are commonly used and the literature overall supports that some of these medications can be helpful for managing knee OA in the short-term but are less effective for long-term management. Additionally, more prolonged use significantly increases the risk of serious associated side effects that are not too uncommon. Disease-modifying osteoarthritis drugs are being researched as a treatment modality to potentially halt or slow disease progression but data at this time is limited and continued studies are being conducted to further investigate their effectiveness. Intra-articular injectables are also implemented to manage knee OA ranging from corticosteroids to hyaluronans to more recently platelet-rich plasma and even stem cells while several other injection therapies are presently being studied. The goal of developing new treatment strategies for knee OA is to prolong the need for total knee arthroplasty which should be utilized only if other strategies have failed. High tibial osteotomy and unicompartmental knee arthroplasty are potential alternatives if only a single compartment is involved with more data supporting unicompartmental knee arthroplasty as a good treatment option in this scenario. Arthroscopy has been commonly used for many years to treat knee OA to address degenerative articular cartilage and menisci, however, several high-quality studies have shown that it is not a very effective treatment for the majority of cases and should generally not be considered when managing knee OA. Improving the management of knee OA requires a multi-faceted treatment approach along with continuing to broaden our understanding of this

complex disease so that therapeutic advancements can continue to be developed with the goal of preventing further disease progression and even potentially reversing the degenerative process.

Key words: Disease-modifying osteoarthritis drugs; Knee osteoarthritis; Disease-modifying osteoarthritis drugs; Osteoarthritis management; Non-steroidal anti-inflammatory drugs; Hyaluronic acid; Arthroscopy; Platelet-rich plasma; Corticosteroids; Stem cells

Core tip: The management of knee osteoarthritis is of growing importance in the world and especially in the United States where an aging population and increasing trends in obesity are increasing the prevalence of this disease. Treatment has traditionally focused on symptom control, however, more recently there has been a greater emphasis placed on developing new modalities that aim to slow disease progression or even reverse the process. This review aims to examine the available literature on such modalities ranging from patient education and weight loss to disease-modifying osteoarthritis drugs to platelet-rich plasma, stem cells, and other emerging injectables.

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INTRODUCTION

Osteoarthritis (OA) is the most common type of arthritis found in the United States population and is also the most common disease of joints in adults throughout the world[1,2]. The knee joint is the most frequently affected of all joints per epidemiological studies with estimates of 37% of United States' adults ⩾ 60 years of age having radiographic evidence of knee OA and 12% having symptoms related to knee OA accompanying radiographic findings[3]. Osteoarthritis risk factors include both genetic and environmental components with multivariable analysis showing significantly higher odds of symptomatic and radiographic knee OA with body mass index ⩾ 30, greater age, non-Hispanic Black race/ethnicity, and among men with manual labor occupations[2,3]. Symptomatic knee OA has also been highly associated with self-reported activity limitations, need for assistive walking devices, and increased use of prescription medications for pain relief[3]. With an aging United States' population and increasing trends in obesity prevalence, it can be expected that the burden of OA on the population, healthcare system, and overall economy will continue to increase in the future without major improvements in management of knee OA. While the synovium, bone, and cartilage are recognized as the main structures being destroyed during disease progression, further research in the field is revealing that OA is not simply a biomechanical process placing excess load on the affected joint but contributions from catabolic cytokine cascades and production of inflammatory mediators also play a significant role and should be targets for intervention[4,5]. In order to take necessary strides towards improving management of knee OA, it is crucial to recognize the complex pathophysiology of its disease mechanism in which a multi-faceted treatment strategy should be employed using both non-pharmacological and pharmacological options, along with understanding the role for surgical intervention. While numerous treatments aim to offer pain relief to better tolerate the symptoms of knee OA, other modalities are attempting to slow the disease progression, halt it, or even reverse it by trying to affect the damaged articular cartilage. Various treatment strategies, both commonly used and newer advances, for the management of knee OA will be reviewed in this present article focusing mainly on non-operative treatments.

NON-OPERATIVE MANAGEMENT

Non-pharmacological

Education and self-management: Multiple societal guidelines and expert panels recognize patient education and self-management strategies as important components of knee OA management[6]. A systematic review and meta-analysis in 2011 evaluated the effectiveness of self-management programs on pain and disability for chronic musculoskeletal pain in which small to moderate effects in improving pain and disability at the long-term level were found using self-management programs[7]. Recent randomized clinical trials have also highlighted benefits from education and self-management, specifically Ravaud *et al*[8] showed that goal-oriented visits focusing on education on OA and treatment management, information on physical exercises, and information on weight loss led to improvement in weight loss and time spent on physical activity[8,9]. These programs can play more significant roles when implemented in conjunction with weight loss and exercise programs by increasing adherence.

Weight loss and strengthening

While genetic and other endogenous risk factors can contribute to knee OA and its progression, it is important to recognize the negative effects that increased stress on the knee joint can have

in the development and progression of OA. Both weight gain and decreased strength of surrounding musculature can increase the load seen by the knee. With the average body weight of the US population increasing across all ages but more significantly in adult population and this being an issue in other parts of the world, weight loss should be addressed as part of the management of knee OA. The Framingham Study by Felson *et al*[10] demonstrated that women with an approximately 5 kg weight loss had a 50% reduction in the risk of development of symptomatic knee OA. Christensen *et al*[11] used a meta-regression analysis of randomized controlled trials to evaluate if there were changes in pain and function when overweight patients with knee OA achieve a weight loss. The study concluded that disability could be significantly improved when weight was reduced > 5.1% over a 20-wk period, or at the rate of > 0.24% reduction per week[11]. Conversely, Riddle *et al*[12] found there to be a significant dose-response relationship between the extent of percentage change in body weight and the extent of change in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function and WOMAC pain scores, specifically those who gained ⩾ 10% of body weight had worse WOMAC physical function score. Not only has weight change been shown to affect pain and function, it has also been associated with MRI changes as Teichtahl *et al*[13] showed that obese individuals with OA who lost as little as 1% of their body weight were able to reduce the amount of medial femorotibial cartilage volume loss. The relationship between obesity, muscle strength, activity level, and knee OA is complex and it can be difficult to determine which factor is contributing most to the disease. While some studies have suggested that people engaging in relatively high levels of activity have an increased risk of developing knee OA compared to sedentary people, other studies have shown a protective effect. Regarding those who have already developed knee OA, a 2011 systematic review demonstrated moderate effect of strength training and exercise in reducing pain and improved physical function significantly. Furthermore, a 2013 meta-analysis including 60 trials showed that an approach combining exercises to increase strength, flexibility, and aerobic capacity was the most effective in managing lower limb OA with trials largely of patients with knee OA[14]. However, another systematic review and meta-analysis in 2014 included 48 randomized controlled trials and found similar effects in reducing pain from knee OA with aerobic, resistance, and performance exercise. In contrast to the 2013 meta-analysis, it concluded that optimal exercise programs for knee OA should have one aim and focus on improving aerobic capacity, quadriceps muscle strength, or lower extremity performance rather than combining the exercises. While both of these analyses demonstrate a positive effect of exercises on knee OA, the most beneficial regimen is still debatable[15]. The IDEA Randomized Clinical Trial included 3 groups in which participants either were involved with intensive weight loss (⩾ 10% body weight), exercise (1 h for 3 d/wk), or both. After this 18 mo randomized control trial, WOMAC pain scores were reduced to no or little pain in 20% in the weight loss only group, 22% in the exercise only group, and 40% in the weight loss and exercise group[16]. This further supports the notion that both weight loss and exercise are important in managing knee OA as they are more effective in combination than either one alone.

Biomechanical interventions (knee braces, knee sleeves, foot orthoses)

Using an appropriate specialist, assessment of biomechanics and incorporating corrective devices may be an effective intervention for knee OA. A key concept in understanding potential benefit from foot orthoses and knee bracing is in relation to the knee adduction moment (KAM) during gait in which excessive KAM has been associated with radiographic knee OA severity, radiographic knee OA progression, and pain with knee OA[17-19]. However, Zifchock *et al*[20] contended that medial joint space and peak adduction angle, not peak adduction moment, were the best predictors of knee pain. A systematic analysis on the effectiveness of knee braces and foot orthoses in conservative management of knee OA produced results suggesting that knee brace and foot orthoses are an effective means of decreasing pain, joint stiffness, and use of pain medication with minimal adverse effects[21]. However, the authors recognized that conclusions of this systematic analysis were limited due to poor quality of trials and heterogeneity of interventions. Lateral wedge insoles, also designed to reduce KAM and therefore decrease medial knee joint loading, have shown mixed results in studies with some claiming no benefit and others arguing its use as an alternative to valgus bracing for medial knee OA[22,23]. A benefit was well demonstrated in a retrospective study of 51 older adults with mild-to-severe medial knee OA in which a significant reduction in pain and improvements in function and quality of life were found with the prescription of a custom-made lateral wedge insole with arch support[24]. With regards to knee OA bracing, it is designed to create either valgus or varus force to alter the contact pressures especially with unicompartmental knee OA. A Cochrane review of orthoses for knee OA included 4 trials in which 1 investigated effectiveness of a knee brace while 3 examined foot orthoses[25]. The study on knee bracing compared a medial compartment unloader brace group, a neoprene sleeve group, and to a control

group in those that had varus deformity of the knee. Both the brace and sleeve group demonstrated significant improvement in disease specific quality of life and function compared to the control group with the brace group also demonstrating statistically significant improvement compared to the sleeve group per WOMAC pain scores[26]. The three studies on orthoses in the Cochrane review were able to conclude that there is some, though limited, evidence that a laterally wedged insole decreases non-steroidal anti-inflammatory drug intake compared with a neutral insole, patient compliance is better in the laterally wedged insole compared with a neutral insole, and a strapped insole has more adverse effects than a lateral wedge insole[25]. Haim *et al*[27] evaluated whether a biomechanical training program could effectively reduce knee adduction moments at 3 and 9 mo in which his results showed not only was there a significantly reduced knee adduction moment, there were also reduced pain and improved function in these subjects with bilateral knee OA[27]. While studies suggest the potential benefit from knee braces, knee sleeves, foot orthoses, and biomechanical training programs, they also highlight the need for more high quality studies which are currently lacking and for more effective ways to determine which subset of knee OA patients are likely to benefit from these interventions. Future research can include utilization of video gait analysis and 3D motion analysis using computer software to further assess biomechanics and individualize interventions in correcting abnormalities.

PHARMACOLOGICAL TREATMENT

Oral analgesics/anti-inflammatories

Several oral medications are prescribed for treatment of knee OA, mostly addressing the issue of pain. Many supplements are available in the United States that claim to be effective in the treatment of OA, however, few have been well studied for efficacy. Additionally, supplements are not held to the same product quality standards as FDA approved medication and thus variability in product may exist from company to company further making it difficult to determine if certain supplements are beneficial and if they should be considered in the management of knee OA. Glucosamine/chondroitin is the most extensively studied supplement for the treatment of knee OA. This oral supplement is alleged to be absorbed and incorporated into articular cartilage thus potentially allowing for the halting of disease progression and even reparative process[28]. There have been many conflicting studies showing both efficacy and lack of efficacy of glucosamine and/or chondroitin supplements which may be partially due to the difference in quality of products being such as those that are pharmaceutical grade. Fransen *et al*[29] in a double-blind randomized placebo-controlled trial showed that the combination of glucosamine-chondroitin resulted in a statistically significant reduction in joint space narrowing at 2 years of use. While there was also a reduction in knee pain over the study period, none of the groups reach a reduction of pain that statistically significant compared to placebo[29]. In a review of the available literature, many studies demonstrated OA pain relief with glucosamine and chondroitin sulfate use and given its excellent safety profile that is equal to placebo in most studies, this therapy is suggested as one that should be discussed with patients regarding potential benefits and considered as an initial treatment modality[30]. Acetaminophen has been commonly used for the treatment of knee OA and a Cochrane review in 2006 including fifteen RCTs involving 5986 participants showed acetaminophen was superior to placebo in five of the seven RCTs, however, when compared to NSAIDs the evidence suggested that NSAIDs were superior to acetaminophen for the treatment of knee OA[31]. Additionally, acetaminophen had previously been viewed as a safe medication to use as a short-term analgesic of knee OA based on a 2010 systematic review that found a low-level effect for OA pain, however, both this review and a safety review in 2012 have raised concern of its safety profile and suggest that this medication should be used more conservatively in both dosing and duration[32,33]. Many studies have demonstrated the ability for NSAIDs to provide symptoms relief for knee OA with the American Academy of Orthopaedic Surgeon's (AAOS) "Treatment of Osteoarthritis of the Knee: Evidence-Based Guideline, 2nd Edition" concluding that NSAIDs as a group should be recommended for patients with symptomatic OA of the knee and it received a strong strength of recommendation. This was determined after 19 studies were included for review with 202 favorable outcomes comparing either selective, non-selective, or topical analgesics to placebo. Out of the 202 total outcomes, 171 were statistically significant in favor of the experimental group. Fifteen outcomes were above the MCII threshold and 63 outcomes were possibly clinically significant[34]. While NSAIDs should be recognized as a good short-term treatment to manage symptomatic knee OA, it is important to acknowledge their side effect profile which makes this medication class a poor long-term treatment. A comparative effectiveness review in 2011 indicated that NSAIDs are associated with an increased risk of serious gastrointestinal (GI), cardiovascular (CV), and renal injury when compared to placebo[35]. The review also found that Celecoxib had a lower risk of ulcer complications compared to non-selective NSAIDs but had a moderately higher risk of CV complications highlighting the need to use NSAIDs conservatively by limiting dosage to lowest required to achieve pain relief and avoid prolonged use[35]. For those with a moderate comorbidity risk of GI complications,

a proton-pump inhibitor should be considered for co-prescribing with non-selective NSAIDs or this medication class should be avoided all together if there is a high risk. Topical NSAIDs can also be considered as a safer and better tolerated treatment although they have a higher risk of dermatological adverse effects. Tramadol and opioids have been evaluated as medications that may offer pain relief for symptomatic OA. Although opioids were found to have a small to moderate benefit compared to placebo in a 2009 Cochrane review, these benefits were outweighed by large increases in the risk of adverse events and therefore it was recommended they not be routinely used, even if osteoarthritic pain is severe[36]. Tramadol has been studied due to its increasing use for the treatment of OA since it does not produce GI bleeding or renal injury compared to NSAIDs. However, similarly to opioids, its benefits appear to be small in relation to pain reduction with a number of adverse events that cause participants to stop taking the medication[37]. While there are a variety of medications available to help reduce pain related to knee OA, their safety profiles need to be considered when initiating treatment and these should not be viewed as good long term treatment modalities in the management of knee OA.

Disease-modifying osteoarthritis drugs

Disease-modifying osteoarthritis drugs (DMOADs) are drugs that halt or significantly slow the progression of structural joint degeneration, specifically cartilage destruction. Several drugs have been investigated including the tetracycline antibiotic, doxycycline, as *in vitro* studies have shown that it may possess the ability to inhibit collagen degradation. Brandt *et al*[38] conducted a randomized, placebo-controlled, double-blind trial studying subjects with knee OA and measured if joint space narrowing in the medial femorotibial compartment could be reduced with doxycycline. The treatment group received 30 mo of 100 mg of doxycycline twice a day and after 30 mo, the treatment group had 33% less joint space narrowing on radiographic imaging compared to the placebo group. Doxycycline did not reduce the mean severity of joint pain and did not have any effect on either joint space narrowing or pain in the contralateral knee[38]. Additionally, when Snijders *et al*[39] evaluated doxycycline in the management of knee OA in their triple-blinded, randomized controlled trial, it was not effective in reducing symptoms over a 24-wk study period and was associated with an increased risk of adverse events[39]. Bisphosphonates have been studied after they have shown the ability to slow progression of OA in animal models and have decreased pain in states of high bone turnover[40]. When the Knee OA Structural Arthritis study tested the efficacy of risedronate in providing symptom relief and slowing disease progression in patients with knee OA, risedronate did not improve signs or symptoms of OA and did not alter progression of OA compared to placebo, however, it did show a reduction in the level of a marker of cartilage degradation[40]. Strontium ranelate is another drug that has been studied because it has been shown to be able to inhibit subchondral bone resorption and increase cartilage matrix *in vitro*. The SEKOIA trial was a 3-year randomized, double-blind, placebo-controlled trial that studied patients with moderate knee OA who received strontium ranelate 1 g/d, 2 g/d, or placebo. Treatment with strontium ranelate decreased progression of knee OA with estimates for annual difference in joint space narrowing versus placebo found to be 0.14 mm for 1 g/d and 0.10 mm for 2 g/d, with no difference between strontium ranelate groups and all values reaching statistical significance. Strontium ranelate 2 g/d also improved WOMAC total score and pain subscore with the treatment being well tolerated[41]. The SEKOIA trial has sparked more interest in strontium ranelate and has led to further studies that are currently underway which include evaluating its effect on loss of cartilage volume and bone marrow lesions using quantitative MRI. While these drugs will continue to be studied in order to more clearly understand their potential role in the management of knee OA, they will also stimulate new research into other DMOADs in hopes of providing better options to those suffering from the progressive nature of knee OA.

Intra-articular corticosteroid injections

Intra-articular (IA) corticosteroid injections for knee OA appear to be an effective way to decrease pain in the short-term and should be used when signs of inflammation arise. A 2006 Cochrane review of the current literature found that IA corticosteroids were more effective than the placebo group for pain reduction and patient global assessment at 1 wk post-injection. There was continued effect seen between 2 and 3 wk post-injection but at 4-24 wk, there was a lack of evidence of effect on pain and function. Comparing IA corticosteroids to IA hyaluronic acid injections, there was no statistically significant difference between weeks 1-4, however, between 5-13 wk post-injection, IA hyaluronic acid was more effective than IA corticosteroids for one or more of the following variables: WOMAC OA Index, Lequesne Index, pain, range of motion (flexion), and number of responders. The review concluded that IA corticosteroid injections appear to offer good short-term benefits with less evidence to support long term benefit[42]. Another review by Bannuru *et al*[43] compared the efficacy of IA hyaluronic acid with corticosteroids for knee OA. While there short-term analysis differed slightly from the Cochrane review in that the results from baseline to 4 wk showed that IA corticosteroids appear to be relatively more

effective for pain than IA hyaluronic acid, it similarly found that after 4 wk the IA hyaluronic acid continued to show superiority over IA corticosteroids further supporting the notion that IA corticosteroids should be implemented for reducing acute inflammation and relieving pain in the short-term but it is not a good treatment option for long-term management of knee OA[43].

Hyaluronic acid injections

Hyaluronans are also known as sodium hyaluronate or hyaluronic acid. Hyaluronic acid is a natural complex sugar of the glycosaminoglycan family and a normal component of synovial fluid and cartilage in the knee. Its viscosity and elasticity allow it to act as both a joint lubricant and shock absorber, respectively. Hyaluronic acid injections, often referred to as viscosupplementation, are marketed in the United States as several different formulations with some being produced from rooster comb and some from fermentation of the nonpathogenic bacterium Streptococcus zooepidemicus. The different products also vary by molecular weights, concentration of hyaluronic acid, elasticity, viscosity, and number of injections per treatment course[44]. A systematic review in 2011 showed evidence of a small but significant efficacy of IA hyaluronic acid injections for knee OA pain by week 4 post-injection with a moderate clinical significance at week 8 and continued residual benefit until 24 wk[45]. Another review, already mentioned in the previous section, compared IA corticosteroids to hyaluronic acid injections and demonstrated IA hyaluronic acid's superiority over corticosteroids after 4 wk post-injection[43]. The AAOS' "Treatment of Osteoarthritis of the Knee: Evidence-Based Guideline, 2nd Edition" gave a controversial recommendation in 2013 in which it stated they "cannot recommend" using hyaluronic acid for patients with symptomatic knee OA which was a change from their earlier 2008 recommendation that was "inconclusive" based on the available studies to recommend for or against IA hyaluronic acid injections. This update came from changes in their article selection criteria for analysis that included 14 studies, 3 of which were of high strength and 11 of moderate strength. Despite their negative recommendation, their meta-analyses of WOMAC pain, function, and stiffness subscales scores all found statistically significant treatment effects of IA hyaluronic acid compared to placebo and the WOMAC pain and WOMAC total score each were found to be clinically significant but not all of the improvements met the minimum clinically important improvement thresholds (MCII) established by the AAOS panel[34]. It should be noted that their application of the MCII has been called into question by several organizations including the Arthroscopy Association of North America who criticized the statistical analysis and inappropriate use of MCII[46]. A Cochrane review that included 40 trials comparing IA hyaluronic acid to placebo found that at the 5-13 wk post-injection period there was an improvement from baseline of 28%-54% for pain and 9%-32% for function for those receiving IA hyaluronic acid injections for knee OA. They did not find any of the different available hyaluronic acid products to be superior over another and there were very few adverse events reported in the studies. They concluded that viscosupplementation is an effective treatment for OA of the knee with benefits on pain, function, and patient global assessment. The authors also concluded that this review supports the use of the hyaluronic class of products in the treatment of knee OA and that these products provide not only statistically significant effects but also clinically important ones[47]. Some question the true efficacy of IA hyaluronic acid injections because a large placebo effect has been appreciated in several studies being as high as 30%-40%. However, reasons for this large placebo effect may include patient expectation, the Hawthorne effect of participating in a clinical trial, some "placebo" groups were actually receiving an active treatment of saline and/or arthrocentesis, and studies may not account for rescue analgesia or co-therapy being used simultaneously. The safety profile of hyaluronic acid injections is overall minimal. The most common side effects are joint effusion, arthralgia, joint warmth, and injection site erythema which all occur in less than 2.5% of patients and are clinically manageable with short-term use of ice, NSAIDs and do not have long-term sequelae[48-51]. The hylan G-F 20 product appears to have a unique side effect termed a local pseudoseptic reaction in those receiving more than one course of treatment which is hypothesized to be due to the chemical cross-linking used to increase the molecular weight and may occur in up to 21% of patients[52]. This event is not a contraindication to using other hyaluronic acid products and there is no increased risk of recurrence using other products. It should be emphasized that hyaluronic acid injection's excellent safety profile makes it a more appealing treatment for long-term use compared to NSAIDs which have risk of gastrointestinal, renal, and cardiovascular complications. Hyaluronic acid injections also have no known medication interactions making it a good option for patients on multiple medications. Overall, the body of literature appears to support the use of IA hyaluronic acid injections for the treatment of knee OA and future studies of high-quality will continue to be helpful to determine the most appropriate utilization in clinical practice.

Platelet-rich plasma

The use of platelet-rich plasma (PRP) has expanded over the past several years to not only just include the treatment of tendon and ligament injuries, but

also in the treatment of cartilage injuries such as in knee OA. PRP is derived from centrifuging whole blood in order to obtain a platelet concentration above baseline[53]. Growth factors including platelet-derived growth factor (PDGF), insulin growth factor (IGF), vascular endothelial growth factor, and transforming growth factor beta-1 are believed to be key components of PRP for structural repair. Drengk *et al*[54] showed that PRP has a proliferative effect on autologous chondrocytes and mesenchymal stem cells in an *in vitro* study. When Petrera *et al*[55] compared chondrocytes supplemented with either fetal bovine serum, PRP, or platelet-poor plasma, the presence of PRP in the culture media enhanced the *in vitro* formation of cartilage the most with increased glycosaminoglycan content, greater compressive mechanical properties, and maintained characteristics of hyaline phenotype. A randomized control trial involving dogs with documented symptomatic arthritis in a single joint was conducted by Fahie *et al*[56]. Dogs in the test group received a single injection of PRP in the affected joint and the control group dogs received a saline injection in the affected joint. After 12 wk, comfort and function improved by 55% and weight placed on the affected limb improved by 12% in the PRP group compared to the control group[56]. Further helping to understand ways in which PRP may be helpful in treating knee OA regarding anti-inflammatory effects, van Buul *et al*[57] in the Netherlands showed that PRP reduced several different effects of interleukin (IL)-1β which is involved in the catabolic process of articular cartilage in knee OA. Kon *et al*[58] did a prospective study on 115 knees with OA receiving a series of 3 PRP injections in which statistically significant improvement of all clinical scores was observed at 12 mo with maximum improvements at 6 mo[58]. Several studies have compared PRP to hyaluronic acid with each of them demonstrating positive results for these treatments of knee OA compared to placebo. PRP and hyaluronic acid have shown similar results in older patients with more advanced OA but PRP has shown better results compared with hyaluronic acid in younger patients affected by cartilage lesions or early OA[59-61]. When Cerza *et al*[61] compared PRP to hyaluronic acid, PRP was found to be more effective and there was also no statistically significant difference in the effect of PRP with regards to the severity of the knee OA. These findings counteract the argument that PRP is only helpful for milder cases of knee OA. Patel *et al*[62] compared 1 *vs* 2 PRP injections to treat knee OA and they found a single dose of PRP to be as effective as 2 injections to alleviate symptoms in early knee OA which further questions whether multiple subsequent injections are needed rather than a single injection only. A prospective cohort study following patients 1 year after PRP therapy for knee OA was conducted by Halpern *et al*[63]. Twenty-two patients with a Kellgren grade of 0-Ⅱ with knee pain were treated with PRP for early knee OA which was confirmed with a baseline MRI. Pain scores significantly decreased by 56.2% at 6 mo and 58.9% at 12 mo with 88% of patients showing improvement of at least 25% at 12 mo. Additionally, WOMAC overall score improved by 45.1% at 6 mo and 56.2% at 12 mo. In this same study by Halpern *et al*[63], qualitative MRIs demonstrated no change in the medial knee compartment in 73.3% of cases at 1 year despite the expected typical progression of knee OA and joint space narrowing. A systematic review of 59 articles (26 *in vitro*, 9 *in vivo*, 2 both *in vivo* and *in vitro*, and 22 clinical studies) analyzing the use of PRP for joint degeneration reinforced that the preclinical literature shows an overall support toward PRP with clinical studies displaying positive effects of PRP with a more significant benefit appearing to be in the younger patients with earlier stages of knee OA[64]. Cavallo *et al*[65] demonstrated that a comparison of different PRP formulations induced distinct effects on human articular chondrocytes *in vitro*, likely attributable to the differences in the concentrations of platelets, leukocytes, growth factors, and other bioactive molecules. This study highlights the fact that differences in technique and PRP composition may produce different outcomes when treating knee OA and make it difficult to compare results between various studies. However, it does appear that PRP can be a useful treatment for knee OA and certainly additional studies are needed before conclusions regarding true efficacy can be confirmed. Future studies are also needed to determine the optimal composition of PRP (*i.e.*, platelet concentration, leukocyte-rich or poor).

Stem cells

Mesenchymal stromal cells [mesenchymal stem cells (MSCs)] are multipotent cells that can be isolated from several human tissues. The immunomodulatory, reparative, and anti-inflammatory properties of MSCs have been tested in a variety of animal models and appear to have potential clinical applications which includes tissue repair[66]. One such study used scaffold-free MSCs obtained from bone marrow to directly inject intra-articularly in a rabbit model of OA. OA was induced by transecting the anterior cruciate ligament of the knee joint of rabbits and radiological assessment confirmed the development of OA after 12 wk. The rabbits then received either MSCs or medium without MSCs and at 20 wk post-operatively, the rabbits receiving the MSCs showed a lower degree of cartilage degeneration, osteophyte formation, and subchondral sclerosis compared to the control group[67]. While the exact mechanism by which MSCs are able to regenerate articular cartilage in patients with OA is not exactly clear,

these cells can induce proliferation and differentiation of resident progenitor cells and they have an innate differentiation potential to chondrocytes[68]. Orozco *et al*[69] conducted a pilot study where 12 patients with chronic knee pain unresponsive to conservative treatments and radiologic evidence of OA were treated with autologous expanded bone marrow MSCs by IA injection. They found that the patients exhibited rapid and progressive improvement in function that approached 65% to 78% by 1 year and that quantification of cartilage quality by T2 relaxation measurements demonstrated a highly significant decrease of poor cartilage areas (on average, 27%), with improvement of cartilage quality in 11 of the 12 patients[69]. This study, however, contained a small patient number and there was no control group for comparison. When Filardo *et al*[70] conducted a systematic review of the use of MSCs for the treatment of cartilage lesions, they included 72 preclinical papers and 18 clinical trials. In regards to the clinical trials focusing on cartilage degeneration, there were no randomized trials, 5 comparative studies, 6 case series, and 7 case reports. Of further note, 2 involved the use of adipose-derived MSCs, 5 the use of bone marrow concentrate, and 11 the use of bone marrow-derived MSCs. While multiple studies showed positive effects of MSCs for the treatment of OA or other cartilage defects, the authors acknowledge that these results are preliminary data on this topic due to only having available preclinical studies along with clinical studies that are of low quality due to weak methodology, small number of patients, and short-term follow-up[70]. Safety concerns have also arisen surrounding the use of MSCs which include but not limited to the neoplastic potential of MSCs due to their proliferative capacity and susceptibility to infection given their immunomodulatory effects[71]. In a systematic review by Lalu *et al*[71] to evaluate the safety of MSCs, they did not identify any significant safety issues other than a transient fever and concluded that this review should provide some assurance that MSC therapy appears to be safe. As in PRP, the use of MSCs is a therapy in that it goes beyond simply attempting to treat symptoms and instead offers the potential to stop disease progression and regenerate articular cartilage. While the possibility of such a regenerative treatment for knee OA is intriguing, before this therapy can be recommended confidently for clinical use there needs to be further studies that are of higher quality to better determine the efficacy, safety, and optimal source and preparation of cells for the treatment of knee OA.

Other injectables

Several other emerging injection therapies have been evaluated although the amount of quality studies are lacking or are still in early trial phases making it difficult to provide appropriate judgment on the efficacy of these products for the treatment of knee OA. IA botulinum toxin type A (BoNT-A) is hypothesized to have anti-nociceptive and potentially anti-inflammatory effects. Boon *et al*[72] conducted a pilot study to evaluate IA BoNT-A in painful knee osteoarthritis. Subjects were randomized to receive a single injection of corticosteroid, low-dose BoNT-A (100 units), or high-dose BoNT-A (200 units). The primary end point was pain visual analog scale score at 8 wk, which decreased in each group but only the low-dose BoNT-A group achieved statistical significance. Each of the groups did show statistically significant improvements in WOMAC Index scores (pain, stiffness, function) at 8 wk and there were no serious adverse events were noted in any group. The study overall supported a possible role for BoNT-A as a treatment option for symptomatic knee OA however it was recognized that larger double-blind randomized studies are needed[72]. Bone Morphogenic Protein-7 (BMP-7) has been studied due to its apparent strong anabolic effect on cartilage as it stimulates synthesis of cartilage matrix components, increases proteoglycan and collagen synthesis, while antagonizing catabolic mediators of cartilage such as IL-1[73]. In a rabbit model, Badlani *et al*[73] delivered BMP-7 *via* an osmotic pump to the knee 4 wk after ACL transection and when compared to a control group for the progression of knee OA, the BMP-7 group showed less cartilage degradation than the controls. In a phase I safety and tolerability study of BMP-7 for symptomatic knee OA, results showed that by week 12, all treatment groups with BMP-7 and the placebo group had improvement in pain scores with a trend toward more symptomatic improvement in the BMP-7 treatment groups although statistical significance was not achieved[74]. Fibroblast growth factor-18 (FGF-18) has also been studied for use as an IA injection to treat knee OA. Moore *et al*[75] demonstrated in animal models that there FGF-18 increased chondrogenesis and cartilage repair. Lohmander *et al*[76] conducted a proof-of-concept double-blind placebo-controlled randomized trial to evaluate the efficacy and safety of IA sprifermin, a recombinant human FGF-18, in patients with symptomatic knee OA. Their results found no statistically significant dose-response change in central medial femorotibial compartment cartilage thickness. Sprifermin though was associated with statistically significant dose-dependent reductions in loss of total and lateral femorotibial cartilage thickness and volume and in joint space width narrowing in the lateral femorotibial compartment with no association with any local or systemic safety concerns[76]. Other IA injection being studied for treatment of knee OA include IL-1 inhibitor, PDGF, IGF, amongst several others currently being studied. While trial data and preliminary studies have been

done for many of these therapies, more studies are needed to establish that they are both effective and safe.

OPERATIVE MANAGEMENT

This review has discussed many non-operative treatments that are utilized to prolong the need for total knee arthroplasty (TKA), however, there are other surgical procedures that are sometimes performed as alternatives in hopes of preventing the need for TKA. These surgical procedures include arthroscopy, high tibial osteotomy to correct abnormal alignment, and unicompartmental knee arthroplasty. High tibial osteotomy and unicompartmental knee arthroplasty are potential alternatives if only a single compartment is involved with more data supporting unicompartmental knee arthroplasty as a good treatment option in this scenario. An in depth discussion of these surgical procedures are beyond the scope of this review article, although it is important to note that arthroscopy, in the vast majority of patients, is no longer viewed as an appropriate treatment for knee OA or for meniscal degeneration in the setting of significant knee OA. Moseley *et al*[77] conducted a randomized, placebo-controlled trial in which a total of 180 patients with knee OA were randomly assigned to receive arthroscopic debridement, arthroscopic lavage, or placebo surgery consisting of skin incisions with a simulated debridement without insertion of the arthroscope. Outcomes were assessed at multiple points over a 24-mo period and they were no better after arthroscopic lavage or arthroscopic debridement than after a placebo procedure[77]. Another randomized, controlled trial was conducted by Kirkley *et al*[78] comparing surgical lavage and arthroscopic debridement together with optimized physical and medical therapy to treatment with physical and medical therapy alone. Arthroscopic surgery for knee OA was shown to provide no additional benefit to optimized physical and medical therapy and even analyses of WOMAC scores at interim visits and other secondary outcomes also failed to show superiority of surgery[78]. Arthroscopy has also been commonly used in the setting of knee OA to treat meniscal tears, although it is critical to recognize that in a study of incidental findings on knee MRI, among persons with radiographic evidence of knee OA, the prevalence of a meniscal tear was 63% in those who had knee symptoms and still remained 60% among those without symptoms[79]. When comparing surgical intervention to conservative management for meniscal degeneration in the setting of knee OA, outcomes are no better for those undergoing surgical intervention[80,81]. Based on the current literature comprised of several high-level studies, arthroscopy should not be included in the treatment algorithm for knee OA, especially without evidence of mechanical symptoms such as knee locking, as it is has not been shown to be an effective method to treat changes seen in the setting of knee OA which include degeneration of the articular cartilage and menisci.

CONCLUSION

The management of knee OA is of growing importance in the world and especially in the United States where an aging population and increasing trends in obesity are increasing the prevalence of this disease. Not only is this disease a burden on the individual patient, it is a burden on the healthcare system and overall economy. Treatment has traditionally focused on symptom control with some attention being given to prevention strategies and only more recently has there been a greater emphasis placed on trying to develop new modalities that aim to slow disease progression or even reverse the process. While there are many treatments available for knee OA, this review has attempted to provide evidence from the available literature to help guide management with the understanding that some of these modalities may be better options depending on the individual patients and clinical scenario. It is important to recognize the complex pathophysiology of this disease process and that a multi-faceted treatment approach is necessary to improve pain and function. Based on this review, education and self-management strategies should always be a part of managing knee OA as it can be used in conjunction with other treatments. Weight loss should be encouraged for patients who are overweight along with an beginning an exercise program that may involve a combination of aerobic activity, strengthening, and improving flexibility. While the optimal program regimen may be debatable, the literature demonstrates that they offer benefit to patients with knee OA and that weight loss with exercise is better than either one alone. There are several studies that have looked at the usefulness of biomechanical interventions and many of them have demonstrated potential benefit from knee braces, knee sleeves, foot orthoses, and biomechanical training programs warranting their incorporation into the management of knee OA. However, more studies are needed to better determine which patients specifically will benefit most from these various interventions. Glucosamine/chondroitin is a supplement with conflicting studies which may be partially due to the difference in quality of products being used in the studies, however, with its excellent safety profile and some studies demonstrating its superiority to placebo, it is a therapy that should be discussed with patients for potential use. Acetaminophen and NSAIDs, and to a lesser extent Tramadol and opioids, can be helpful in the short-term management of knee OA, but given their side effect profiles, they should be considered a poor long-term treatment. DMOADs were discussed in this review to

present available literature on oral medications being studied to alter the course of knee OA, however, at this time there is not enough evidence to suggest the common use of these treatments in managing knee OA. Injectables are another category of treatment for knee OA that should be considered beginning with the use of IA corticosteroids that have shown the ability to decrease pain in the short-term and should be used when signs of inflammation arise. The body of literature overall supports the use of IA hyaluronic acid injections for the treatment of knee OA and demonstrates it is a superior option for long-term management of knee OA compared to IA corticosteroids. Additionally, hyaluronic acid has an excellent safety profile making it a more suitable for being used for an extended period of time.

PRP is another injectable that when compared to hyaluronic acid has shown similar results in older patients with more advanced OA and may have better results in younger patients affected by cartilage lesions or early OA. PRP should be considered as a treatment option especially if the patient has used the other injectables mentioned without success, however, additional studies are needed before conclusions regarding true efficacy can be confirmed and these studies are also needed to help determine the optimal composition of PRP (*i.e.,* platelet concentration, leukocyte-rich or poor). The use of stem cells is emerging and while the possibility of such a regenerative treatment for knee OA is intriguing, before this therapy can be recommended confidently for clinical use there needs to be further studies that are of higher quality to better determine the efficacy, safety, and optimal source and preparation of cells for the treatment of knee OA. Several other emerging injection therapies were discussed in this review, but the amount of quality studies are lacking or are still in early trial phases making it difficult to provide appropriate judgment on the efficacy and safety profile of these products for the treatment of knee OA. While surgical interventions for knee OA were beyond the scope of this review, the current literature comprised of several high-level studies provide evidence that arthroscopy should not be included in the treatment algorithm for knee OA as it has not been shown to be an effective method to treat changes seen in the setting of knee OA with degeneration of the articular cartilage and menisci. This review hopes to provide a better understanding of treatment options available and their efficacy but it is important to highlight the need for continued research with regards to the management of knee OA. This research should focus on investigating the efficacy of new drugs such as the DMOADs or injectables as well as better understanding their safety profiles. Rather than develop treatments that target symptoms, the emphasis needs to be on developing advanced therapies that can slow or prevent further disease progression and hopefully even initiate a regenerative process. Additional research should also be directed at determining which subset of patients with knee OA may benefit from certain treatments and who are more likely to have a positive response to a given intervention so that more individualized treatment strategies can be established.

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REVIEW

Upper aerodigestive tract disorders and gastro-oesophageal reflux disease

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Abstract

A wide variety of symptoms and diseases of the upper aerodigestive tract are associated to gastro-oesophageal reflux disease (GORD). These disorders comprise a large variety of conditions such as asthma, chronic otitis media and sinusitis, chronic cough, and laryngeal disorders including paroxysmal laryngospasm. Laryngo-pharyngeal reflux disease is an extraoesophageal variant of GORD that can affect the larynx and pharynx. Despite numerous research efforts, the diagnosis of laryngopharyngeal reflux often remains elusive, unproven and controversial, and its treatment is then still empiric. Aim of this paper is to review the current literature on upper aerodigestive tract disorders in relation to pathologic gastro-oesophageal reflux, focusing in particular on the pathophysiology base and results of the surgical treatment of GORD.

Key words: Clinical management; Gastro-oesophageal reflux; Extraoesophageal disease; Upper aerodigestive tract disorders; Etiopathogenesis; Therapy

Core tip: Despite a growing number of clinical evidences, the association between gastro-oesophageal reflux disease (GORD) and extraoesophageal manifestations still derives from uncontrolled studies on small groups of patients. The evidences in the literature to support the proton pump inhibitor treatment of respiratory symptoms associated with GORD, in the absence of typical symptoms of reflux (heartburn and regurgitation), are scanty. A specific diagnostic tool, of respiratory symptoms associated with GORD, is missing even if oesophageal 24-h pH monitoring has been recommended. Large and prospective studies to assess the successful outcome of antireflux therapy, as well as surgical therapy, are still missing.

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INTRODUCTION

Gastro-oesophageal reflux disease (GORD) is a

recognized cause of oesophageal symptoms (*i.e.,* heartburn, regurgitation, chest pain, and dysphagia) and inflammatory damages such as erosive esophagitis and intestinal metaplasia (*i.e.,* Barrett's oesophagus). The association between upper airways disease and pathologic gastro-oesophageal reflux was firstly made in 1968, when laryngeal contact ulcers and granulomas were noted to occur in patients suffering from GORD[1,2], although the concept that GORD could have an impact on laryngeal and pharyngeal disorders has been fully developed in the last 30 years. The reported extraoesophageal manifestations of GORD include asthma, chronic cough, laryngeal disorders, chronic sinusitis, otitis media, and postnasal drip[1]. Laryngo-pharyngeal reflux disease (LPRD) is the term suggested by some authors to define GORD beyond the oesophagus up to the laryngeal and pharyngeal level, thus causing extraoesophageal damages[2,3]. Despite a growing number of clinical evidences to support the association between GORD and extraoesophageal disorders[1], presently the majority of reports still derive from uncontrolled studies of small groups of patients[1]. Nonetheless, in most of the published series, it is difficult to establish a firm connection between GORD and upper aerodigestive disorders (even within the laryngopharyngeal areas), since the presence of gastric content in supraoesophageal structures has been always difficult to document[1,2,4].

This article reviews the current available evidence on extra-oesophageal manifestation of GORD, devoting special attention on the pathophysiology base and results of the surgical treatment of GORD, particularly in relation to arodigestive tract disorders.

RESEARCH

The PubMed database was searched up to June 2014, for meta-analysis, systematic reviews, randomized controlled trials, and controlled trials. Full text articles were obtained when the title, abstract or keywords suggested that the study could be eligible for this review. The search was carried out independently. The search was restricted to adults, while no language restriction was applied.

The medical subject heading used included "gastroesophageal reflux", "laryngopharyngeal reflux", "gastroesophageal reflux ethiopathogenesis", "extraoesophageal gastroesophageal reflux disease symptoms", "reflux laryngitis", "posterior laryngitis".

EPIDEMIOLOGY

GORD is the most common disease of the oesophagus, possibly the most frequently faced by the gastroenterologist. Surveys in the United States have shown that it affects about 20% of the population, while about half experiences heartburn as a minimum once in a month, and 5% to 7% of the population have symptoms related to GORD every day[2,5,6].

Also because of the many clinical variables, the true prevalence of GORD among patients with suspected upper aerodigestive disorders secondary to pathologic gastro-oesophageal reflux is difficult to determine accurately, and it varies depending on the population analysed. For instance, in a study by Koufman *et al*[7], it has been estimated that about 10% of patients presenting to ears, nose and throat (ENT) clinician may have symptoms and/or findings related to GORD. In another study, it has also been reported that about two-thirds of laryngeal and voice disorders had either pathologic gastro-oesophageal reflux as primary cause or as a significant etiological co-factor[8], and that the prevalence of GORD among patients with laryngeal stenosis is 78%, reflux laryngitis 60%, globus sensation 58%, and chronic cough 52%[9,10]. In another survey, symptomatic reflux was diagnosed by pH monitoring in 30% to 60% of adults affected by asthma and chronic cough and nearly 40% of patients had endoscopic signs of esophagitis[2,11]. More recently, a systematic review has demonstrated typical symptoms of GORD in 59% of 10491 patients with asthma[12]. The proportion of asthma patients with GORD remained as high as 51% when more stringent criteria to prove GORD were adopted (*i.e.,* ambulatory 24-h pH monitoring). The average prevalence of asthma in patients with GORD was 4.6% as compared to 3.9% in controls. The overall odds ratio was 5.5 (95%CI: 1.9-15.8) for studies reporting the prevalence of GORD symptoms in patients with asthma and 2.3 (95%CI: 1.8-2.8) for those studies measuring the prevalence of asthma in patients with GORD. Interestingly, two studies that assessed whether GORD precedes asthma gave inconsistent results. The authors concluded that the analysis indicated a significant association between GORD and asthma, but the direction of causality remained undetermined[12].

PATHOPHYSIOLOGY

Upper aerodigestive tract disorders from pathologic gastro-oesophageal reflux appear to be sustained either directly or secondarily. Direct injury can be due to the result of a direct contact of gastric contents with the mucosa of the extra-oesophageal structures. Alternatively, a neurally mediated vagal reflex can be stimulated by the refluxate in the oesophageal body affecting indirectly the bronchopulmonary system, thus triggering cough, bronchial constriction or laryngospasm[6,13]. However, the evidence confirming the mechanisms of injury in LPRD is still inadequate, and in the literature very few laboratory investigations with animal models have substantiated the noxious effects of the refluxate on these anatomic sites by

both direct and indirect mechanisms[14,15].

Certainly, microaspiration of gastric contents can occur during gastro-oesophageal reflux episodes[16]. Direct contact of the refluxate with the mucosa of the pharynx and larynx could therefore represent the main mechanism of injury in LPRD. Unlike the distal oesophagus, the airways are not protected by anti-reflux clearance mechanisms or intrinsic mucosal properties. Moreover, it has been shown that a low lower oesophageal sphincter pressure as well as ineffective oesophageal motility may frequently be present in patients affected by GORD with associated respiratory disease (chronic cough, asthma, laryngitis)[17,18]. It is possible that just a single reflux episode above the oesophagus can be responsible of pharyngeal, laryngeal, and respiratory disorders.

The triggering of a vagal reflex has also been proposed as a consequence of the direct aspiration of refluxed acid into the pharynx or upper airways, besides the stimulation of the distal oesophageal mucosal receptors by the refluxed gastric content[17]. When stimulated, airway nociceptors activate protective responses such as cough and bronchospasm. It is also interesting to evidence that the pathways of some oesophageal and airway sensory nerve fibres terminate within the same regions of the central nervous system; thus, connections among oesophageal nociceptors and airway sensory nerves can exacerbate cough and the asthma-like disorders associated with GORD[19]. So, given the common vagal innervations of lungs and oesophagus, it is not surprising that many patients with asthma and chronic cough also have GORD, and that reflux often precipitates respiratory symptoms that are clinically indistinguishable from asthma[2,19].

Also the specific reflux agent or agents responsible for producing otolaryngology symptoms and pharyngo-laryngeal injury are currently debated[20]. Potential candidates include gastric contents (*i.e.*, acid and pepsin) as well as duodenal contents, including both bile acids and the pancreatic enzyme trypsin. Several animal studies suggested an injurious potential for both acid gastric contents and pepsin[2,20,21].

CLINICAL AND DIAGNOSTIC FEATURES OF AERODIGESTIVE TRACT DISORDERS RELATED TO GORD

The Montreal evidence-based global consensus, defining GORD and its constituent syndromes, recognized oesophageal syndromes and established an association between GORD and asthma, chronic cough, and laryngitis, while proposed an association with pharyngitis, sinusitis, and otitis media[22]. The Montreal consensus also acknowledged that such extra-oesophageal disorders have a multi-factorial aetiology and pathologic gastro-oesophageal reflux may well be a co-factor rather than a cause. Thus, patients with asthma, chronic cough or laryngitis should firstly be evaluated for causes not related to GORD, considering that extra-oesophageal syndromes rarely occur without concomitant typical symptoms of GORD[22]. However, the diagnosis of GORD as the cause of extra-oesophageal symptoms is very challenging and relies on the following investigations.

PPI TRIAL

Traditionally, otolaryngologists have commonly used an empiric course of double dose of proton pump inhibitors (PPIs) (*i.e.,* PPI trial) to initially diagnose and treat patients with upper aerodigestive tract disorders suspected to be related to GORD, deeming the resolution of symptoms with such a treatment as diagnostic of LPRD[3,5,6,23]. PPIs have been shown to improve asthma outcomes in terms of a significant reduction in the proportion of subjects experiencing respiratory symptoms including dyspnoea, cough, wheeze in randomized controlled trials[24,25], although a recent meta-analysis of 11 randomized trials found only small improvements of the respiratory function in adult patients with asthma, unlikely to provide a real clinical benefit[26]. Another meta-analysis of randomized trials by the Cochrane Collaboration regarding cough control with PPIs in GORD reported that PPIs were not better than placebo to resolve cough in such a patient, although they improved cough scores[27]. Finally, also for suspected GORD-related chronic laryngitis a meta-analysis of randomized trials has demonstrated no advantage of PPIs *vs* placebo[28]. Therefore, the evidence to support the treatment with PPIs in the absence of typical symptoms (*i.e.,* heartburn and regurgitation) or objective pathologic gastro-oesophageal reflux (*i.e.,* esophagitis on upper endoscopy or positive ambulatory pH monitoring) is scant[29].

ENDOSCOPY

The most frequent laryngoscopic findings that have been related to reflux are oedema and erythema: (1) of the arytenoid cartilages mucosa; (2) of the interarytenoid region; and/or (3) of the posterior third of the true vocal folds (*i.e.,* posterior laryngitis). A reflux finding score based on the presence and the severity of at least eight different grades of lesions at laryngoscopy has been proposed by Belafsky *et al*[30] to improve the diagnostic accuracy. However, laryngoscopy has revealed laryngeal irritation in more than 80% of healthy controls prospectively evaluated[31] and the concordance among ENT physicians for signs of reflux laryngitis is low when blindly evaluated[32]. Thus, a causal relationship between GORD and laryngitis should not be posed

relying on laryngoscopy findings alone.

Indeed, upper endoscopy has excellent specificity for the diagnosis of GORD in the presence of erosive esophagitis[33]; however, only one third of patients with symptoms of GORD, and even less following treatment with PPIs, have erosive esophagitis which does not establish *per se* a causal relationship between GORD and aerodigestive tract disorders[34,35].

AMBULATORY PH MONITORING

This is the only test that can objectively demonstrate the presence of abnormal oesophageal acid exposure, characterize the reflux episodes and determine their association with symptoms. The pH monitoring has high sensitivity and specificity in the presence of erosive esophagitis (both up to 100%); but its sensitivity lowers (about 70%) in patients without erosive esophagitis, although may be increased adopting impedance pH monitoring (up to 90%)[36,37].

The use of dual pH monitoring (with a probe at the level of the upper oesophageal sphincter) has been proposed by some authors to investigate for respiratory symptoms associated with GORD[23,38]. However, this procedure is not universally performed due to the significant practical problems performing pH monitoring in the pharynx[23,38].

Certainly, there is a great variability in the prevalence of abnormal pH monitoring reported in patients with asthma, chronic cough, and laryngitis[12,39-41]. However, a negative pH monitoring may address the diagnostic investigations toward aerodigestive disorders non-related to GORD, while a positive pH monitoring establishes a diagnosis of GORD, although it does not imply that the latter is the cause of the respiratory symptoms. The temporal association between reflux episodes and respiratory symptoms may be evaluated by the symptom index (SI, *i.e.,* percentage of symptoms preceded by a drop in oesophageal pH below 4.0 within a 5-min time window divided by the total number of symptoms)[42] and the symptom association probability (SAP, *i.e.,* statistical probability with which symptoms and reflux episodes are associated)[43]. The patient must promptly record the symptoms, while the machine should accurately detect the reflux episodes (*i.e.,* drop in oesophageal pH below 4.0) in order to evaluate precisely the temporal association between symptoms (*i.e.,* asthma attacks or cough events) and acid reflux episodes. A positive symptom association is declared if the SI is greater than or equal to 50% (*i.e.,* at least half of the reported symptoms are preceded within a 5-min time window by an intra-oesophageal pH below 4.0) or if the SAP is greater than 95% (*i.e.,* the probability of this association having occurred by chance is less than 5%). Unfortunately, both sensitivity and specificity of symptom association analysis tools is limited and there are no outcome studies to support treatment of extra-oesophageal GORD based on this parameter alone[29]. Recently, Smith *et al*[39] by using a microphone to record cough concurrently with the pH-impedance recording, to overcome patients not always recording timely their symptoms during pH monitoring, reported 6 to 18 times more coughing than with patient reported cough, and 2 to 3 times more than relying on manometry to suppose when cough possibly occurred. If these data will be confirmed by further studies, the evaluation of the temporal association between reflux episodes and respiratory symptoms will be improved.

ASTHMA

Some authors have reported about the possible relationship between asthma and GORD, since a percentage between 30% to 80% of asthmatic patients, have been found to have GORD and/or esophagitis[43-45]. Nonetheless, a cause effect association between GORD and asthma has not been found yet[43-45]. Most of the reports show that GORD medical therapies such as histamine H2 antagonists or PPIs can be effective on asthma outcome[45,46], even if such medications have not been reported to improve asthma symptoms or pulmonary function[43-45].

Finally, on the contrary, few reports have claimed that inhaled b2 agonists and oral corticosteroids, currently used for asthma therapy, may increase oesophageal acid refluxate[2,45-50].

CHRONIC COUGH

Chronic cough is also believed to be possibly related to GORD as proposed by several studies[51-54]. In fact Harding[44] and Pacheco-Galván *et al*[49] have reported that both, medical and surgical therapy of pathologic reflux, can improve or even resolve chronic cough in up to 51% to 100% of adult patients. Unfortunately, most of the data available in the literature come from uncontrolled studies with small sample sizes of patients, and evidences about the efficacy of therapy are still lacking. Long term follow-up studies with a large number of patients are missing.

LARYNGEAL DISORDERS

GORD is also considered to be a possible cause of laryngeal disease: it has been suggested that the aetiopathogenetic mechanism underlying laryngeal disorders, such as chronic laryngitis, could be caused by the contact of the acid refluxate with the laryngeal mucosa. Therefore, patients affected by chronic laryngitis who lack anomalies at the laryngoscopic evaluation should be addressed to a pH monitoring and gastroesophageal endoscopy in order to reveal signs of reflux[55-57]. Some authors have already

reported that they have successfully treated with PPIs some laryngeal diseases such as chronic laryngitis as well as contact granuloma and acquired subglottic stenosis[58-60]. In the study by El-Serag *et al*[61], patients treated with PPIs showed efficacious resolution of laryngeal symptoms when compared to a placebo group. Nonetheless, the small amount of patients involved, as well as the limited follow-up, represent the main drawbacks of this and of similar studies[2,49,56,61,62].

CHRONIC SINUSITIS

Some reports have advocated GORD to have a possible role in the aetiopathogenesis of chronic sinusitis and that medical anti-reflux therapy may be useful for these patients[63]. It has been speculated that GORD may cause sinonasal congestion and alteration of sinusal drainage with consequent inflammation[2,49,64].

PAROXYSMAL LARYNGOSPASM

Also paroxysmal laryngospasm episodes have been associated by some authors to GORD, and medical anti-reflux therapy with PPIs has been reported to be of benefit for these patients. According to the aetiopatogenetic mechanism indicated by these authors, paroxysmal laryngospasm could be considered as a vagally mediated reflex response of the larynx to acid refluxate, a potentially injurious stimulus[2,49,63,65-67].

OTITIS MEDIA

To date, there are only few reports indicating GORD as a possible cause of persistent middle ear problems (*i.e.,* otitis media with effusion). Unfortunately studies considering this specific issue, in adults and children, still are scant[68-70].

POSSIBLE DIAGNOSTIC ALGORITHM

The diagnosis of LPRD is still very controversial, both in clinical practice and research. Most guidelines and reviews recommend starting the diagnostic work-up and treatment of patients with upper aerodigestive symptoms of GORD with an empiric trial of PPI therapy at a double dose given for at least three months[3,5,6,23]. Traditionally, in clinical practice, otolaryngologists have considered diagnostic of LPRD the resolution of symptoms following such a PPI trial. Failure to respond, on the other hand, would indicate incorrect diagnosis of GORD or inadequate dosing or resistance to the treatment. Nonetheless, in patients who do not respond to the empirical trial, further investigations (*e.g.,* ambulatory 24-h oesophageal pH monitoring) have been recommended[2,3,5,23].

MEDICAL TREATMENT

As stated above, PPIs are the main proposed treatment for LPRD. Caution must be used, however, interpreting the available literature, as it is hampered by studies lacking strict inclusion and diagnostic criteria investigating large populations and, consequently, inconclusive meta-analyses. Nonetheless, partial improvement of both symptoms and laryngoscopic signs of laryngitis has been reported with PPI treatment and behavioural changes. Lifestyle modifications comprise the avoidance of heavy and late meals, alcohol consumption, and smoking. Also, to elevate the head of the bed and to reduce the body weight may be beneficial[6]. Most handbooks and reviews suggest a three-month treatment with PPIs at a double dose as the first step in the diagnosis and treatment of patients with upper aerodigestive symptoms attributed to GORD[3,5,6,23]. Patients who do not respond, however, are indeed particularly challenging. Several factors have been suggested to explain refractory cases, such as inadequate dosing or resistance to PPIs, sensitivity to non-acid refluxate, and incorrect diagnosis of GORD. Thus, the dosages of PPIs as well as the frequency of their administration can be increased and pro-motility agents and histamine receptor antagonists may be added. Finally, in patients with signs and symptoms of LPRD despite PPIs treatment, 24-h ambulatory pH monitoring while the patient is on medication may demonstrate persistent acid refluxate due to the lack of acid control[6].

SURGICAL TREATMENT OF AERODIGESTIVE TRACT DISORDERS RELATED TO GORD

Historical background

In 1956, Rudolph Nissen, a German surgeon, opened the era of modern anti-reflux surgery describing a complete plication of the gastric fundus around the abdominal portion of the esophagus that restored an anti-reflux barrier[71]. The Nissen operation has been modified throughout the years, new valves around the abdominal oesophagus, either complete (360°) or partial (240°-270°) have been described, but the basic principle of the operation remained unchanged: to restore a high pressure zone (HPZ) at the gastro-oesophageal junction[72-80]. In 1991, Dallemagne *et al*[81] reported the first laparoscopic anti-reflux operation. In the following decade the technique has been adopted worldwide becoming the gold standard for surgical management of GORD.

Indications and technical details

The surgical treatment of GORD is focused on restoring a HPZ at the lower oesophageal sphincter (LOS), while medication aim to modify the pH of

the refluxate. Nowadays, this purpose is achieved by a fundoplication performed laparoscopically, which offers excellent results combined with the postoperative advantage of a short hospital stay, minimal discomfort, and fast recovery time as compared to the open (*i.e.,* laparotomic) traditional operation[82-85]. According to the 2010 guidelines of the Society of American Gastrointestinal Endoscopic Surgeons, the surgical operation should be considered in the following situations: (1) failure of medical treatment because of inadequate symptom control, persistent severe regurgitation or disturbing side effects; (2) preference of the surgical treatment despite symptom control on PPIs due to quality of life, refusal of lifelong need for medication or costs of medications; (3) presence of Barrett's oesophagus or peptic stricture; and (4) extra-oesophageal symptoms such as asthma, hoarseness, cough, and chest pain or aspiration[86].

The surgical literature is full of eponyms of anti-reflux operations that quite often do not even correspond to the operation originally described by the authors[87]. Therefore, it seems very reasonable to go beyond such eponyms, and stress the surgical elements, common to most of these operations, that have been shown to guarantee long term control of reflux for the patient, namely: (1) to reduce the hiatal hernia in the abdomen; (2) to mobilize extensively the oesophagus and gastro-oesophageal junction; (3) to reduce the hiatus; (4) to interrupt the gastro-splenic ligament; (5) to construct a partial or complete fundoplication of adequate length and tightness; and (6) to fix with posterior and coronal stiches the wrap[87].

Results of anti-reflux surgery

Anti-reflux surgery (*i.e.,* fundoplication) has been shown in clinical studies to control GORD symptoms in 93% and 89% of patients after 5 years and 10 years, respectively[82]. Surgical fundoplication restores the LOS competence and improves the oesophageal peristalsis[88]. Of note, due to the restoration of a HPZ, the reflux control is equally effective when the patient is supine or upright[83]. Anti-reflux surgery has been shown to be safe and effective also in elderly patients affected by GORD[84]. In a randomized trial at a Veteran Affairs Cooperative comparing medication to anti-reflux surgery for GORD, patients on medication at 10-year follow-up in the medical therapy group as opposed to the surgical group were 92% and 62%, respectively[89]. The surgical treatment of GORD may, however, expose patients to some morbidity and increased risk of mortality. The most common complication related to anti-reflux surgery is the so called gas-bloating syndrome, affecting 15% to 20% of patients. Recently, a meta-analysis concluded that a partial (240°) fundoplication as compared to a complete (360°) wrap was associated to less postoperative dysphagia and inability to belch in patients undergoing surgical treatment of GORD[90]. A Cochrane review including more than 1200 patients from four randomized trials comparing medical to surgical therapy has demonstrated higher improvements in GORD specific quality of life after surgery, although a meta-analysis of such data was not performed[91]. Symptoms of heartburn, regurgitation, and bloating improved more after surgical fundoplication then with medication, even if small proportion of patients had persistent dysphagia after surgery. Nonetheless, the surgical operation is associated with some risk of complications and the decision to perform a surgical fundoplication needs to be thoroughly discussed with the patient.

Results on respiratory symptoms

The control of respiratory symptoms in patients with GORD undergoing anti-reflux surgery is less predictable. In the era of the open (*i.e.,* laparotomic) surgical operation, objective data regarding the ability of a fundoplication to control respiratory symptoms in patients with GORD were scarce[92,93]. For instance, Pellegrini *et al*[93] reported the successful results of a complete fundoplication performed in a small group of patients in whom GORD-induced aspiration had been diagnosed. In the past two decades, due to the advent of laparoscopic anti-reflux surgery, the number of patients undergoing fundoplication for GORD has greatly increased[87,94]. Hunter *et al*[94] reported resolution or improvement of respiratory symptoms in 76 out of 87 patients (87%) undergoing laparoscopic fundoplication. However, outcomes of patients with extra-oesophageal symptoms undergoing anti-reflux surgery are not always predictable. A Veteran Affairs Cooperative study, reported no significant improvement in pulmonary function tests one year after fundoplication, even in those patients presenting abnormal preoperative tests[95]. Analogously, a randomized trial showed that both medical and surgical therapy did not increase significantly the forced expiratory volume in 1 s after 6 mo[96]. Anti-reflux surgery can control extra-oesophageal symptoms in carefully selected patients with GORD, although these patient should be informed that the success rate is lower than in patients with typical symptoms[97]. It is particularly important to carefully evaluate the response of such patients to PPIs, as in patients who do not respond to medications, even in the presence of oesophageal acid exposure demonstrated by pH-monitoring, the results of fundoplication are not effective[98].

CONCLUSION

Upper aerodigestive tract disorders related to pathologic reflux appear to be a common but controversial disease, with conflicting data on pathophysiology, diagnosis, and treatment. Whereas trends are observed and many clinical practices are accepted widely on the basis

of experience, definitive, prospective, and controlled studies are strongly needed[2,6].

Also considering the possible implication of GORD in the development of supra-oesophageal neoplasms, as advocated by several investigators, more efforts are necessary to support the relation between extra-oesophageal disorders and GORD, in terms of prospective randomized trials[2].

A better comprehension of the physiopathological mechanisms of these conditions can help clinicians in the management of such patients. In particular, further large randomized-controlled trials in order to clarify LPRD pathophysiology, as well as to evaluate diagnostic algorithms and treatment approaches could be then particularly useful for the diagnosis and the management these disorders.

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REVIEW

Review and update on the molecular basis of Leber congenital amaurosis

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Abstract

Inherited retinal diseases are uncommon pathologies and one of the most harmful causes of childhood and adult blindness. Leber congenital amaurosis (LCA) is the most severe kind of these diseases accounting for approximately 5% of the whole retinal dystrophies and 20% of the children that study on blind schools. Clinical ophthalmologic findings including severe vision loss, nystagmus and ERG abnormalities should be suspected through the first year of life in this group of patients. Phenotypic variability is found when LCA patients have a full ophthalmologic examination. However, a correct diagnosis may be carried out; the determination of ophthalmologic clues as light sensibility, night blindness, fundus pigmentation, among other, join with electroretinographics findings, optical coherence tomography, and new technologies as molecular gene testing may help to reach to a precise diagnosis. Several retinal clinical features in LCA may suggest a genetic or gene particular defect; thus genetic-molecular tools could directly corroborate the clinical diagnosis. Currently, approximately 20 genes have been associated to LCA. In this review, historical perspective, clinical ophthalmological findings, new molecular-genetics technologies, possible phenotype-genotypes correlations, and gene therapy for some LCA genes are described.

Key words: Gene therapy; Leber congenital amaurosis; Retinal dystrophies; Childhood blindness

Core tip: Leber congenital amaurosis (LCA) is the most severe retinal dystrophy causing blindness before the age of 1 year. Clinical ophthalmological findings together with electroretinogram study, OCT imaging and retinal molecular-genetic technologies provide a precise diagnosis in these individuals. Gene-specific phenotypic features exist in LCA, and in this way is possible to predict the underlying genetic defect in some patients on the basis of ophthalmological clues. Clinical, molecular-genetics, phenotype-genotype and gene therapy aspects of LCA are described.

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INTRODUCTION

Photoreceptor and retinal pigment epithelium dystrophies are inherited retinal disorders that result in severe visual impairment in childhood and adult years. They affect more than two million individuals worldwide[1,2] and are sorted according to the inheritance trait (autosomal recessive, autosomal dominant, X-linked or mitochondrial); however, these methods of subdividing retinal disease are unsatisfactory due to the fact that they do not always discern the etio-pathogenesis of retinal degeneration[3]. Over the last decade, new molecular-genetic technologies have classified the pathogenic nucleotide variants (mutations) in a more exact way; thus, at this moment, approximately 221 genes are known to cause these diseases[4]. Retinal degeneration phenotypes have variable expressivity that can range from mild retinal dysfunction (night blindness, color blindness) to poor vision and total blindness[5].

Leber congenital amaurosis (LCA) is the most severe and earliest form of the inherited retinal diseases that causes childhood blindness[6]. This dystrophy is a genetically heterogeneous recessive disease affecting 1 in 30000[7] to 1 in 81000[8] subjects; although in consanguineous populations or isolated communities may be more frequent[9]. LCA represents almost 5% of all retinal dystrophies and 20% of children with visual impaired in special schools[10]. Although LCA have a broad expression variability, some clinical features may be specific to individual genetic abnormalities, providing a useful means of determining which gene may be responsible, thus narrowing the number of genes that may need to be tested and thereby significantly reducing the involved cost[11]. To date, eighteen genes involved in LCA have been identified, which encodes proteins important in several retinal developmental and physiologic pathways[4]. Recently, therapeutic gene replacement trials for a specific form of human LCA have started, and represent the first example for inherited blindness treatment. In the following sections, we will describe the historical perspective, the clinical characteristics, the involved genes and their functions, the genotype-phenotype correlations, and the current gene therapy treatments for LCA.

HISTORICAL CLINICAL PERSPECTIVE

In 1869, Theodor Leber described a blind child with vision loss, wandering nystagmus, amaurotic pupils, and congenital retinitis pigmentosa (RP). These characteristics were present at or close birth. This German ophthalmologist classified the disease as a new group of pigmentary retinal dystrophy, or tapetoretinal degeneration[12].

In 1957, a reduced or non-recordable ERG was identified as an essential component in the LCA diagnosis[13]. In such report, congenital keratoconus/keratoglobus and cataracts were features associated with this dystrophy, which was named LCA[13,14]. At the same year, Alstrom *et al*[15] reported that in a study from Sweden 20% of blind children had LCA (*heredoretinopathia congenitalitis monohybrid recessive autosomalis*), which had predominantly an autosomal recessive inheritance. In 1963, Waardenburg *et al*[16] described intrafamilial expression variability and association with keratoconus and cataracts.

CLINICAL CHARACTERISTICS

An appropriate clinical evaluation and ophthalmological history, as well as the determination of suggestive retinal clues make a correct diagnosis of the early-onset childhood retinal dystrophies. The utilization of newer diagnostic tools as optical coherence tomography (OCT), join to electrophysiological test (ERG) support the diagnosis. However, at present, genetic-molecular testing is necessary to obtain a definitive diagnosis of retinal dystrophies through pathogenic variants identification[10].

LCA is characterized by at least three findings: severe and early visual impairment, sluggish or near-absent pupillary responses, and severely subnormal or non-detectable ERG[12,13,17]. In LCA patients the absent of fixation or oscillations of the eyes may be seen as early as 6 wk of life. Phenotypic variability on the retina can be identified; thus, fundus appearance ranged from normal or mild retinal involvement to macular coloboma or maculopathy, bone-spicule pigment migration, marbleized fundus, among others. Refractive errors as high hypermetropia, photoaversion (photophobia), nyctalopia and the oculodigital sign, are also commonly observed[17,18].

Visual function

Visual function and visual acuity (VA) are broadly variable, generally range from 20/200 to perception of light or inclusive no perception of it[18]; thus, the prognosis in these patients are complicated. The natural history of visual impairment has been divided into three types: a stable development in most of affected subjects, visual progressive decline, and an appreciable improvement in a minority[8]. In this way, VA, fundus appearance, and systemic findings were assessed in 55 patients with LCA. Twenty-two patients were seen for follow-up examinations (5 years). Seventeen (77%) patients were found to have stable VA, four (18%) had deterioration of VA, and one patient (5%) improvement[19]. Another

longitudinal study carried out in 14 patients reported that 50% of them have invariable VA, 29% with VA deterioration, and 21% with visual improvement[20]. In a small series of nine LCA patients was showed VA stability was demonstrated in 55% of patients, while 11% and 33% demonstrated decline and improvement, respectively[21]. In summary, in all studies, 90 patients were examinated: 15%, 75%, and 10% of cases have showed deterioration, stability and improvement, respectively[8]. Patients with mutations in specific LCA genes have demonstrated distinctive VA among the different LCA subtypes. We will return to this point later on.

Ophthalmological features associated to LCA

Refraction defects are variable. Subjects with LCA most commonly are hyperopic[19,22,23]; although, they may also be highly myopic[24]. It has been proposed that an unusual emmetropic development may be caused by severe visual impairment[23]. Some children with LCA children are photophobic[24], whereas others LCA patients can have nyctalopia[25] and these symptoms may be gene-specific as we will soon see[2]. Franceschetti´s oculo digital sign, comprising eye poking, pressing, and rubbing is usual in LCA children; it is not pathognomonic for this retinal dystrophy and it can be found in other diseases[26,27]. Some LCA patients may present keratoconus and cataract, which exacerbate the poor vision of this pathology. Mutations in *AIPL1* and *CRB1* genes may be identified in these patients[28-31].

No ophthalmological features associated in LCA

Mental retardation was the most significant systemic association in LCA patients. It was reported in up to 52% on this disease[15,32-35]. As in most of these reports cerebral imaging studies were not performed, it seems that this figure is overestimated. In more recent studies where the brain was evaluated, numerous cases were found to have cerebral anomalies as cerebellar involvement (Joubert syndrome), thereby excluding LCA diagnosis[18].

Stereotypic movements and behavior (hand and rubbing movements, hair touching, facial grimaces, among others) are particularly marked in LCA[6].

Olfactory dysfunction has been described in some LCA patients (and carriers) due to mutations in the *CEP290* gene[36].

DIFFERENTIAL DIAGNOSIS OF LCA

Some inherited retinal no syndromic diseases share similarities with LCA. Achromatopsia and congenital stationary night blindness may present poor eye fixation and nystagmus, which are similar to LCA, but they show normal retinal fundus. On the other hand, ocular albinism also have nystagmus and poor fixation; however, it has albinotic retinal fundus (absent retinal pigment and choroidal vessels visible) and foveal hypoplasia[8].

Complete achromatopsia or colorblindness is an autosomal recessive pathology that presents marked photophia-photoaversion and blepharospam, decreased VA, and inability to discriminate color. At night, they have a significantly improvement. Incomplete form of achromatopsia or blue-cone monochromacy is a congenital stationary cone dysfunction that presents the same symptoms, although it is less severe. In both subtypes of cone dystrophies ERG recordings have rod photoreceptor normal function, while cone function is absent or subnormal[8,18].

CSNB is a heterogeneous group of nonprogressive retinal pathologies that present reduction of VA, myopia, strabismus, and mainly impaired night vision. ERG report absence of rod function in the complete form of CSNB, while in the incomplete form there is a subnormal rod function response[8,18].

Since the sixth week of age albinism may be confused with LCA; however, several features present in albinism as hypopigmentation of the skin, hair and eyes, and a normal ERG make a differential diagnosis[8,18].

Some syndromic inherited disorders may present similar ocular characteristics to LCA. For this reason it is important search features as mental retardation, deafness, kidney disease (nephronophthisis), skeletal anomalies, cerebral and cerebellar anomalies, among others, which can be associated to retinal photoreceptor degeneration.

Bardet-Biedl syndrome (BBS) is an autosomal recessive disorder with a retinal degeneration that presents a rapid progress, characterized by poor vision and night blindness since the first decade of life and total blindness before the second decade. Nystagmus is extremely infrequent. Different forms of retinal dystrophy have been described, including a cone-rod dystrophy or rod-cone dystrophy, choroidal dystrophy, and so-called global severe retinal dystrophy[37]. Truncal obesity and diabetes mellitus, postaxial polydactyly, hypogonadism in males and genital anomalies in females, renal malformations, developmental delay/behavioral anomalies, ataxia, anosmia, cardiovascular anomalies, among others, can be seen in BBS[38]. Alström syndrome is an autosomal recessive disease similar as BBS that also affects severely vision since early ages; but they do not present polydactyly[39].

The neuronal-ceroid-lipofuscinosis are heterogeneous disorders characterized by intracellular storage of ceroid lipofuscin. Progressive vision loss, retinal degeneration, macular degeneration and optic atrophy cause blindness since the age of two years. Developmental delay/mental retardation, psychomotor degeneration, hypotonia, ataxia, seizures, spatiscity, and death are common characteristics seen in this syndrome. ERG shows early non-recordable res-

ponses[40,41].

Senior-Loken syndrome has 2 major features: cystic kidney known as nephronophthisis and early childhood-onset retinal degeneration (retinitis pigmentosa or LCA). Similar features join to cerebellar hypoplasia may be seen in Jourbert syndrome and Meckel syndrome, both diseases known as cerebello-oculo-renal syndromes. Anomalies in cilia proteins (which are essential for the normal development and function of a wide array of specialized tissues as retina, inner ear, kidney, and brain) have been associated in these entities. Thus, mutations in several genes related to centrosomal and ciliary function (as *CEP290*) can cause phenotypic heterogeneity, ranging from LCA to the syndromes above mentioned[42,43].

Refsum disease, neonatal adrenoleucodystrophy and Zellweger syndrome are peroxisomal disorders that have similar ocular LCA phenotype; however, the systemic cerebral, hepatic, and renal features dominate the phenotype, and the patients almost always suffers an early death[18].

MOLECULAR GENETICS OF LCA

LCA is a highly clinical and genetic heterogeneous disease that is inherited as an autosomal recessive trait in most of the affected. Recent advances in knowledge based in molecular genetics of the retina have allowed the improvement and widen of the clinical diagnosis. In this way, patients with LCA or childhood early retinal dystrophies are sooner identified, and new mutations and LCA genes are being discovered[12,15,44].

Identification of LCA genes

Mutations in least 22 genes (Table 1) have been identified in patients suffering from LCA, nonetheless in 30%-50% of LCA patients no genetic cause is confirmed (Table 1). The advent of new genotyping technologies such as DNA microarrays or next generation sequencing (NGS) offers the opportunity of discovering new LCA loci[4]. Currently, some old methods (linkage analysis and candidate gene approach) or newer methods (homozygosity/autozygosity mapping and NGS) are used for LCA genes identification.

Linkage analysis has identified some LCA genes including *AIPL1*, *GUCY2D* and *RDH12*[45-49]. On the basis of retinal expression other group of genes related to LCA have also been found (*RPE65*, *LRAT*, *CRB1*, *IMPDH1*, *CRX*, and *RPGRIP1*)[50-56].

Recently, microarrays technology is utilized to identify mutations that had already been described in other retinal dystrophy reports. This method has the advantage that is relatively cheap and fast; although it has the disadvantage that new mutations will be missed and will not identified. Thus, at least one pathogenic mutation will be found in approximately 60% of the patients when this technology is used. Another method based in microarray technology named homozygosity mapping is important in autosomal recessive diseases where the same ancestral allele is present in affected patients. Thus, this genetic-method is used for detect homozygous mutations (the same mutation in both alleles). *CEP 290*, *LCA5*, *IQCB1*, and *SPATA* are some genes that have been identified by this microarray technology[57].

New mendelian syndromes, new disease genes discovered and even new mechanism of pathogenicity have been identified[58]. A combination of homozygosity mapping and/or exome sequencing have successfully identified mutations in novel LCA genes including *KCNJ13*[59], *ALMS*[60], *CNGA3*[60], *MYO7A*[60], *BBS4*[61], *NMNAT1*[62,63] and *PRPH2*[64].

Genes, function and genotype-phenotype correlation

LCA exhibits a wide intra-and interfamilial clinical heterogeneity. However, it has been recognized that in some instances the retinal phenotype can suggest the underlying molecular defect. This phenotype-genotype correlation may help to determine rapidly a responsible gene, thus decreasing both the number of genes to be analyzed and the cost of molecular analyses. In the next sections we describe some of the most frequently mutated LCA genes.

***GUCY2D* (LCA1, OMIM #204000):** *GUCY2D* gene encodes a transmembrane protein termed guanylyl cyclase 1 which is specifically expressed in the retina and localized in the outer segment of the photoreceptors[65]. This enzyme is involved in the resynthesis of cGMP, a key step in the phototransduction recovery process. GUCY2D mutations accounts for 6%-21% (Table 1) of recessive LCA and up to 40% of dominant cone dystrophies[4,66]. Most *GUCY2D* mutations produce truncation of the protein and total loss of its function[67].

Patients with GUCY2D mutations had markedly poor vision early in life without an obvious subjective degree of progression and their visual acuity can range from 20/200 to light perception[68,69]. Patients have poor responses to visual stimuli, photophobia, preference for dim lights, hyperopia, nystagmus, and do not report night blindness[70]. Retinal fundus generally remains without abnormal findings throughout life. Patients can develop peripheral mild pigmentary changes, optic disc pallor and vascular attenuation[69]. Non-recordable ERGs are typical while OCT imaging shows a significant retinal thinning in the perifoveal area[69].

***RPE65* (LCA2, OMIM #204100):** *RPE65* encodes a retinal pigment epithelium-specific 65-Kd protein[65], which forms a complex with LRAT to act as the isomerohydrolase in the process of visual

Table 1 Leber congenital amaurosis genes and phenotype-genotype correlations

Locus name	Gene symbol	Chromosomal locus	Protein name	Protein function	% of LCA	LCA phenotype	Other retinal dystrophies	Mutations number
LCA1	GUCY2D	17p13.1	Retinal guanylyl ciclase 1	Hydrolysis cGMP	6-21	Marked poor vision, photophobia, hyperopia, nystagmus. Normal appearing fundus or mild granular pigmentary changes in periphery. OCT with significant thinning perifoveal	dCRD, dCD	155
LCA2	RPE65	1p31.3-p31.2	Retinal pigment epithelium protein 65	Isomerohydrolase in vitamin A visual cycle	3-16	Night blindness, nystagmus, poor vision on the first year, transient vision improvement and later deterioration in their third to fifth decades. OCT: thinner retina in both central and perifoveolar areas	rRP, dRP, RPci	138
LCA3	SPATA7	14q31.3	Spermatogenesis-associated protein 7	Possible vesicular transport	Approximately 3	Transient photophobia on the first year, but at three years old all patients had night blindness. Visual acuity at the end of the first decade remained stable. After, only hand motion and 20/200 can be seen. Fundus with typical appearance of RP rapidly progressive	rRP	18
LCA4	AIPL1	17p13.1	Aryl hydrocarbon interacting protein	Rod PDE chaperone	5-10	Keratoconus, cataract, and hyperopia. Variable night blindness or light sensibility. Poor vision. Fundus with bone spicules pigmentation and variable degree of maculopathy. OCT with reduced macular thickness	dCRD, rRP	52
LCA5	LCA5	6q14	Lebercilin	Ciliary functions	1-2	Severe reduced vision at, or near birth. Nystagmus and high hypermetropia. Visual acuity range between 0.20 to light perception. Extensible peripheral field loss. Fundus examination with widespread atrophy of the retina and RPE. Scattered white dots at RPE. Macula is normal most time, but in few patients may be seen macular coloboma. OCT: macular atrophy, disruption of retinal lamination and presence of hyporeflective well-circumscribed area in the outer nuclear layer, with a hyperreflective border (rossettes). Fundus autofluorescence shows hypofluorescence in the macula	No	35
LCA6	RPGRIP1	14q11	RP GTPase regulator-interacting protein 1	Connecting cilium, disc morphogenesis	4-6	Severe loss of vision early in life. Acuity visual worse than 20/200. At the beggining normal retina is seen, then it progress to pigmentary retinopathy. OCT shows remaining photoreceptor in the fovea	rCRD	82
LCA7	CRX	19q13.3	Cone-rod homeobox	Elongation of photoreceptor outer segment, photoreceptor development, phototransduction	1%-3%	Severe vision impairment is expected early in life. Nystagmus and high hyperopia. Fundus grayish with clumping or dot-pigment deposits and macular coloboma-like defect. OCT shows macular atrophy without noticeable signal of the junction between inner segments and outer segments	dCRD, dRP dLCA and rLCA	58
LCA 8	CRB1	1q 31-32.1	Crumbs homologue	Determining ad maintaining photoreceptor architectura	9-13	Nictalopia, nystagmus, keratoconus, corioretinal atrophy and nanophthalmos. Fundus with numular pigment clump, bone spicules and para-arteriolar preservation. Coloboma-like lesions and Coast like lesions	RPpa, rRP	
LCA9	NMNAT1	1p36.22	Nicotinamide nucleotide adenylyltransferase 1	Rate-limiting enzyme NAD (+) biosynthesis	----	Severe form of retinal hereditary degeneration, mainly atrophic macular lesion. Macular pseudocoloboma. Retina´s remainder with pigmentary changes. Nistagmus and severe loss of vision (only light or hand movements perception)	----	44
LCA 10	CEP290	12q21.32	Centrosomal protein Cep290	Ciliary function	20	Nystagmus, hyperopia, keratoconus and cataract. Photophobia. Light perception or no vision. Atrophic spot (dot-like) in RPE, intraretinal bone spicules in most patients. A striking tapetal reflex (specific intraretinal greyish and white marbled areas). Perifoveal thinning by OCT	Syndromes (Senior-Loken, Joubert, Meckel)	187
LCA 11	IMPDH1	7q32.1	Inosine 5´-monophosphate dehydrogensase 1	De novo synthesis de guanine nucleotide	8	Nystagmus with no fixation to light. Retina showing diffuse RPE mottling. No pigmentary deposits	dRP	18

LCA12	RD3	1q32.3	Protein RD3	Transcription and splicing. Suppress retinal membrane guanylate cyclase activity. Role in retinal maturation	< 1	Night blindness, severe nystagmus. Initial refraction was hypermetropic and changed to myopic in the disease´s course. Severe impaired visual acuity. Attenuated vessels, salt and pepper aspect, and bone spicules are seen on fundus. Macular changes as hammer beaten appearance were note on the third decade of live. OCT reveal disorganization of all retinal layers	----	9
LCA13	RDH12	14q23.3	Retinol dehydrogensase 12	Unusual dual specificity for all-trans-retinol and cis-retinols	4-5	Poor vision. Night blindness. Chorioretinopathy (reticular or fishnet pattern) with dense hyperpigmentation and bone spicules. There is little or no autofluorescence on the macula. SDOCT: severe macular thinning and loss of the foveal laminar architecture	dRP	76
LCA 14	LRAT	4q31.3	Lecithinretinol acyltransferase	Esterification essential in vitamin A visual cycle	< 1	Poor vision, nyctalopia, and visual field constriction since childhood. Peripheral RPE atrophy with little pigment migration into retina. Asteroid hyalosis occurs more frequently than RP (37% *vs* 3%). Reduced AF signal	rRP, EORD	13
LCA 15	TULP1	6p21.3	Tubby-like protein	Protein transport from the photoreceptor inner segment to the outer segment	----	Night blindness, nystagmus, moderately to severely limited visual field. Severely disturbed color vision. Fundoscopic findings are variable; pronounced maculopathy in older patients, pigmentary retinopathy in all patients. Pigmentary spicules also are variable affected	rRP	47
LCA 16	KCNJ13	2q37	Inwardly-rectifying potassium cannel subfamily J members	Maintaining resting membrane potential	----	Poor night vision, nystagmus. Cataract. Fundoscopy reveals considerable levels of pigments at RPE and a different configuration that the one seen on typical RP	dVRD	6
LCA 17	GDF6	8q22.1	Grow differentiation factor 6	Codes for a widely expressed growth factor in the TGF-b pathway specifying the dorsal-ventral retinal axis	----	Ocular and skeletal features. Limited vision to detect hand motions	Klippel Feil syndrome, dominant microphthalmia	15
	CABP4	11q13.1	Calcium binding protein 4	Modulate voltage dependent calcium channel	----	Poor vision, nystagmus, photophobia, poor visual acuity	rCSNB, rCRSD	6
	CNGA3	2q11.2	Cone photoreceptor cGMP-gated cation channel alpha subunit	Important for normal vision and olphatory signaling transduction	----	LCA phenotype is not described	Colour blindness total, achromatopsia, cone dystrophy	82
	ALMS1	2p13.1	ALMS1	ALMS protein	----	LCA phenotype is not described	Alstrom syndrome	129
	IQCB1	3q21.1			----	LCA phenotype is not described	Recessive Senior Loken syndrome	
	MYO7A	11q13.5			----	LCA phenotype is not described	Usher syndrome, congenital deafness without RP	304

dLCA: Dominant Leber congenital amaurosis; rLCA: Recessive Leber congenital amaurosis; dCRD: Dominant cone-rod dystrophy; dCD: Dominant con dystrophy; rRP: Recessive retinitis pigmentosa; dRP: Dominant retinitis pigmentosa; Rpci: Retinitis pigmentosa with choroidal involvement; PDE: Phosphodiesterase; recessive retinitis pigmentosa with para arteriolar preservation (rRPpa); EORD: Early onset retina dystrophies; AF: Autofluorescence; dVRD: Dominant viteroretinal degeneration; rCSNB: Recessive congenital stationary night blindness; CRSD: Recessive cod-rod synaptic disorder.

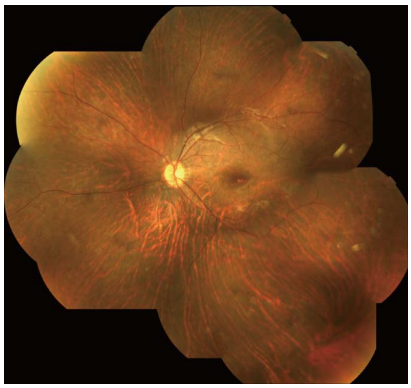

Figure 1 Patient´s fundus with *RPE65* mutations.

pigment regeneration. RPE65 is highly expressed in the RPE cells[71]. High RPE65 concentrations have demonstrated by immunocytochemistry and immunoblotting in the central area of the retina. LCA2 patients show an evident early cone loss, although residual cone preserve structure and function that may be present for many years in humans, supporting the existence of alternative pathways for cone survival[18]. RPE65 mutations account for 6%-16% of LCA cases and for approximately 2% of recessive RP cases[72]. Mutations in the *RPE65* gene are associated to severe visual loss; shortly after birth or in the first few years of life, affected child is noted to be less visually responsive than normal child[72].

In LCA2 patients, night blindness is a common characteristic and for that reason they prefer being in well-illuminated environments. Patients typically have nystagmus and poor vision since the first year of life. Improvement of visual function over the first few years of life can occur and vision may be relatively fair through teenage years, with later deterioration as patients reach their third to fifth decades[2,11]. Myopia and cataract are frequently associated[69]. The fundus appears normal at birth, but several abnormalities can progressively develop. Most patients present optic disc pallor, vascular attenuation and pigmentary retinal changes. Bull's eye maculopathy can be present at early stages while geographic atrophic lesions, diffuse hypopigmentation (dot-like changes) and pigment clumping can be observed at late stages (Figure 1). SD-OCT show 1-3 retinal layer with progressive disorganized lamellar structures. Patients with RPE65 have significantly thinner retinas in both the central and perifoveal areas[69].

***AIPL1* (LCA4, OMIM #604393):** *AIPL1* gene encodes the aryl hydrocarbon receptor protein-like 1, which is involved in nuclear transport or chaperone activity for rod phosphodiesterase (PDE)[4]. This protein is expressed early during human development in the central and peripheral retina, coinciding with rod and cone development; in contrast, *AIPL1* expression is restricted to rod photoreceptors in the adult retina[73]. Mutations in *AIPL1* resulting in blinding diseases can be classified into three categories: Class Ⅰ and class Ⅱ changes (missense and stop mutations) results in LCA (5%-10% of recessive LCA cases), while class Ⅲ mutations (small in-frame deletions) originate dominant forms of cone dystrophy (CORD5) or juvenile retinitis pigmentosa (RP13)[18,74].

The phenotype of LCA patients due to *AIPL1* mutations is relatively severe and is characterized by maculopathy and pigmentary retinopathy since young ages[31,75]. Nystagmus is observed in all patients starting at birth or at early infancy[75]. Keratoconus (26%-30%) and cataract (26%-60%) are commonly associated ocular findings[31,76] while hyperopia is the most common refraction error[2,76]. In addition, light gazing, night blindness, and photophobia can also be present[2,76]. Patients show markedly decreased visual acuities since early ages, ranging from 20/600 to no light perception associated with severe visual fields loss, and extinguished ERGs responses[76]. Fundus examination can vary from normal fundus to a salt-and-pepper retinal dystrophy and no apparent macular involvement in young patients; in contrast, older patients can exhibit typical features of retinitis pigmentosa as mild retinal vessel attenuation, bone spicule pigmentation, nummular pigmentation, and pale optic disc in combination with macular anomalies that can vary from mild foveal atrophy to macular coloboma. Autofluorescence (AF) imaging in AIPL1 young patients demonstrates mild generalized reduction in AF at the posterior pole and a relatively preserved macular AF, which demonstrate some degree of structurally intact photoreceptors and retinal pigment epithelial cells[77]. OCT imaging indicates a reduction in macular thickness in all patients (with salt-and-pepper dystrophy or RP-like lesions) with retinal lamellar structures partially retained, displaying 3 retinal layers with preservation of the outer nuclear layer and photoreceptor inner/outer segment juncture[76].

***CRB1* (LCA8, OMIM #613835):** The *CRB1* gene encodes a transmembrane protein named crumbs homolog 1 that is expressed in brain and retina and plays a central role in determining and maintaining the apico-basal cell polarity and adherens junction in embryonic epithelia[18,66]. CRB1-associated LCA is suggested to be caused by a developmental defect in the retina, since LCA patients with mutations in CRB1 have a thickened retina and lack of distinctive layering, resembling an immature retina[78]. Mutations in this gene cause multiple retinal phenotypes including LCA, retinitis pigmentosa, early onset rod-cone dystrophy, and cone-rod dystrophy[4]. The frequency of LCA8 varies considerably between populations in different geographic regions and

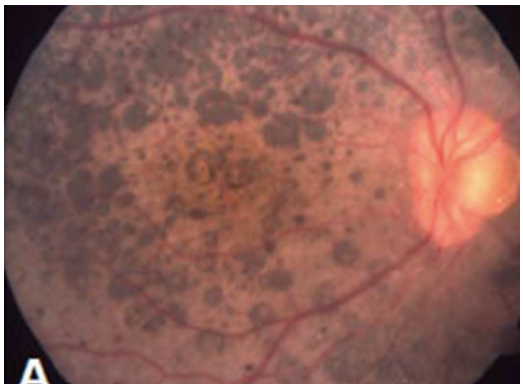

Figure 2 Patient´s fundus with *CRB1* mutations.

ranges from 17% in Spain to 0% in India[79,80].

Nystagmus is a common finding and visual acuities vary widely; thus the majority of patients retain walk-around vision in their first decade, during which median visual acuity is approximately 20/200. Later, visual acuity deteriorates with advancing age[29]. However, some reports have described VA as good as 20/40[2]. Approximately half of patients also have high hypermetropia[2,81]. Night blindness is present in the majority of affected; however, decrease of central vision and photophobia may present in some cases[81]. Keratoconus, occurring in 14%-70% of cases, contributes to visual deficiency in patients with LCA8[80]. Patients carrying CRB1 mutations have shown to be predisposed to chorioretinal atrophy[82] and nanophthalmos[83]. The fundus retinal hallmark of LCA8 is nummular pigment clumps (Figure 2), which are found in more than half of the patients. Although these feature are typical of *CRB1* mutations, it is not pathognomonic and has also been associated with mutations in other retinal dystrophy genes as *NR2E3*[82], *NRL*[84] or *TULP1*[85]. Bujakowska *et al*[81] reported two patterns of fundus pigmentation in their cohort: a typical bone spicule-shaped pigment migration within the peripheral retinal, and clumped pigmentary changes of nummular appearance at the level of the RPE[81]. Preservation of the para-arteriolar retinal pigment epithelium, retinal telangiectasia with exudation (Coat's-like vasculopathy), and macular lesions as coloboma-like lesions in macular or cystoids edema may also be seen[81,84]. SD-OCTs in patients with *CRB1* mutations show increased retinal thickness and loss of the outer limiting membrane[84,85].

***CEP290* (LCA 10, OMIM #611755):** *CEP290* gene encodes the centrosomal protein 290 which is a centrosomal protein with a probable ciliary function and expressed at high levels in the photoreceptor connecting cilium. This protein putatively interacts with the protein retinitis pigmentosa GTPase regulator and also with nephrocystin-S, which is mutated in nephronophthisis type 5[66]. *CEP290* mutations account for 6%-22% of non-syndromic LCA, depending on the population studied[18].

Although there is some inter-intrafamilial variability, patients carrying *CEP290* mutations exhibit a relatively homogeneous distinctive phenotype[86]. Most of the patients present roving eye movements or nystagmus with sluggishly papillary reactions since early childhood. Eye poking, enophthalmos, hyperopia, keratoconus and juvenile cataract are frequently observed[86]. Photophobia is present later in life, and night blindness has sometimes been described. Most patients have severe visual deficiency and visual acuity is either light perception or no vision at all from birth. In some patients visual capability may be equal to or more than hand motion and most of them are able to record progressive deterioration of visual acuity in succeeding years[86]. Fundoscopic findings are variable, from no changes to small (dot-like), well defined, atrophic spot at the level of the RPE to more pronounced RPE atrophy with intraretinal bone spicule-like pigmentation and a preserved macular region. Pasadhika *et al*[69] described LCA 10 patients with various degrees of macular changes, from a blunted foveal reflex to bull's eye maculopathy and optic disc drusen. In several patients, a striking tapetal reflex consisting of intraretinal greyish white marbled areas, more noticeable in the younger patients, is observed[86-88]. The small atrophic spots at the RPE layer and tapetal reflex-like changes seem to be specific of CEP290-associated LCA, since they have not been described in other forms of LCA. A distinct yellow scleral rim and pseudopapillary edema are also suggestive of this specific type of LCA[86]. Retinal SD-OCT analysis of patients with *CEP290* mutations shows segmentation into only three layers. ONL was notably preserved at the central macular area, but was thinner from the perifoveal area to the periphery. Such preservation tended to decline with an increase in the patient's age. Photoreceptor inner/outer segment was poorly defined in the central macula, but was invisible in the periphery. Moreover, cyst-like macular lesions can be identified in up to 43% of LCA 10 patients[69].

***RDH12* (LCA 13, OMIM #612712):** Retinol dehydrogenase 12 (*RDH12*) gene encodes a RDH12 protein that is a photoreceptor-specific enzyme involved in all-trans-and cis-retinol transformation[66]. RDH12 is expressed in the mouse and human photoreceptor inner segments and ONL[18]. Most *RDH12* mutations result in reduced expression and activity of the retinal dehydrogenase 12 enzyme, which in turns disrupts the cycle of synthesis of the visual pigment chromophore, 11-cis-retinal, from 11-trans-retinal[66]. *RDH12* mutations account for 4%-5% of recessive LCA, but may also cause other phenotypes as progressive rod-cone dystrophy, macular atrophy,

Figure 3 Patient´s fundus with *RDH12* mutations.

and early-onset RP[4].

LCA 12 patients exhibit a homogeneous clinical picture characterized by poor visual function in early life, a transition period with visual improvement, and a progressive period of decline in visual function due to rod and cone degeneration[89]. At young ages (4-6 years), patients have visual acuities in the range of 40/100 to 50/100, and visual fields are relatively well preserved; however, an age-related progressive loss of visual acuity is evident, with values from 10/100 to light perception on people at ages above 20 years. In younger subjects, residual rod and cone ERGs responses are recordable, with preferential preservation of cone function documented by use of multifocal ERG recordings; however, both rod and cone ERG are undetectable in patients older than 20 years[90]. Night blindness is the predominant symptom of this type of LCA[2]. This subjective symptom together with visual field constriction may not be frequently reported at time of presentation, but may be commonly recognized later in the disease progression[91]. Most LCA 12 patients have no photophobia while mild posterior subcapsular cataract and mild hyperopia can occur[90]. A marked pigmentary retinopathy, ranging from mild RPE atrophy and mid peripheral hyperpigmentation to severe chorioretinopahty (reticular or fishnet pattern) with dense hyperpigmentation has been associated to this form of the disease[90]. Bone spiculae are almost always present (Figure 3)[90]. There is little or no autofluorescence at macula in severe disease. SD-OCT imaging demonstrates severe macular thinning as well as excavation and loss of the foveal laminar architecture[91].

Gene therapy in LCA

Recent advances in the knowledge of the genes and the pathophysiology associated with mutations in those genes, has opened a new era of mechanism-based molecular therapeutics in ophthalmology. Immune privilege, small organ size, easy access and compartmentalization, as well as contralateral control, make the eye a perfect organ for gene therapy treatment[92,93]. Thus, to date, several independent phase I/II clinical trials for inherited retinal dystrophies including LCA2 (*RPE65*), choroideremia (*CHM*), Usher syndrome 1b (*MYO7A*), Stargardt disease (*ABCA4*), Leber hereditary optic neuropathy (*ND4*), and autosomal recessive retinitis pigmentosa (*MERTK*) are being studied[93].

Human Therapy: *RPE65*: Recently, three independent clinical trials of gene replacement therapy for LCA (specifically by *RPE65* gene) are carrying out to evaluate safety and efficacy[94-96]. Clinical assessment of these LCA2 patients analyzed ERG results, pupillary light reflex, nystagmus, and fundus abnormalities. Patients were treated in the most affected eye with a unique retinal injection of adenovirus vector (AAV2) carrying *RPE65* gene. A safety assessment has not showed the presence of serious adverse event in all trials. The reports of short-term follow-up of these trials have demonstrated an improvement in selected measures of vision, including best-corrected visual acuity, kinetic visual field, nystagmus testing, pupilarry light reflex, microperimetry, dark-adapted perimetry, and dark-adapted full-field sensitivity testing[97]. Soon, the third clinical trial phase of RPE65 replacement in these patients, will start.

Animal models in other LCA genes: Preclinical promise: In several genetic-molecular studies, *GUCY2D* is the most common *LCA* gene affected. A normal retinal fundus evaluation and relatively preserved rod-cone architecture make this group of LCA patients aspirants for gene therapy treatment. GUCYKO mouse containing recombinant AAV-*GUCY2D* gene has restored and preserved cone function during long time[98,99]. A recently study carried out in non-human primate demonstrated a persistent function in both rod and cone cells, mainly in foveal, perifoveal and parafoveal photoreceptors. These results suggested that *GUCYD2* gene therapy replacement could be a good treatment for LCA patients[100].

Other LCA genes considered for gene therapy are *AIPL1* and *CEP290*. Recently, a study developed in hypomorphic and null function mouse model shown long time rescue of rod-cone photoreceptors. Thus, these results showed that CEP290 gene therapy could be applied to patients with partial or complete loss of gene function, mainly when intervention occurs early in life[101]. Another recent study, using self-complementary viral vector has achieved functional vision rescue for this rapid retinal dystrophy[102]. CEP290 mutations may maintain cone cell structure in macular region, mainly in the fovea; in this way, this group of patients are a perfect target for a new gene therapy. Recently, Burnight *et al*[103] built a viral vector containing the *CEP290* gene and they demonstrated in cells culture that some mutated

cells developed cilia after this therapy. Thus, this gene therapy rescued the ciliogenesis anomaly, and could be effective affected subjects[103].

CONCLUSION

Current technology, such as gene testing, OCT or autofluorescence imaging studies together with the knowledge of the ocular-phenotype features of distinct LCA diseases has increased the individual diagnosis of this retinal dystrophy. This will lead to better prognosis and treatment options for LCA patients. Currently, gene therapy for RPE65-LCA2 patients is a fact, and new similar emerging therapies will be soon available. Thus, the knowledge of genotype-phenotype is necessary for a better patient management.

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REVIEW

Dengue and its effects on liver

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Abstract

Dengue has emerged as an important arboviral disease with significant impact on the disease burden in population residing in tropical countries. Dengue is spread by the bite of Aedes mosquito. The virus seems to have some hepatotoxic effects. Affliction of liver in form of derangements in the liver function tests is common and may include mild elevations in serum bilirubin, elevated transaminases and derangements in serum albumin. Although asymptomatic in most cases, clinical manifestations like jaundice, and acute liver failure (ALF) may occasionally complicate the clinical picture. Indeed, dengue has been implicated as an important cause of ALF in endemic countries. The present review focuses on the hepatic manifestations and the pathogenesis of the liver injury in dengue.

Key words: Dengue; Liver; Viral hepatitis; Acute liver failure; Transaminases; Bilirubin

Core tip: Dengue is an important cause of febrile illness in the tropical countries. It may affect the liver but the hepatic involvement is usually asymptomatic. However it is recognized as an important cause of acute hepatic failure in endemic counties. Dengue must be considered as a differential in the evaluation of acute hepatic failure and as an acute precipitant in patients presenting with acute on chronic liver failure.

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INTRODUCTION

Dengue or "break bone fever" has gradually evolved as one of the important causes of febrile illness in the tropical and subtropical region. Second only to malaria, dengue is a common mosquito-transmitted disease, and currently, it is the most common cause of arboviral disease globally. Around 2.5 billion people in 100 endemic countries are believed to be susceptible, so are the equally significant number of travelers to these tropical and subtropical regions[1,2]. Presenting with a wide range of severity, "severe" dengue (Group C) as categorized by World Health Organization (WHO) in 2009 includes the dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS)[3]. Despite the inadequate surveillance of cases from the underdeveloped tropical countries, the average number being reported per year has

increased drastically[1,4]. A host of factors including the relentless urbanization with poor hygiene, dilapidated health systems to increasing international travel fuel the spread of this disease geographically and increase the disease burden of tropics significantly[1,2].

This disease has been found to have profound effect on multiple organ systems, the commonest being the liver. Starting from asymptomatic elevated transaminase levels to acute liver failure (ALF), dengue has all the properties of a hepatic illness. In this paper we review, the pathogenesis, pathology, clinicobiochemical parameters and management of the effects of dengue on liver.

DENGUE VIRUS

Dengue virus (DENV) has 4 serotypes (DEN 1-4) and is a member of the Flaviviridae family and the genus Flavivirus[5]. Though initially DEN1 and DEN2 were found around Central America and Africa, and all 4 serotypes found in Southeast Asia, currently all the serotypes have diffused in all tropical and subtropical regions of the world[1,6]. The serotypes sharing a mere 65% of the genotype among each other produce a uniformly wide array of manifestations, with most of them being asymptomatic[2].

DENVs are transmitted *via* the species Aedes aegypti, and less commonly by Aedes albopictus. The Aedes aegypti mosquito with its anthropophilic nature is well adapted for urban thriving and frequently bites several times before completing oogenesis[3,7].

If during the 5 d period of human viremia, the mosquito feeds, it gets infected and the DENV migrates from insect mid-gut to the salivary glands. After 8-12 d of life cycle of DENV inside the mosquito, with optimum high temperatures, the mosquito becomes infective, and can bite and transmit the virus to another host[1,3]. High concentrations of virus are exhibited in mosquito cell cultures with persistent infection[8].

DENV is an RNA virus with a single-stranded positive-sense RNA acting as the genome. The virus has an envelope and is icosahedral in shape. The structural proteins encoded by the DENV are capsid, precursor membrane, and envelope [E]. The virus also encodes for seven non-structural (NS) proteins one of which (NS1) has found use as a diagnostic antigen in initial phases of the disease. The E glycoprotein plays a crucial role in the biology of the DENV, starting from receptor binding to immune response[1,9].

Endocytosis of virus occurs after binding mediated by various molecules including glycoproteins like heparin sulfates as also dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin, and a carbohydrate recognizing mannose receptor[10,11]. Upon internalization, the acidic pH induces change in the classically described "herring-bone" pattern of E glycoprotein. The uncoating and release of the genome occurs once the nucleocapsid is exocytosed into the cytoplasm[12].

CASE DEFINITION

Before going into the various hepatic manifestations of dengue, the evolution of dengue case definition will be briefly discussed. Dengue has been traditionally classified into dengue fever (DF), DHF and DSS (WHO 1997 Classification)[13,14].

DF: Fever and at least two features: ocular pain, headache, muscle or joint pains, cutaneous rash, bleeding manifestations and reduced leukocyte count.

DHF: Fever, thrombocytopenia ($\leqslant 100 \times 10^9$/L), bleeding manifestations and evidence of plasma leakage.

DSS: DHF with tachycardia or low pulse pressure (< 20 mmHg) or hypotension (systolic blood pressure < 90 mmHg).

The modified categorization of WHO in 2009 includes dengue with or without warning signs or severe dengue[3].

Dengue: Fever and two of these: nausea, vomiting, skin rash, bodyache, leukopenia, or any warning sign.

Warning signs include pain in the abdominal or presence of tenderness, persistent vomiting, clinical evidence of fluid accumulation like effusions and ascites, bleeding, lassitude or restiveness, liver enlargement, or rise in hematocrit ($\geqslant$ 20%) with rapid reduction in thrombocyte count (< 50000/mm^3).

Severe dengue: Evidence of severe plasma leakage, bleeding and organ impairment. Organ impairment includes hepatic involvement in form of transaminases elevated beyond 1000 IU/L and central nervous system manifestations like alteration in sensorium or cardiac or other organ involvement.

In spite of the recent categorization, the majority of the studies widely use the more popular DF, DHF and DSS classification for case definition.

DENV INFECTION AND LIVER

With DENV infection, high level of viremia is associated with involvement of different organs (liver, brain) in the severe form of the disease[15]. The liver is the commonest organ to be involved in dengue. Hepatic manifestations are either a result of direct viral toxicity or dysregulated immunologic injury in response to the virus. The spectrum of involvement includes asymptomatic elevation of hepatic transaminases to occurrence of severe manifestation in form of ALF.

PATHOGENESIS OF LIVER INJURY

Hepatic dysfunction is a crucial feature seen in DENV

infection. Hepatocytes and Kupffer cells are prime targets for DENV infection[16-18], as confirmed in biopsies and autopsies of fatal cases[19]. For infecting cells, the major rate limiting step is the viral attachment to the receptors present on surface of host cell. The E protein has a role in the attachment of the virus[20], although the nature of the receptor used is yet to be determined[18]. Heparan Sulphate plays a pivotal role for the intrusion of the DENVs into liver (HepG2) cells[21]. A cell to be infected by a virus requires essentially viral entry and a conducive environment for the invader to grow inside the host cell and this property is influenced by viral serotype, strain and cell type. For example, the G_2 phase cells are more prone to infectivity and enhance virus replication[22]. It has been postulated that the binding of DENVs onto hepatocytes is facilitatory, one binding promotes the binding of successive particles, similar to binding of oxygen on hemoglobin. After binding of the virus, internalization is by either direct fusion or endocytosis. The entry pathway may either be mediated through the presence of receptors or even in their absence[18].

An eventual outcome of hepatocyte infection by DENV is cellular apoptosis, a phenomenon demonstrated both *in vivo* and *in vitro*[23]. After apoptosis, what stays of the cells are the Councilman Bodies[19]. The various pathways involved in this apoptotic process include viral cytopathy, hypoxic mitochondrial dysfunction, the immune response[17] and accelerated endoplasmic reticular stress. Expression of DENV-induced TRAIL[24] and TNF-α and Fas signaling[25] have also been implicated in this process. Activation of the mitochondrial cell death pathway stems from the functional and morphological defects of these mitochondria[26].

Enhancement of immune reaction due to recurrent infections is believed to be responsible for causation of severe dengue disease. DHF and DSS occur as a consequence of several factors interacting, involving the microbial and host features, with antibody-dependent enhancement which explains the phenomena of more severe disease on second infection[27]. Dengue infection induces a cytokine storm and concentrations of cytokines like interleukin (IL)-2, IL-6, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ reach peak levels in the initial 3 d. IL-4, IL-5 and IL-10 contribute to later in the course of disease[28]. Currently, the exact mechanism by which the host immunity damages liver is unknown, albeit a role of T cells entering the liver causing cytopathology cannot be ruled out. Thus, pathogenesis of hepatic injury in dengue is believed to be primarily a T cell mediated process involving interaction between antibodies and the endothelium and a concomitant cytokine storm often labeled as cytokine "Tsunami," and host factors like genetic polymorphisms.

PATHOLOGY

A wide spectrum of hepatic histological changes have been noted in dengue. This comprises fatty change (micro vesicular), hepatocyte necrosis, hyperplasia and destruction of Kupffer cells, Councilman Bodies and mononuclear cell infiltrates at the portal tract[29,30]. Hepatocyte injury including necrotic changes commonly involves the midzonal area followed by the centrilobular area. Probable explanation for such a finding could be that the liver cells in this area are more sensitive to the effects of anoxia or immune response or may be a preferential target zone of the DENVs. A recent autopsy series of dengue patients from Myanmar[31] showed varying degrees of damage in the liver, with majority of subjects having sinusoidal congestion of moderate to severe degree with predominant midzonal and centrilobular area cell death. Diffuse fatty change was noted within the hepatic lobules. The investigators noted no evidence of any significant fibrosis[31].

CLINICOBIOCHEMICAL PROFILE OF HEPATIC INVOLVEMENT

Clinical features suggesting dengue related hepatic involvement are the presence of liver enlargement and elevated transaminases[32].

Among the clinical features of hepatic involvement, patients have abdominal pain (18%-63%), nausea/vomiting (49%-58%) and anorexia[33,34]. Symptoms such as abdominal pain and anorexia have been found to be significantly more common in DF than DHF[35]. Hepatomegaly is present in both DF and DHF but more common in DF[35]. The frequency of hepatomegaly in the adult dengue patients ranges from 4%-52%[34-36]. Clinical jaundice has been detected in 1.7%-17% in various series[33,35,36] and hyperbilirubinemia has been found to be as high as 48%[34].

The commonest abnormality detected has been raised transaminase levels (Table 1). Raised AST levels have been seen in 63%-97% of patients, while raised ALT levels in 45%-96% of patients. In a majority of the studies, elevation in AST is more than ALT, more during the first week of infection, with a tendency to decrease to normal levels within three weeks[37]. The AST released from damaged myocytes could explain the higher levels of AST than those of ALT in patients with dengue fever at an earlier stage[38]. The increased AST/ALT ratio is useful for differential diagnosis from acute hepatitis caused by the hepatitis A, B or C viruses where it is rarely observed.

The average levels of AST ranged from 93.3 U/L[39] to 174 U/L[33], while ALT from 86 U/L[39] to 88.5 U/L[33] in various studies. More than a 10-fold rise

Table 1 Liver function abnormalities in dengue patients

Ref.	Patients	Raised AST	Raised ALT	AST > ALT	Hyper-bilirubinemia	> 10 fold rise (AST, ALT)
Kuo *et al*[37]	270	93.30%	82.20%	+	7.20%	11.1%, 7.4%
Souza *et al*[39]	1585	63.40%	45%	+	-	3.4%, 1.8%
Itha *et al*[41]	45	96%	96%	Equal	30%	-
Wong *et al*[40]	127	90.60%	71.70%	+ in 75.6%	13.4%	10.2%, 9.5%
Parkash *et al*[33]	699	95%	86%	+	-	15%
Trung *et al*[36]	644	97%	97%	+	1.7%	-
Lee *et al*[14]	690	86%	46%	-	-	1%
Karoli *et al*[34]	138	92%		+	48%	-
Saha *et al*[35]	1226				16.9%	

AST: Aspartate transaminase; ALT: Alanine transaminase.

has been seen in 3.8% cases in a large study from Brazil[39], whereas in other studies were between 1.8% and 11.1% of cases[34,40]. Severe hepatitis was present in 15% in one study[33], while in another study it was 1%[41]. The level of increase in hepatic transaminases can easily mimic acute viral hepatitis.

The median Aspartate transaminase (AST) and Alanine transaminase (ALT) values have been found to be higher for severer forms of dengue than for uncomplicated dengue fever[14,35,39,42]. This hints at a possible association between increased transaminase levels with increasing disease severity. Interestingly the values of liver enzymes were noted to be higher in the febrile and the severer phases of dengue vis-à-vis the convalescent phase[14].

AST has various sources including the heart, striated muscle, erythrocytes, *etc*., apart from the liver, whilst ALT primarily is hepatic in origin[14,43]. Acute insult to these non-hepatic tissues by the DENV can result in higher elevations of AST when compared to ALT rise. Therefore, rise in AST might not be a true reflection of hepatic involvement. Moreover, patients with high levels of enzymes may be labeled as severe disease without any effect on the final outcome.

Liver damage has been found to be more common among females in the large study from Brazil[39] (74.6% of females compared to 52.2% of males) with 4.2% of them having acute hepatitis. However, no significant difference could be elicited between males and females as far as the level of transaminase elevation was concerned.

Hypoproteinemia or hypoalbuminemia have been seen in 12.9% in one of the large studies from Kolkata, India[35], while it ranges from 16.5%-76% in various other studies[34,40,41]. The heterogeneity in the population and severity of the disease may be responsible for such a wide range observed in the various studies.

Coagulation abnormalities have been found in multiple studies. International normalized ratio (INR) > 1.5 have been found in 11% of patients in one study[35], while abnormal prothrombin time (PT), partial thromboplastin time noted in 34%-42.5% of the cases in other studies[34,40]. Increasing bleeding episodes have been found with increasing AST/ALT levels[33,37], but only a weak correlation could be demonstrated between PT and transaminase levels during the convalescent period, suggesting that liver synthetic function in terms of coagulation factor production was generally well compensated.

Dengue has a slightly different profile of hepatic involvement among children (Table 2). They have been found to have a higher percentage of liver enlargement as compared to adults.

Various factors which predict liver damage are DHF, secondary infection, thrombocytopenia, high blood concentration, female sex and children[39,40,44].

DENGUE AND LIVER FAILURE

The liver injury in dengue, as already mentioned, ranges from asymptomatic hepatic transaminase elevation to fatal ALF. Dengue related ALF has been well described in the literature, although the majority of reports are amongst children with few case reports in adults[32,49-55]. Although viral hepatitis and drugs are the predominant cause of ALF, infectious diseases such as dengue are being more and more recognized as an etiological agent.

In a study from Thailand, Poovorawan *et al*[56] found dengue to be a major cause of ALF among children, with 12 out of 35 children (34%) aged 1-15 years of age, enrolled between February 2000 to December 2001, having positive dengue serology. In a further extension, the same group enrolled 14 children of ALF from June 2002 to December 2006, in a recent study and found 2 of them to be due to dengue[57]. Jagadishkumar *et al*[46] have reported 5 (18.5%) confirmed dengue cases in a study cohort of 27 children with ALF from Northern India. The presentation can be varied, either classical presentation of dengue with hepatitis and shock syndrome or there may be less classical dengue characteristics[46]

Deepak *et al*[58] in a study from Mumbai, India, have found 5 cases of dengue associated ALF out of a total of 56 cases (8.9%) of ALF, while Tan *et al*[59] from Malaysia showed 8 out of 155 adult ALF cases (5.2%)

Table 2 Liver function abnormalities among children with dengue

Ref.	Patients (*n*)	Raised AST/ALT	Hepatomegaly	Jaundice	Hypoalbuminemia
Pires Neto Rda *et al*[45]	32	96%	37.50%	-	77%
Mohan *et al*[44]	61	87%	74%	25%	-
Jagadishkumar *et al*[46]	110	-	79%	4.50%	66%
Kulkarni *et al*[47]	948	90%	36.70%	0.95%	-
Roy *et al*[48]	120	94%	80.80%	60%	-

AST: Aspartate transaminase; ALT: Alanine transaminase.

to have dengue. Adult dengue patients developed ALF at a median of 7.5 d (5 to 13 d) after the inception of fever. Occasionally, ALF may in patients who seem to be recovering from dengue[59]. Dengue can mimic ALF and needs to be considered in differential diagnosis of acute liver failure and cerebral malaria in endemic areas[60]. Occasionally, dengue has been reported to cause ALF in patients with underlying liver disease including a HBV carrier[61].

After a period of 3-7 d incubation, the natural course runs in form of fever lasting for 2-7 d, and subsequently a critical phase may occur during defervescence starting from 3-7 d of the illness when plasma leakage dominates the clinical picture[59]. Those surviving this phase of plasma leakage would eventually recover[3,62]. More severe disease is associated with higher viral load[63].

ALF due to paracetamol (PCM) overdose may be due to either a single large overdose or cumulative, multiple overdoses. The latter has been increasingly being recognized as an important cause of ALF due to PCM overdose. Mild to moderate hepatitis is well known in dengue. However there have been ample evidences, obtained both *in vitro* and *in vivo*, that the metabolism of PCM is reduced in patients with hepatitis [64,65]. Moreover, WHO guidelines discourages the use of other nonsteroidal antiinflammatory drugs, such as ibuprofen or antipyretics, in DF[3].

Interestingly, dengue has also been implicated as the cause of worsening of chronic liver disease, *i.e.*, being the acute component of acute on chronic liver failure (ACLF)[61,66,67]. Therefore in endemic areas one should be aware of dengue as a possible cause of ACLF.

Dengue pathogenesis as outlined earlier is not fully understood and is multi factorial ranging from direct viral injury, dysregulated immune response to hypoxic/ischemic injury and even secondary to drugs such as PCM used commonly for such symptoms. Mortality data are comparable with other causes of ALF, although adults have been reported to have a slightly better prognosis as compared to children, in whom it is 50%-66%[68].

In the management of patients with dengue with ALF, besides supportive measures specific measures have also been tried with success. There have been reports of use of N-acetyl cysteine (NAC) in various case series; use of NAC by Senanayake *et al*[69] from Sri Lanka on seven children and Lim *et al*[70] from Singapore on a single child showed clinical improvement. Kumarasena *et al*[71] used NAC on 8 adult patients, 5 of which having grade I-II hepatic encephalopathy and recovered completely while the remaining 3 with higher grades of encephalopathy (grades Ⅲ and Ⅳ) died. Use of molecular adsorbent recirculating system (MARS) has also been[51] reported in dengue associated ALF. Liver transplantation becomes a difficult proposition in lieu of hemodynamic compromise, bleeding, and organ impairment seen during dengue infection.

CONCLUSION

Dengue has a wide spectrum of manifestations. The effects on liver are usually asymptomatic but can be atypical and have varied severity. From asymptomatic elevated transaminase levels to fulminant hepatic failure, the variable manifestations are a big challenge to the clinicians treating the condition. Hepatic involvement is more common and more severe in children as compared to adults. Management is primarily supportive and the outcome is usually good. Care must be taken regarding the diagnosis and use of drugs which may worsen the liver damage.

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MINIREVIEWS

Role of third molars in orthodontics

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Abstract

The role of third molars in the oral cavity has been extensively studied over the years. Literature includes numerous diagnostic and treatment alternatives regarding the third molars. However, an issue that has not been discussed at the same level is their involvement in orthodontic therapy. The aim of this study is to present a review of the contemporary literature regarding the most broadly discussed aspects of the multifactorial role of third molars in orthodontics and which are of general dental interest too.

Key words: Crowding; Extraction; Eruption; Third molar; Orthodontics; Impaction

Core tip: There are multiple factors associated with the eruption or impaction of third molars. According to the existing literature, orthodontic extraction treatment is not directly associated with the eruption of third molars, but might have a positive effect on their position and angulation. There is currently no reliable research evidence supporting the prophylactic removal of non-pathological impacted third molars for the prevention or relief of mandibular incisor crowding.

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INTRODUCTION

The development of third molars and their interaction with the rest of the dentition has been of great concern to general dentists and dental specialists for a long time. Third molar is a tooth characterized by variability in the time of its formation and calcification, its crown and root morphology, its course of eruption and final position, presence or absence in the oral cavity[1,2]. Third molars start appearing on radiographs as early as the age of 5 years and as late as the age of 16 years, usually erupting in the oral cavity between the ages of 18 and 24[3] and they present the highest rate of impaction[4,5].

Although, in the majority of cases, third molars are not directly involved in orthodontic treatment, the fact that, in some cases, they can influence the latter or be influenced it, dictates their direct involvement in treatment planning.

The main issues, concerning the third molars that are related to orthodontic treatment and have been most extensively reported throughout the literature are: the possibility of their eruption or impaction in relation to genetically predetermined factors, the possible repercussion of orthodontic treatment extractions in their position and their influence in orthodontic post-treatment mandibular incisor relapse. These are the topics that are going to be presented and discussed in the herein review.

For the purpose of this study, an extensive online search of PubMed database was conducted. The main focus of the investigation was on original research articles in English. No chronological or other limits were applied.

FACTORS INFLUENCING THE ERUPTION OR IMPACTION OF THIRD MOLARS

The possibility of eruption of third molars is of important consideration in treatment planning and in the long-term maintenance of the dentition and, therefore, of particular interest to dentists and orthodontists[6].

The presence or absence of third molars from the oral cavity has been related to genetically predetermined skeletal and/or dental factors. As early as 1936, Bowdler *et al*[7] suggested that the individual growth pattern is an important factor for the eruption of the third molar. Broadbent[8] believed that the inability of the mandible to achieve its full growth potential may be contributing to the impaction of third molar, whereas, according to Begg[9], the impaction of third molars is attributed to insufficient forward movement of the teeth of modern man due to the lack of interproximal attrition that was observed in ancient skulls.

Björk *et al*[10], in an early study, reported that in 90% of third molar impaction cases the retromolar area space was limited. A few years later, in a longitudinal cephalometric study[11] of 243 cases with the use of implants, he identified two skeletal and two dental factors that were linked with the impaction of mandibular third molars. These factors were: a vertical direction of condylar growth, a reduced mandibular length, a backward-directed eruption of the mandibular dentition and a retarded maturation of the third molars. However, in the same study, it is also stated that, depending on the case, these three factors "may either amplify or neutralize each other".

Ricketts *et al*[12], used longitudinal records in an attempt to predict the amount of mandibular growth and to estimate the amount of space for forward and upward development of the molars. He concluded in that, in order the third molar to have a 50% chance of erupting, 50% of the crown must lie ahead of the external ridge. In a previous study[13], he had also claimed that the direction of tooth eruption plays a critical role in the impaction of third molars.

Kaplan[14] also agreed that cases with impacted third molars exhibit a larger angle of mandibular growth compared with cases with erupted third molars. The distance from Xi cephalometric point to the distal surface of the second permanent molar, was used by Schulhof[15], in an attempt for a computerized prediction of third molar impaction. When this length decreased below 25 mm impaction became more likely and, conversely, less likely as the length increased towards 30 mm. However, this method of prediction presupposes impaction being solely related to available space.

Richardson[16], in a longitudinal study of a group of 95 subjects observed that skeletal Class Ⅱ cases, with a shorter in length, narrower in width and more acute angled mandible, were more prone in third molar impaction. There was also a reduced amount of mandibular growth in cases with impacted third molars, which also had a tendency, although non-significant, to be relatively larger in size. The developmental initial mesial angulation of third molars in relation to the mandibular plane was also increased in subjects with impacted third molars. Ades *et al*[17], after studying the data from cephalometric radiographs and study models from 97 patients, found no significant differences in mandibular growth between those who had impacted or fully erupted mandibular third molars.

Capelli[18], using a sample of 60 patients who had received orthodontic treatment, including the extraction of four premolars, stated that, according to his results, the impaction of third molars is associated with a vertical component of mandibular growth, high mesial inclination of the lower third molar crown in the ascending ramus and reduced mandibular length. Hattab[19], in a radiographic follow-up study of 36 students with an average age of 19.7 years, discovered that a significant proportion of mesially impacted mandibular third molars changed their angulation and became fully erupted by the time the individuals reached 24 years of age. Therefore, he concluded that the positional changes and the eruption of impacted mandibular third molars are two unpredictable phenomena.

Erdem *et al*[20] examined the data from lateral cephalograms, orthopantomograms, periapical radiographs and study models of 27 patients and came to the conclusion that impaction of lower third molar is an unpredictable event. However, they also stated as a conclusion that the chances of eruption for mandibular third molars are more increased in patients with a more vertical growth pattern in general and a vertical direction of condylar growth, with anterior rotation of the mandible. In addition, a greater mesial inclination of the impacted lower molars was also mentioned as a possibly contributing

factor in their occurrence of impaction.

Artun *et al*[21], in an attempt to identify risk factors for maxillary third molar impaction, examined the radiographs of 132 adolescent patients. According to the results of their analyses, the most predictive parameters of impaction were a mesial angulation and a distal angulation of more than 30 degrees of the maxillary third molars relative to the occlusal plane, a reduced retromolar space and a small mandibular plane/Sella-Nasion plane (MP/SN) angle. In a study published in the same year, Artun *et al*[22] retrospectively investigated the lateral cephalograms, panoramic and/or periapical radiographs and study models of 389 patients who had received orthodontic treatment with or without extractions. They concluded that mandibular third molars angulated more than 40 degrees mesially relative to the occlusal plane at the end of treatment may also be at increased risk of impaction.

Behbehani *et al*[23], in a retrospective radiographic study of 134 patients, concluded that increased mesial angulation of the third-molar buds and signs of pronounced forward mandibular growth rotation increase the risk of impaction. Eruption space and mandibular growth rotation were also indicated as the most predictive parameters of impaction. Breik *et al*[24], in the contrary, reported that subjects with horizontal facial growth pattern demonstrated two times lower incidence of third-molar impaction than subjects with vertical growth pattern. Legović *et al*[25], on the other hand, in the same year, had not found any significant differences between the position of lower third molars and type of facial growth.

Finally, Hassan[26], in a retrospective cephalometric study of 121 Saudi patients, concluded that third molar impaction is more likely to occur when the retromolar space is inadequate. The latter was attributed to different skeletal and dental features, including an increased width of the mandibular ramus and a backward rotation of the posterior teeth.

EFFECT OF PERMANENT TEETH EXTRACTIONS ON THIRD MOLARS

Orthodontic treatment, especially during the period of active growth, may significantly influence the development of the dentition. Third molars too, according to the existing literature, are affected by orthodontic therapy in various ways. One of them is the orthodontic extraction treatment, the effect of which on third molars has been broadly investigated. The teeth that are usually removed for orthodontic reasons are the premolars, the first and the second permanent molars, either bilaterally of unilaterally, depending on the individual treatment requirements.

When it comes to extraction therapy, Kaplan[14] was one of the first authors to suggest that premolar extractions increase the probability of third molar eruption. According to the same author, when eruption does not occur in extraction cases, an insignificant resorption of the anterior border of the ramus is probably responsible, which is associated with vertical growth type.

Williams *et al*[27], in a study examining the effect of different extraction sites on orthodontic incisor retraction in 260 cases of patients of the same age at (mean age 13 years), treated with the Begg technique, also investigated on the influence of extractions on third molar eruption. According to their results, the change in the rate of third molar eruption following premolar extractions was indifferent, in contrast with first molar extractions or a combination of first premolar and first molar extractions, which had a significantly positive impact.

Rindler[28], in his investigation, examined the data from the casts and lateral oblique radiographs of 78 patients between 10 and 15 years of age, with a Class II initial malocclusion and crowding in the lower arch. The patients were treated with different techniques and had both their second mandibular molars extracted at the same time with the initiation of root development of the third molars. In 21 cases no additional orthodontic treatment was involved and, in the rest of the cases, lower first molars were moved distally with the use of activators (9 cases) and fixed appliances (48 cases). As they reported in the summary of their study, the third molars successfully replaced the second molars in most cases (77%).

Haavikko *et al*[29], after the analysis of a set of 110 longitudinal orthopantomograms of patients with a mean age of 13.5 years at the start of treatment, 50 of which had had two lower premolar extractions, concluded that the possibility of lower third molar eruption increased only occasionally and that extraction treatment seamed to merely accelerate and not promote eruption. Gaumond[30] used a relatively smaller study group of 11 patients, with different types of malocclusion, which were treated with germectomy of their second molar buds, as soon as the germ of a respective third molar was visible on a radiograph. As he reported, 19 of the 22 third molars that were followed-up achieved "satisfactory of very satisfactory" positions with acceptable final angulations. Based on the outcomes of this study, the author's belief was that every case with mild or moderate mandibular crowding should be treated in this way, rather than with four premolar extractions.

Cavanaugh[31], in a clinical and radiographic evaluation of third molars after second molar extractions in 25 patients, all of which, except for 2, had had some kind of orthodontic treatment, suggested that third molars usually successfully erupt into the space provided by the removed second molars. Richardson[32] conducted a retrospective investigation

of the records (casts and sixty-degree cephalometric radiographs) of a group of 48 subjects that had had unilateral or bilateral mandibular first premolars extractions and of a control group with no mandibular extractions. She concluded that there was a significantly increased space for third molar eruption in the group of the extraction cases. She could still, though, not explain the fact that a number of third molars had become impacted in extraction cases.

Gooris *et al*[33] conducted a study using 95 sets of panoramic radiographs of patients, within an age range of 9 to 19 years, who had received orthodontic treatment involving second molar extractions and first molar distalization. Their measurements indicated that almost all erupted third molars presented with a mesial inclination. Staggers *et al*[34], in a retrospective study of panoramic radiographs from 78 orthodontically treated subjects, 33 of which had been treated with four premolar extractions, concluded that there was no relative considerable impact of the extractions on third molar angulation. All the patients used in the study had Class I skeletal and dental relationships, they were treated with straight-wire appliances and the age range was roughly 11-26 years for the extraction group and 11-17 for the non-extraction group.

Richardson *et al*[35] cooperated in a retrospective study regarding the evolution of third molars after second permanent molar extractions. In total, 63 sets of records (lateral cephalographs and study models) were selected, from patients that had bilateral or unilateral (8/63) second molar extractions. Twenty-three/sixty-three patients had acceptable initial occlusion and had not received additional orthodontic treatment. Based on the results of this study, the authors suggested that there was a tendency of mandibular third molars to autocorrect their bucco-lingual inclination subsequent to second molar extraction and that the earlier the developmental stage of a third molar is at the time of extraction the higher are the chances for their eruption.

Moffitt[36] evaluated a subgroup of 56 patients, 28 of which had unilateral maxillary second permanent molar extractions, clinically, radiographically and *via* their study models, regarding the effect of extractions in the third molar eruption and function. The results showed that after second molar extractions maxillary third molars erupted in most cases in acceptable positions and that their eruption was also accelerated in variable degrees. Orton-Gibbs *et al*[37] aimed to assess with their study the final position of third molars after the extraction of second molars, in a retrospective radiographic analysis of the records of 63 patients, with a mean age of 13 years and 3 mo and different initial types of malocclusion. According to the results of this study, both maxillary and mandibular third molars in most cases erupted in "good or acceptable" positions, based on "Richardson's score system"[35]. They also noted that the angulation of mandibular third molars improves further after the end of active treatment.

Elsey *et al*[3] conducted their own study with the objective to evaluate the influence of the extraction of mandibular premolars and subsequent orthodontic closure of the extraction spaces on the third molar development. A set of 30 consecutive patients' records with bilaterally impacted lower third molars and a history of lower premolar extraction treatment. A control group with lower premolar and third molar extractions was also used. Measurements were made on panoramic radiographs. Retrospective analysis of the collected data indicated a positive influence of lower premolar extraction on the position and inclination of impacted third molars.

Kim *et al*[38], in a retrospective study of the diagnostic records of 157 patients, 105 of which had four premolar extraction-treatment during their active growing stage of development, suggested that there was a clinically significant reduction in the impaction rate of both maxillary and mandibular third molars in these patients in comparison to the non-extraction group.

Janson *et al*[39], comparing the records of two groups of 55 patients in total, in their late adolescence, with and without maxillary premolar extractions, concluded that the number of erupted maxillary third molars was greater in the extraction group. He also claimed that the mesio-distal angulations of the un-erupted molars appeared relatively decreased and, therefore, more favorable to eruption.

De-la-Rosa-Gay *et al*[40] conducted a retrospective study based on data from panoramic radiographs, with the aim not only to assess third molar eruption after second molar extraction orthodontic treatment, but to identify the risk factors of unsuccessful eruptions too. Their sample included 48 patients, treated with fixed appliances (Ricketts or straight-wire techniques), with a median age of 14.8 years. The analysis of their results indicated that maxillary and most mandibular third molars successfully erupted and eventually obtained upright positions. Both late developmental stage of third molars and increased mesial inclination or lack of proximal contact in the beginning of treatment were identified as risk factors for an unsuccessful eruption.

Salehi *et al*[41], assessing the effect of first premolar extractions on third molar eruption, evaluated the clinical records of three groups of subjects: a group with first premolar extractions, a group with no extractions that had received orthodontic treatment and a control group with neither extractions nor orthodontic treatment. According to their results, there was a significant difference in the third molar eruption rates in the extraction (42%), non-extraction (12%) and control (20%) groups. These

findings indicate that first premolar extractions may increase the possibility of third molar eruption.

Jain *et al*[42], in a retrospective study that they conducted with the use of panoramic radiographs also investigated on the effect of first premolar extraction treatment. Their study sample consisted of 50 dental Class Ⅰ patients, between the ages of 11 and 19, half of which had received four first premolar extractions. In addition, no more than the 2/3 of the third molars had been formed in the initial radiographs and extraction spaces had been eliminated in the end of orthodontic treatment. The analysis of the collected data indicated a positive influence of first premolar extractions on the angulation of third molars.

Bayram *et al*[43] investigated the influence of orthodontic treatment involving four first molar extractions on the third molars. It was a retrospective study on panoramic radiographs from 41 patients, with a mean age of 16.6 years of age, 21 of which were treated with extraction of all four first permanent molars. No extraoral forces were used for the treatment of the above patients. According to their conclusions, first molar extractions may considerably increase the eruption space of third molars, whereas they normally have a more favorable effect on the angulation of the maxillary than of mandibular third molars. The main conclusion of this study was that the extraction of first permanent molars considerably reduces the frequency of third molar impactions.

Livas *et al*[44] used for their study lateral cephalometric radiographs from a group of 91 subjects, with a mean age of 13.2 years of age, treated with the orthodontic Begg technique and an initial Class Ⅱ Division 1 malocclusion. The subjects were divided in a group with first molar extractions and a control group with no extractions, which consisted of Class Ⅰ and Class Ⅱ cases. The findings of this study suggest that the position of third molars was significantly improved during orthodontic treatment involving the extraction of first molars.

Gohilot *et al*[45], almost two years ago, published an investigation regarding the impact of first premolar orthodontic extraction treatment on third molars. The study sample included 60 Indian patients, between 14-19 years of age, 30 of which had all first premolars extracted and the rest serving as a control non-extraction group. The root development of third molar roots did not exceed the 2/3 of its full length at the initial radiographs, all patients had been initially diagnosed with a skeletal and dental Class I malocclusion, which meant that they all had been high-anchorage cases during treatment and there were no extraction spaces in the end of treatment. Based on their results, they concluded that premolar extractions had a positive effect on maxillary third molar angulations, whereas they did not notice any difference in mandibular third molars' positions. They also suggest that borderline extraction cases with favorable third molar angulations could benefit by premolar extractions.

Türköz *et al*[46], comparing two groups of 22 non-growing patients, with and without first premolar extractions in a retrospective study, also revealed a positive influence of premolar extraction therapy in the size of retromolar space and a significantly lower impaction rate of third molars in the corresponding extraction group. Mihai *et al*[47] evaluated the panoramic radiographs of 20 initially Class I patients, who had received orthodontic treatment, with and without premolar extractions and the crowns of their third molars had already been formed in the beginning of treatment. The results of this study indicated the third molars with the most favorable positions, were the ones in the mandibles of the extraction group.

Al Kuwari *et al*[48] conducted a cross-sectional radiographic study, using 40 sets of patient records from a university clinic. Half of these patients were orthodontically treated with first premolar extractions. According to their results, orthodontic treatment premolars extraction treatment seems to have improved the angulation of impacted third molars in most cases. Finally, Halicioglu *et al*[49] recently published a large retrospective study of the panoramic radiographs of 294 patients, aged from 13 to 20 years, with at least one permanent first molar extraction. Among other conclusions, they report that the development of the third molars was significantly accelerated on the extraction sites of these patients.

THIRD MOLARS AND MANDIBULAR INCISOR CROWDING

The effect of third molar position and eruption stage on the rest of the dentition has also been the subject of many investigations and is also of great concern to the orthodontists. Especially the role of third molars in the development of a secondary mandibular incisor crowding has been an object of debate for many years.

As early as 1917 Dewey[50], examining the role of third molars in malocclusion, suggested that, in some cases, the mandibular third molars need to create space in the dental arch in order to erupt, causing crowding of the anterior teeth. Since then, numerous investigations have been conducted in an attempt to objectively identify a possible correlation between third molars and mandibular incisor crowding. Bergström *et al*[51] studied 60 subjects with unilateral molar agenesis and noted that there was greater crowding in the quadrants in where third molars were still present, than in those in which third molars they were absent. Vego[52] also found a greater percentage of dental crowding in subjects with erupting third molars in comparison to subjects with congenitally missing third molars.

Sheneman[53], in an investigation of 49 patients for a mean period of 66 mo, concluded that patients with congenitally missing third molars showed comparatively greater dental stability.

Woodside[54], on the other hand, suggested that in cases where mandibular third molars were not present, a more distal settling of the lower dentition occurred in response to growth and soft tissue pressure, implying a passive role for the third molar, which was acting as an obstacle to the settling of the dentition, rather than actively applying pressure to anteriorly positioned teeth.

Lindqvist *et al*[55], in their study, examined a group of 52 patients with bilateral third molar impactions. It was a "split mouth" design study, with extraction of the impacted molars on one side and use of the contralateral quadrant as a control side. Their data indicated the existence of less crowding on the extraction side, in 70% of the patients. Forsberg[56] conducted a study with the objective to identify the relationship between the eruption status of third molars and the relative space in the dental arches. Two groups of 75, in total, adult, non-orthodontic patients were used; one group with patients that had all third molars erupted and another group with all third molars missing due to extraction. The degree of crowding was found to be higher in the first group, although only with a small difference.

Southard *et al*[57] attempted to detect the presence of a mesial force exerted by the unerupted third molars on the rest of the dentition, by measuring and comparing proximal contact tightness before and after bilateral third molar extractions in 20 patients. The authors concluded that the removal of third molars for the relief of "interdental pressure" and, therefore, for the prevention of mandibular incisor crowding could not be supported by the results of their study. Pirttiniemi *et al*[58] examined the effect of impacted third molar extraction on the dental arches in patients with a mean age of 23.2 years. As it is stated in their conclusions, the results of this investigation could not justify the prophylactic removal of third molars, due to the absence of relative evidence regarding their association with undesirable changes in the dental arches.

van der Schoot *et al*[59] conducted an investigation with the aim to determine the relationship between dental crowding and the presence of third molars. Their sample included 99 orthodontically treated patients. According to their results the presence of third molars did not have a clinically significant relationship with the development of post-treatment crowding. Basdra *et al*[60], in an evaluation of 19 patients, who had been recalled in a university dental clinic and had had orthodontic Class Ⅱ treatment with bilateral or unilateral upper second molar extractions, reported that all third molars had erupted in very good positions.

Sidlauskas *et al*[61] investigated in their study the effect of lower third molars in lower incisor crowding, by studying the records (study models and panoramic radiographs) of 91 patients, who had not received orthodontic treatment before the collection of the records. The study group included patients with present, removed or genetically missing third molars. They concluded that the third molars in their study group were not responsible for any considerable difference in the development of lower anterior dental arch crowding. Hasegawa *et al*[62] studied a group of Mongolian subjects, with a mean age of 21 years, in order to evaluate the influence of third molars on lower anterior crowding. The analysis of their data did not reveal any significant relationship between the presence and angulation of mandibular third molars and lower incisor crowding.

Karasawa *et al*[63], in a cross sectional-study, aimed to reveal a correlation between the presence of third molars and mandibular incisor crowding in a large group of 300 subjects, with a mean age of 20.4 years. Their final results revealed no correlation between maxillary or mandibular third molars and the incisor crowding. Nevertheless, in patients that had had orthodontic treatment there was a small correlation, although this result did not reach statistical significance.

Costa *et al*[64] recently conducted a systematic review in order to investigate whether the prophylactic removal of third molars is justified as a treatment option. After filtering of the initial studies with the use of specific eligibility criteria, only 4 papers of medium (3) and low (1) quality and inadequate sample sizes eventually contributed in the analysis. As stated by the reviewers, the currently available data is inadequate for the formation of safe conclusions, which could be used in clinical treatment decisions. However, their results point towards the opinion that prophylactic third molar extraction is unjustifiable.

DISCUSSION

With regards to the possibility of third molar eruption, it seems that most investigators agree on the fact that there is a correlation between third molar impaction and certain skeletal characteristics[7-9,10,12-16,18,20-24,26], although not everyone shares the same opinion[17,19,25]. The common associated factor is the shortage of the available eruption space, due to distally directed eruption of the dentition and/or lack of adequate resorption of the anterior border of the mandibular ramus or compensatory periosteal bone apposition at the posterior outline of the maxillary tuberosity. Another factor that is linked with third molar impaction is the existence of a vertical facial growth pattern, with a vertical direction of condylar growth. Finally, increased third molar angulation is also considered to be significantly linked to third molar impactions.

Concerning the impact of extraction treatment,

the majority of investigators have reported a positive influence of the removal of teeth for orthodontic reasons on third molar position, angulation and/or eruption[3,14,27,28,30,31,33,35-48,60]. The improvement of the position and reduction of the inclination of third molars, although not directly associated with their eruption, seems to be considered as a very positive effect. Many authors also believe that orthodontic borderline extraction cases with favorable initial third molar angulations could benefit from extraction therapy[41,44,47]. In addition, even in the event of a possible future extraction of impacted third molars, a more upright position could facilitate the surgical procedure and minimize possible complications and post-operative complications[3,8,41].

However, it is important to note that there is a variety of confounding factors that could have affected the results of the above studies and were not co-evaluated in most cases, including the age of the patients, their ethnical background, the developmental stage of third molars at the time of the extractions, the initial types of malocclusion and the type of mechanics that were used for the needs of the orthodontic treatment.

Further, concerning the role of third molars in mandibular incisor crowding, it is very interesting to note the differences between the authors' beliefs and results before the after the 1990's. In the chronologically older studies[50-56] third molars seem to be more significantly associated with the occurrence of crowding in the lower arch. In contrast, more recent studies[57-59,61-64] tend to exculpate third molars and characterize their prophylactic extraction as unjustifiable. Nonetheless, both recently conducted systematic reviews on this matter, although clearly not in favor of prophylactic extractions, reported the insufficiency of high quality studies, required for the formation of secure conclusions.

The fact still is that, currently, there is no sound research evidence supporting the prophylactic removal of non-pathological impacted third molars. However, in cases where extraction is indicated, it is preferable third molars to be removed before adulthood in order to decrease the risk of complications[65].

Finally, other important clinical issues, including the impact of orthodontic first molar distalization on third molar position, the effect of third molar eruption stage on the efficiency of first molar distalization, the orthodontic force application on autotransplanted third molars, the orthodontic extraction of third molars in unfavorable positions or in close proximity to the inferior alveolar nerve and the decision of the extraction of third molars before orthognathic surgery, are also still under investigation and are, hopefully, going to be included in other reviews.

CONCLUSION

Despite the fact that the role of third molars has been a subject of research, clinical interest, discussion and dispute for so many years, there is still a lack of scientific evidence from high quality clinical studies on that matter. Several weaknesses have been pointed out, including the heterogeneity of data and the small size of the examined samples. However, the information collected from the studies presented in this review contributes to our knowledge and allows us to create a fuller picture regarding the issues that have been examined.

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Clinical outcomes for Conduits and Scaffolds in peripheral nerve repair

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Abstract

The gold standard of peripheral nerve repair is nerve autograft when tensionless repair is not possible. Use of nerve autograft has several shortcomings, however. These include limited availability of donor tissue, sacrifice of a functional nerve, and possible neuroma formation. In order to address these deficiencies, researchers have developed a variety of biomaterials available for repair of peripheral nerve gaps. We review the clinical studies published in the English literature detailing outcomes and reconstructive options. Regardless of the material used or the type of nerve repaired, outcomes are generally similar to nerve autograft in gaps less than 3 cm. New biomaterials currently under preclinical evaluation may provide improvements in outcomes.

Key words: Plastic surgery; Reconstructive surgical procedures; Nerve tissue; Conduit; Scaffold

Core tip: Nerve autograft is the gold standard for peripheral nerve reconstruction with gap. However, shortcomings of autograft have led researchers to investigate various biomaterials to improve outcomes. Clinical studies of peripheral nerve reconstruction with conduit other than autograft show similar outcomes in gaps less than 3 cm.

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INTRODUCTION

The gold standard of peripheral nerve repair is primary end-to-end coaptation of nerves. Unfortunately, this treatment is not always feasible in clinical situations. Avoidance of tension during repair is the ultimate goal to enhance potential nerve regeneration[1,2]. Prior studies have shown that injury tends to occur when nerves are stretched to greater than 10% of their original length. It may even initiate the process with stretching as little as 4%-6%[3,4]. Negative outcomes have been reported with tension greater than 25 g[5].

Most surgeons do not attempt primary closure when encountering gaps greater than 4 mm[6]. Tensionless closure is paramount to satisfactory clinical outcomes in nerve repair.

Primary treatment for repair of a nerve gap is autologous nerve grafting[7,8]. However, limited availability of donor tissue, sacrifice of a functional nerve, and possible neuroma formation make this option less than ideal[9-11]. Gluck[12] first reported use of a nerve guide in 1880, bridging with a segment of decalcified bone. Other early attempts were equally unsuccessful. In order to overcome these shortcomings, researchers and surgeons continued to improve nerve repair methods. The ideal conduit must be readily available, biocompatible, size matched to the nerve stumps, prevent axonal escape, and prevents ingress of fibroblasts and inflammatory cells. Simultaneously it should allow growth and chemotactic factors to positively influence axonal growth. Also it should prevent compression and injury to the nerve once healed. The conduit should be flexible, yet resilient enough to resist collapse[13]. Currently, such a conduit remains unavailable. Ongoing studies continue to improve the qualities of available biomaterials. Our goal is to present a survey of clinical studies published in the English literature detailing outcomes and reconstructive options.

REGENERATION BY CONDUIT

Williams *et al*[14] demonstrated the basic steps of nerve regeneration with an inert silicone conduit. In the immediate postoperative period, a fluid containing proteins, clotting factors and growth factors fills within the conduit. By 1 wk, a longitudinally oriented fibrin matrix develops. In the second week, fibroblasts, Schwann cells, macrophages, and endothelial cells enter the matrix. At the same time, axons from the proximal nerve cone extend forward. By four weeks the nerve cone has extended about 10 mm.

MATERIALS

Silicone

Silicone is a non-resorbable, nonporous, biologically inert material. Silicone in medical devices and implants are clinically ubiquitous. Since silicone is non-resorbable, presence of conduit material can lead to compression and decreased axonal conduction[15-17]. For this reason, the tubing is frequently removed[18]. With the advent of resorbable synthetic grafts and processed allografts, clinical utilization of silicone conduits have declined.

Lundborg *et al*[19] first reported in a prospective randomized study the clinical use of silicone tubes in peripheral nerve reconstruction. He reconstructed median nerve gaps of 3 to 5 mm. He then compared silicone conduit to standard repair. He found no differences in motor function. Patients experienced improved sensory recovery within the silicone group. Braga-Silva[20] reported a case series of 26 patients with median, ulnar, or median and ulnar nerve injury. Patients presented with a nerve gap ranging from 2.5 to 5.5 cm. While motor scores for each patient were not published, size of the nerve gap negatively correlated with motor function outcomes.

Expanded polytetrafluoroethylene

Expanded polytetrafluoroethylene (ePTFE) is another nonresorbable, biologically inert material. It is commercially available as Gore-Tex (W.L. Gore and Assoc., Flagstaff, AZ). Like silicone, reports of ePTFE have declined over the years.

Stanec *et al*[21] first reported clinical use of ePTFE in 43 patients exhibiting median and ulnar nerve gaps ranging from 1.5 to 6 cm. Patients with smaller gaps (up to 4 cm) had significantly improved outcomes *vs* larger gaps (78.6% *vs* 13.3% functional recovery).

Pogrel *et al*[22] utilized ePTFE conduits for reconstruction of lingual and inferior alveolar nerve (IAN) injuries in 5 patients. Patients with negative outcomes had nerve gaps greater than 1.0 cm. Pogrel *et al*[22] reported their series of 6 patients with lingual or IAN continuity defects greater than 1 cm. Mixed results were reported.

VEIN

Vein grafts are among the first non-neural biological conduits used for peripheral nerve Usually they are harvested from the dorsum of the hand during digital, median, or ulnar nerve repair. During the regeneration period, they were found to be at risk for kinking or collapse[23-25].

Wrede[26] recorded the first successful use of a vein graft. He repaired a median nerve defect with a 45 mm graft. Platt[27] (1919) also described bridging nerve grafts with autogenous vein. It failed to produce functional return of the musculospiral nerve[27]. Gibb[28] reported a single case of functional restoration using a vein conduit to reconstruct a 1 cm facial nerve gap. It was not until several animal studies demonstrated efficacy that further clinical studies were explored[29,30]. Walton *et al*[25] reported return to normal two point discrimination (2PD; less than 4 mm) in 50% of patients undergoing repair of digital nerves. Nerve gaps ranged from 1 to 3 cm. Poor outcomes were associated with larger gaps. In 1990, Chiu *et al*[24] reported a series of 15 repairs on patients receiving vein grafts for "nonessential" peripheral nerve gaps up to 3 cm. After an average follow-up of 27 mo, the cohort receiving vein graft repair had similar outcomes to autologous nerve graft. However it was inferior to direct repair cohort. Tang *et al*[23] reported 61% good or excellent outcomes in 15 patients undergoing digital nerve repair, with

gaps ranging 0.5 to 5.8 cm[23]. Patients generally had favorable outcomes when gaps were less than 3 cm, thereby corroborating the results from Chiu *et al*[29]. Two years later, Tang published outcomes in median and radial nerve vein grafts. In this study, he inserted nerve fragments from the proximal nerve stump into the vein lumen. His data suggested positive outcomes could be achieved with this technique for gaps up to 4.5 cm[31].

Pogrel *et al*[32] reported a series of 16 patients treated for lingual or IAN nerve defects, ranging from 2 to 14 mm. Using saphenous vein or facial vein, he found that negative outcomes were associated with gaps greater than 5 mm. The author discussed that nerves of trigeminal origin have had poorer outcomes versus other peripheral nerves. It is likely the cause of difficulty in repair of such small gaps (see below).

COLLAGEN

Collagen is a naturally occurring, resorbable structural protein. Purified bovine collagen, the most common source for collagen conduits, has low immunogenicity. Resorption rate can be controlled by the degree of crosslinking induced during preparation. Depending on fabrication method, degradation occurs from 1 to 48 mo[33,34]. Furthermore, preclinical studies have demonstrated that collagen conduits enhance growth and differentiation of many cell types. It is flexible yet durable. This increases its facility as a conduit material[35]. Finally, its permeability allows for diffusion of chemotactic and neurotrophic agents in the extracellular fluid. This type of conduit is commercially available under the name NeuraGen® (Integra LifeSciences, Plainsboro, NJ). Conduit sizes range from 1.5 to 7 mm diameter and are 2 or 3 cm long. Neuromatrix® and Neuroflex® (Collagen Matrix, Inc) are also Type I collagen conduits. No published studies are currently available evaluating its clinical efficacy.

In 2005, Taras *et al*[36] reported the use of commercially available type I bovine collagen in the repair of a variety of peripheral nerves[36]. A prospective series of 22 digital nerve repairs using NuraGen® achieved excellent or good sensory outcomes in 15 of 22 digits. They excluded nerve gaps greater than 20 mm[37].

Ashley *et al*[38] reported treatment of brachial plexus birth injuries with nerve gaps less than 2 cm using collagen conduits. Four of the five patients had favorable outcomes at 2 years postoperative. Lohmeyer *et al*[39] reported a case series of 6 patients undergoing repair of nerve gaps in digital and palmar nerves up to 18 mm. Two-thirds of the patients had excellent 2PD at 12 mo postoperative. They extended follow-up with nine of twelve patients achieving excellent or good sensory scores at 12 mo follow up[40]. Bushnell *et al*[41] reported a series of 12 patients undergoing digital nerve repair for gaps ranging from 1 to 2 cm. Most (88%) had good or excellent 2PD after at least 1 year. In a larger study of 126 nerve injuries in 96 patients, Wangensteen *et al*[42] reported their experience using NeuraGen®. Mean nerve gap was 12.8 (range 2.5 to 20 mm). Overall, nerve function recovery was only 43%. A variety of nerves were repaired, and seven surgeons were involved in the study. Haug *et al*[43] added 45 digital nerve repairs with type Ⅰ collagen to the body of literature. Mean defect was 12 mm (range 5 to 26 mm). All sensory measures improved over 3-, 6-, and 12-mo follow-up interval.

Farole *et al*[44] reported their experience with the NeuraGen® conduit for challenging lingual and IAN repair. In their study, all patients underwent neurolysis with or without resection of neuroma (if present) and placement of the collagen conduit as a "cuff" over coapted nerve ends. They chose this technique to prevent axonal escape, minimize scar ingrowth and nerve entrapment, and to concentrate growth factors at the repair site. Eight of nine patients had improvement after at least one year.

Kuffler *et al*[45] reported a single case of ulnar nerve reconstruction after 3 years. Nerve gap was 12 cm. Using a sheet of collagen, they fashioned a custom-sized conduit. Then they filled it with autologous platelet-rich fibrin. By three months, the patient experienced improvement in neuropathic pain. By 2 years the patient no longer required analgesics. Within 1.5 years, the patient had 4 mm 2PD. Motor function had returned by 2 years. This study showed promising results in the reconstruction of large caliber, mixed function peripheral nerves using collagen conduits. Dienstknecht *et al*[46] recently published a series of 9 patients undergoing median nerve repair. All gaps were 1 to 2 cm long and repaired within 24 h of injury. Average return to work was 8 wk (range 1 to 17). Motor, sensory, pain, and disability scores were satisfactory in 8 of the 9 enrolled patients.

DECELLULARIZED NERVE ALLOGRAFT

Nerve allograft is an alternative to nerve autograft for repair of gaps, but requires the additional administration of immunosuppression for 18 mo. Using a decellularized nerve allograft preserves the three-dimensional collagen scaffolding of a nerve while avoiding immunosuppression[47]. This scaffolding promotes cell migration, nerve fiber elongation, and diffusion of growth factors[48,49]. Laminin, also present, facilitates axonal outgrowth[50]. Human decelullarized nerve is commercially available as Avance® (AxoGen, Inc, Alachua, FL). Available grafts encompass lengths ranging 15 to 70 mm and diameters between 1 and 5 mm.

Karabekmez *et al*[51] were the first to publish clinical data on Avance®. Ten digital nerve repairs were included in the study. Gap length ranged from 0.5 to 3 cm. After an average follow-up of

nearly 9 mo, static 2PD was 5.50 mm and moving 2PD was 4.4 mm. Brooks *et al*[52] then reported a multicenter prospective study with Avance®. These authors examined repair of sensory, motor, and mixed nerves. Of the patients that met follow-up requirements, acceptable outcomes were achieved in every group. Sensory, mixed, and motor nerves recovered at 88.6%, 77%, and 85.7%, respectively. With regards to nerve gap length, short (5 to 14 mm) recovered at 100%, medium (15 to 29 mm) recovered at 76.2%, and long (30 to 50 mm) recovered at 90.9% (mean follow up 265-279 d). Meaningful recovery was defined as S3-4 or M3-5 on the Medical Research Council Classification. Guo *et al*[53] supplemented previous digital nerve repair data with their own case series. Their five patients had a mean nerve gap of 22.8 mm and a mean follow up of 13.2 mo. At the time of final follow up, static 2PD averaged 6 mm and monofilament test ranged positive for monofilaments 4.31 to 4.56. Recently, Taras *et al*[54] reported 18 digital nerve gap repairs treated with processed allograft[54]. Average gap length was 11 mm (range 5 to 30 mm). Overall, 83% of patients had good or excellent results.

Shanti *et al*[55] reported a single case using Avance® for repair of an iatrogenic IAN injury. They did not record the length of the nerve gap. However, they did report improvements in sensory testing at 5 mo postoperative.

POLYGLYCOLIC ACID

Polyglycolic acid (PGA) is a bioabsorbable substance initially used for suture material or mesh[56,57]. Mean resorption time is 90 d[58]. Typically it appears as a tight-weave mesh rolled tube. Its pores are small enough to permit nutrients while impeding invasion by fibroblasts[59]. A tube of PGA is more expensive than suture material used in standard nerve repair[59]. Additionally, PGA is at risk for extrusion prior to complete resorption[59]. PGA is commercially available as Neurotube® (Synovis Life Technologies, Inc.), which has an internal diameter of 2.3, 4, or 8 mm and 2 or 4 cm length.

Initial clinical use of PGA was by Mackinnon *et al*[60] in 1990. Repairing nerve gaps ranging from 0.5 to 3.0 cm, they were able to achieve excellent or good 2PD in 86% of the 15 patients undergoing reconstruction. Weber *et al*[59] (2000) reported his randomized prospective study of 136 nerve injuries treated with either autologous graft or PGA conduit. Although the mean gap length was greater in the PGA conduit group, there was no difference in either moving or static 2PD between the two groups. For either small (less than 4 mm) or large (greater than 8 mm) gaps, the PGA conduit group had better sensory outcomes. Kim *et al*[61] reported successful treatment of a plantar neuroma in an 11-year-old male using a PGA conduit to span a 2.0 cm defect. Pain from the neuroma resolved. Normal sensation returned by 8 mo. In 2005, Navissano *et al*[62] reported their case series of seven patients treated with PGA conduits for traumatic facial nerve terminal branch injuries. Five of seven patients had good or excellent recovery of motor function compared to contralateral side. Nerve gap ranged from 1 to 3 cm.

Battiston *et al*[63] prospectively compared Neurotube® repair of digital nerves to patients treated with vein-muscle grafts. Even though nerve gaps were larger in the Neurotube® group, there were no significant differences in sensory outcomes between the two cohorts. Most (76.9%) of the muscle-vein group had very good results, as did 76.5% of the Neurotube group. Rinker *et al*[64] performed a similar study. They prospectively compared Neurotube repair ® to vein graft repair. PGA conduit group was similar to the vein conduit cohort, including length of nerve gap (9.1 mm mean *vs* 10.3 mm, respectively). There was no significant difference between the cohorts with regards to sensory outcomes. This was true for short (less than 10 mm) or long (greater than 10 mm) gaps.

Rosson *et al*[65] reported 6 cases of PGA used to repair motor nerves. One patient had accessory nerve injury. The remainder had median or ulnar nerve injuries. Nerve gaps ranged from 1.5 to 4 cm (mean 2.8). Follow up ranged from 4 mo to 5.5 years. All patients achieved significant improvement in motor function (rated M3 or greater).

PGA-COLLAGEN

PGA-collagen conduits are composed of a PGA tube coated with 1% amorphous collagen solution. It is then filled with collagen sponge[66]. Fibers usually undergo crosslinking to prevent rapid resorption. To date, this construct is not yet commercially available. Japan was the site of clinical studies of PGA-collagen[67]. Initially it was initially used for reconstruction of intrapelvic nerves damaged during rectal cancer extirpation. Clinical improvement in the patient prompted continued use of the conduit.

In 2004, Nakamura *et al*[67] reported 2 cases using PGA-collagen conduits. The first patient had a 20 mm digital nerve gap. Following treatment, function within normal range by 4 mo. The second patient had a 65 mm superficial peroneal nerve defect with normal sensation by 3 mo. The same group later reported their experience with treatment of Complex Regional Pain Syndrome type Ⅱ[68]. In the two case reports, they described successful resolution of an otherwise challenging clinical entity. It tends to follow a vicious cycle of relapsing pain due to nerve sprouting after injury or resection. The authors theorized that placing the cut ends into the conduit would prevent nerve sprouting and guide the nerve cone to the distal stump. In 2007, Inada *et al*[69] also reported their experience with repair of a frontal branch of the

facial nerve using the same type of conduit, bridging gaps measuring 11 to 30 mm[69]. In both patients, functional recovery was noted by 5 mo. Recently, they also reported chorda tympani nerve reconstruction using their PGA-collagen construct[70]. Average nerve gap was 7 mm among the three patients studied. Electrogustometry measurements returned to normal limits by two weeks postoperative. Dysgeusia resolved between 2 wk to 3 mo.

POLY (DL-LACTIDE-ε-CAPROLACTONE)

Poly (DL-Lactide-ε-Caprolactone) (PLC) is another synthetic bioabsorbable material. Degradation occurs at 1 year. Initial constructs had thicker walls that caused swelling. This negatively impacted nerve healing. Thinner-walled tubes tended to collapse[71]. Increasing the lactide content to 65% reduced the amount of swelling, but lost mechanical strength after 10 wk of implantation[72]. Clinically available PLC may be too rigid for small needles, requiring some softening in water before use[71]. PLC is also transparent, facilitating placement of nerve stumps. It is commercially available by the name of Neurolac® (Polyganics BV, Groningen, Netherlands). They offer 1.5 to 10 mm inner diameters and a length of 3 cm.

After publishing initial clinical studies in 2003, Bertleff *et al*[73] published their follow up findings from a blinded, randomized multicenter trial comparing standard treatment to PLC in repair of peripheral nerve defects of the hand in 54 patients. In treatment of nerve gaps less than 20 mm, they found no significant difference in sensory outcomes compared to controls. Follow up was 12 mo.

FUTURE DIRECTIONS

In addition to the above clinically-tested materials, there is a multitude of materials undergoing preclinical evaluation. These include non-mammalian biodegradable polymers, artificial biodegradable polymers manufactured with electrospinning, conducting polymers, and combinations of the above with Schwann-like neural stem cells and mesenchymal stem cells. Conduits seeded with stem cells, stem-like cells, or support cells theoretically improve nerve regeneration through delivery of growth factors and neurotropic factors into the conduit lumen. Several excellent reviews documenting these advances have been published. They are beyond the scope of the current discussion[74-80].

CONCLUSION

While preclinical studies are essential to bringing new technologies to reconstructive surgeons, further in depth clinical evaluation of materials is warranted. Almost all of the published studies consist of small case series. Outcomes measures are inconsistent from study to study. Furthermore, nerve type, cause of injury, and gap size are extremely variable, making comparison of repair materials and technique difficult. Nevertheless, the above studies suggest that small gaps up to 3 cm can be repaired with available conduits with outcomes similar to nerve autograft. Efficacy of bridging longer gaps with available conduits has yet to be demonstrated. Also, several roadblocks prevent developing technologies from becoming clinically available. Feasibility of stem cell harvest and cost of cutting-edge biomaterials are problematic. These will further delay human studies for these promising therapies.

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MINIREVIEWS

Role of coronary physiology in the contemporary management of coronary artery disease

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Abstract

Coronary artery disease (CAD) remains the leading cause of death worldwide with approximately 1 in 30 patients with stable CAD experiencing death or acute myocardial infarction each year. The presence and extent of resultant myocardial ischaemia has been shown to confer an increased risk of adverse outcomes. Whilst, optimal medical therapy (OMT) forms the cornerstone of the management of patients with stable CAD, a significant number of patients present with ischaemia refractory to OMT. Historically coronary angiography alone has been used to determine coronary lesion severity in both stable and acute settings. It is increasingly clear that this approach fails to accurately identify the haemodynamic significance of lesions; especially those that are visually "intermediate" in severity. Revascularisation based upon angiographic appearances alone may not reduce coronary events above OMT. Technological advances have enabled the measurement of physiological indices including the fractional flow reserve, the index of microcirculatory resistance and the coronary flow reserve. The integration of these parameters into the routine management of patients presenting to the cardiac catheterization laboratory with CAD represents a critical adjunctive tool in the optimal management of these patients by identifying patients that would most benefit from revascularisation and importantly also highlighting patients that would not gain benefit and therefore reducing the likelihood of adverse outcomes associated with coronary revascularisation. Furthermore, these techniques are applicable to a broad range of patients including those with left main stem disease, proximal coronary disease, diabetes mellitus, previous percutaneous coronary intervention and with previous coronary artery bypass grafting. This review will discuss current concepts relevant to coronary physiology assessment, its role in the management of both stable and acute patients and future applications.

Key words: Ischaemia; Coronary physiology; Coronary flow reserve; Fractional flow reserve; Coronary artery disease

Core tip: Coronary artery disease remains the leading cause of death worldwide. There is increasing evidence to suggest that the use of invasive coronary angiography alone may not reliably identify all lesions associated with haemodynamic compromise. Technological advances have enabled the measurement of a number of coronary physiological indices which when incorporated into routine practice are associated with improved outcomes, reduced risks and greater economy. This review will

discuss current concepts relevant to coronary physiology assessment, its role in the management of both stable and acute patients and future applications.

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INTRODUCTION

Coronary artery disease (CAD) is the leading cause of death worldwide[1] with approximately 1 in 30 patients with stable CAD experiencing acute myocardial infarction (AMI) or cardiovascular death each year[2]. The presence of resultant myocardial ischaemia and its extent has been shown to confer increased risk of adverse outcomes[3-6]. With an increasing burden of atherosclerotic coronary disease and the associated high event rate, there is a need to identify both patients at highest risk with most to benefit from revascularisation strategies and also those that would be best managed by a conservative approach to improve clinical outcomes and minimise exposure to procedural risks.

Prevention by risk factor control and optimal medical therapy (OMT) including aspirin[7], beta-blockers[8], statins[9] and angiotensin converting enzyme inhibitors forms the cornerstone of the management of patients with stable CAD[10,11]. However, a significant number of patients present with myocardial ischaemia refractory to OMT and subsequently undergo coronary revascularisation by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) with the aim of reducing ischaemic burden and therefore risk[12].

Historically, visual assessment of coronary lesions by invasive coronary angiography in isolation has been used to determine the severity of coronary lesions in both stable and acute settings. It is increasingly clear that this approach fails to accurately and consistently identify the haemodynamic significance of lesions, especially those that are "intermediate" in severity[13] and that revascularisation based upon angiographic appearances may not reduce coronary events above OMT alone[14]. Recent advances in technology and understanding of coronary physiology have resulted in its central role in the assessment of patients in the catheterization laboratory and their optimal management[15,16]. This review will discuss current concepts relevant to coronary physiology assessment, its role in the management of patients and possible future applications.

CORONARY PHYSIOLOGY

Technological advances have enabled the measurement of a number of physiological indices including the fractional flow reserve (FFR), the index of microcirculatory resistance (IMR) and the coronary flow reserve (CFR). The advantages and disadvantages of each of the coronary physiology indices is summarised in Table 1.

FFR

FFR is the ratio of myocardial blood flow in a stenosed coronary artery at maximal hyperaemia in comparison to normal (proximal) myocardial flow. It quantifies the pressure drop measured across a coronary artery stenosis[17] and therefore the physiological significance of the lesion. The pressure drop is directly proportional to stenosis length, inversely proportional to lumen cross-sectional area and related to the square of the blood velocity. FFR is thus related to both lesion morphology and the volume of viable subtended myocardium and is independent of changes in haemodynamic conditions[18].

CFR

CFR is the ratio of hyperaemic to resting coronary flow and incorporates both the epicardial and microvascular circulations[19]. A value of < 2.0 is correlated with stenosis severity[20].

IMR

IMR is a measure of true microcirculatory resistance and is calculated by measuring the distal arterial pressure at hyperaemia divided by the inverse of the transit time. The IMR is not influenced by the presence or absence of epicardial artery stenosis[21]. There is no absolute validated "normal" value but a cut-off value of 32 units has been shown to be predictive of myocardial recovery following AMI[22].

Technique

To measure the FFR, a wire with a distal pressure sensor is advanced into a guiding coronary artery catheter, the pressure is equalised, and then passed distal to the coronary stenosis of interest (Figure 1A). The aortic pressure (Pa) is measured from the guide catheter and the distal pressure (Pd) from the pressure sensor distal to the stenosis (Figure 1B). To calculate the FFR, hyperaemia is achieved by the administration of intravenous (140 mcg/kg per minute) or intracoronary (20-50 mcg) adenosine and is the ratio of hyperaemia Pd/Pa (Figure 1C). Other hyperaemic stimuli can be used but adenosine is the most widely validated.

In the measurement of IMR and CFR, the shaft of the pressure wire is used to detect changed in the temperature-dependent electrical resistance and thus acts as a proximal thermistor. The sensor at the end of the wire is used to simultaneously measure pressure and temperature at the distal end of the artery. Therefore, the transit time of room-temperature saline injected through the guiding

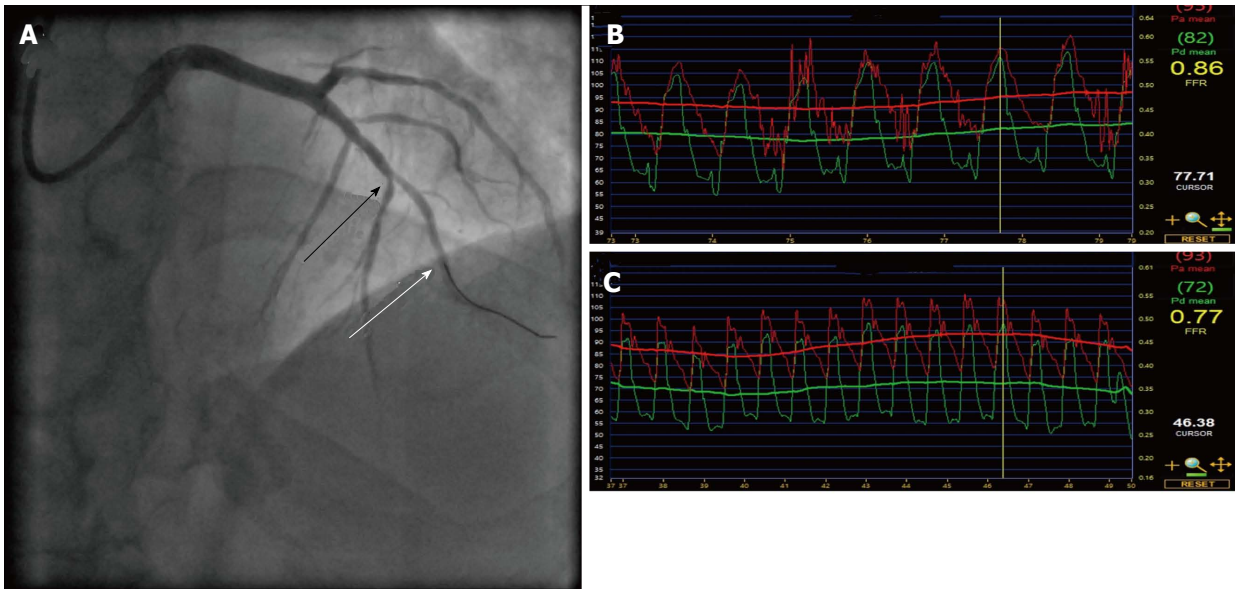

Figure 1 Fractional flow reserve of an "intermediate" lesion in the left anterior descending artery. A: Fluoroscopic image obtained in the right anterior oblique projection demonstrating an angiographically intermediate stenosis (black arrow) and a pressure wire in-situ (white arrow); B: Pressure trace demonstrating a fractional flow reserve (FFR) of 0.86; C: Pressure trace demonstrating a FFR of 0.77 at maximal hyperaemia that is positive. The patient then proceeded to successful percutaneous coronary intervention of the LAD.

coronary artery catheter can be calculated using a thermodilution technique[23]. The initial transit time is recorded (T_{mn}) following three injections of room-temperature saline. Following hyperaemia, three further injections of room-temperature saline are administered and hyperaemia T_{mn} is measured. The thermodilution CFR is calculated by dividing the resting T_{mn} by the hyperaemic T_{mn}. The IMR is calculated as the distal coronary pressure (Pd) at maximal hyperaemia divided by the inverse of the hyperaemic T_{mn}.

MYOCARDIAL ISCHAEMIA

Many studies have demonstrated that the presence and extent of myocardial ischaemia is closely related to adverse clinical events[5,6,24] with the annual rate of cardiac death and AMI positively correlated with the extent of myocardial ischaemia[24]. Coronary revascularisation has been demonstrated to be beneficial in individuals with moderate and severe ischaemia, with OMT being optimal in patients with mild or no ischaemia[25,26]. In patients with demonstrated extensive ischaemia (> 20% myocardium), an early revascularisation strategy (as opposed to OMT alone) is associated with a 30% reduction in risk of all-cause death[25].

The identification of the presence and extent of myocardial ischaemia in patients presenting with stable CAD is critical to their optimal management. Myocardial perfusion imaging is the most commonly used modality however stress echocardiography and magnetic resonance imaging are increasingly being employed.

There is some evidence that an ischaemia-guided revascularisation strategy is associated with improved prognosis and outcome[27,28]. In patients that underwent myocardial perfusion imaging prior to revascularisation (PCI or CABG) and then in the follow up period, the incidence of patients with worsening ischaemia (> 5% of total myocardium) was more common in patients treated medically in comparison to patients who underwent revascularisation (PCI or CABG) and was an independent predictor of adverse outcomes[29].

CORONARY PHYSIOLOGY AND STABLE CORONARY ARTERY DISEASE

PCI reduces mortality in patients with acute coronary syndromes[30], however, in patients presenting with stable CAD, PCI results in an improvement of angina symptoms alone without a mortality advantage in comparison to OMT alone[14]. These results may be a consequence of sub-optimal patient selection due to the sole reliance of visual assessment of coronary lesion by invasive coronary angiography to determine the severity of disease with no information as to the haemodynamic significance of these lesions[31,32]. This can result in inappropriate coronary revascularisation with little benefit and potential procedural risk.

The severity of a lesion (and resultant extent of myocardial ischaemia) is dependant on a number of factors including the severity of luminal narrowing, lesion length and extent of subtended myocardium. As discussed in the previous section, whilst non-invasive techniques can be employed to ascertain

Table 1 Advantages and disadvantages of the different coronary physiology indices

	Advantages	Disadvantages
FFR	Clear "cut-off" value	Requires administration of vasodilator
	Clinically validated	Risk of coronary artery injury
	Can be used in a wide range of patients	Relatively expensive
	Accounts for collateral circulation	
IMR	True measure of microcirculatory resistance independent of epicardial coronary disease	Requires administration of vasodilator
		The full extent of clinical utility is currently unknown
	A tool to potentially predict prognosis in acute patients	
CFR	A tool to potentially predict prognosis in acute patients	Value is affected by both epicardial disease and microvasculature
		The full extent of clinical utility is currently unknown
		Influenced by hemodynamics

FFR: Fractional flow reserve; IMR: Index of microcirculatory resistance; CFR: Coronary flow reserve.

the extent of myocardial ischaemia, many patients present to the cardiac catheterization laboratory without having undergone such assessment and indeed, in the setting of multi-vessel disease, non-invasive stress tests are often not able to definitively detect and localise ischaemia[33]. Furthermore, if a non-invasive image approach is taken, a positive test will result in repeat catheterization for PCI - thus further subjecting a patient to procedural complications, delaying revascularisation and being less economical. The use of coronary physiology provides the unique ability to gain immediate information with regards to the haemodynamic significance of specific coronary lesions in patients already in the cardiac catheterization laboratory attending for coronary angiography and identify those at highest risk who are most likely to benefit from PCI.

In stable CAD, CFR decreases as stenosis severity increases. When compared to non-invasive parameters a value of < 2.0 has been shown to correlate with significant ischaemia[20]. However, because CFR takes account of both epicardial and microvascular circulations, this measure can be influenced by exogenous factors[19] and therefore due to confounding factors is no longer used for stenosis assessment[34].

In the setting of stable CAD, the IMR has recently been shown to be independent of the severity of epicardial stenosis when collateral coronary flow is accounted for[35]. IMR may however, play a role in predicting outcome following elective PCI, with a high IMR pre-PCI predicting peri-procedural myocardial infarction following PCI[36].

FFR is a highly reproducible technique and is insensitive to external factors such as changes in haemodynamics[18]. The normal FFR is 1 with a value of $\leqslant$ 0.75 associated with ischaemia[37] and $\geqslant$ 0.8 not associated with significant ischaemia[38]. There is therefore a "grey zone" of between 0.75-0.8, however the majority of clinical studies to date have adopted a lower normal value of 0.8[12] to define significant ischaemia.

As opposed to relying solely on angiographic appearances, a FFR guided strategy has been shown to identify patients who would most benefit from coronary revascularisation. In the DEFER (deferral versus performance of PCI of non-ischaemia-producing stenoses) study[39], in patients with single-vessel coronary disease and a measured FFR $\geqslant$ 0.75, deferral of PCI was associated with similar event free survival in both OMT and PCI groups at five years[40].

In patients presenting with multi-vessel coronary disease, the clinical utility of myocardial perfusion imaging has been doubted. The technique measures relative differences (normal *vs* abnormal) in myocardial perfusion between coronary artery territories. Thus, in multi-territory ischaemia, the relative differences may be less pronounced resulting in "balanced ischaemia" even in the presence of significant ischaemia as determined by FFR. The FAME study[12] (FFR *vs* angiography for multi-vessel evaluation trial) which investigated patients with multi-vessel coronary disease, supported an FFR-guided strategy in comparison to angiography alone with an associated reduction in mortality or MI at 2 years[15]. This benefit was also found to be true when compared to contemporary OMT in the more recent FAME Ⅱ study[16] that indicated that an FFR-guided strategy resulted in a lower rate of urgent revascularisation.

FFR has been shown to be reproducible both in singe and multi-vessel coronary disease. However in certain instances, caution should be taken in interpreting coronary physiology parameters.

Left main stem disease

In patients presenting with left main stem disease, FFR has been shown to be useful in managing revascularisation strategies[41]. This is also true of left main stem disease and concomitant downstream stenosis if the pressure wire is placed in a non-stenosed downstream vessel and the other vessel does not have a critical proximal stenosis[42].

Post PCI

FFR following PCI has been shown to predict

outcome. Post PCI FFR was found to be the strongest predictor of major adverse cardiovascular events at 6 mo[43]. FFR has also been utilised following bifurcation stenting, illustrating that even in the presence of appearances in keeping with severe pinching of side branches, FFR was rarely $\leqslant$ 0.75 and therefore of no haemodynamic significance[44].

Myocardial scar

Following AMI, irreversibly injured myocardium is replaced by scar tissue that results in a reduction in the microcirculation to this territory. FFR in this context can therefore still be used to guide future management strategies, with the value representing viability of the subtended myocardium, but after an appropriate interval to allow for myocardial healing following AMI to ensure adequate hyperaemia[45].

Grafts

FFR can also safely be used in patients with previous CABG. In an observational study, patients with intermediate stenoses in both arterial and vein graft conduits that were managed by adopting a FFR-guided PCI strategy suffered significantly lower major adverse clinical endpoints as compared to an angiography guided group[46].

Diabetes mellitus

FFR depends upon the vasodilatative capacity of the coronary system and therefore achieving maximal hyperaemia. Patients with diabetes mellitus, suffer abnormalities in microvascular function with altered vasodilatative capacity and increased vascular resistance. Whilst caution should be taken in when using FFR in this patient group[47], a recent study comparing FFR in diabetic and non-diabetic patients has shown that FFR appears to be accurate and applicable in this patient group[48].

These studies highlight the critical role played by coronary physiology in identifying haemodynamically significant coronary stenoses that may benefit from revascularisation, and allow targeted vessel specific treatment beyond the angiographic appearances. The concept of the functional as opposed to the anatomical SYNTAX score appears to stratify patients appropriately to CABG or PCI or patients that would be best managed by OMT. FFR is broadly applicable to all patient groups and is associated with improved outcomes.

CORONARY PHYSIOLOGY AND ACUTE CORONARY SYNDROMES

In the setting of AMI, myocardial inflammation resulting in oedema can result in blunting of the hyperaemic response in the microcirculation resulting in falsely high FFR values, however coronary physiology parameters can potentially still be useful in guiding the management of this patient group.

The IMR when measured in the setting of primary PCI has been shown to correlate with the extent of microvascular obstruction and independently predicted left ventricular systolic function and infarct volume[22,49] and thus provides important prognostic information in this patient group. The clinical utility of this approach, however, is presently unknown.

The thermodilution CFR when measured in the first day after primary PCI also offers important prognostic information with a significant decrease in CFR in patients with impaired left ventricular systolic function. Conversely a greater increase in CFR by day 1 was associated with a higher salvage index[50].

A significant number of patients presenting with acute coronary syndromes also have visually severe "non-culprit" epicardial artery lesions. FFR of "non-culprit" lesions has been shown to be reliable[51] and has been used to guide revascularisation of these lesions. A large prospective multicentre randomised trial is currently underway to investigate the utility of this approach further[52].

LIMITATIONS

The adjunctive beneficial role that coronary physiology plays in the management of CAD has been discussed thus far. There are however, some limitations. The possibility of false negative or false positive results does exist, for example if maximal hyperaemia is not achieved or if instrumentation of the coronary artery induces coronary artery spasm. There is a risk of coronary artery injury (perforation or dissection) with instrumention of the artery to obtain measurements. Finally, there is an additional economic cost when adopting coronary physiology into routine clinical practice with the cost of pressure wires, cost of adenosine, and extra cardiac catheterization laboratory time required. These have all currently limited widespread uptake of these techniques.

FUTURE DIRECTIONS

A current limitation to invasive coronary physiology techniques is the need to induce maximal hyperaemia with agents such as adenosine. Patients may have contraindications to this agent, and additionally there is a time and cost implication. More recently an adenosine independent index of stenosis severity - the instantaneous wave-free ratio (iFR) has been developed[53]. The accuracy of this ratio in comparison to FFR has been shown to be approximately 80%[54] and outcome data from the on-going DEFINE-FLAIR (functional lesion assessment of intermediate stenosis to guide revascularisation) study[55] are awaited to ascertain if this index can be used routinely in clinical practice.

In the future, there may be non-invasive anatomical

and functional imaging surrogates for FFR. Current anatomical imaging modalities [*e.g.*, computed tomography (CT)] correlate poorly with lesion haemodynamic significance and do not capture information related to translesional energy/pressure losses[56]. Newer techniques including CT myocardial perfusion[57], the measurement of contrast gradients in conventional CT angiography[58] and the use of three-dimensional luminal anatomy are currently being evaluated to investigate if they correlate with FFR values for the evaluation of coronary stenoses[59]. Current technologies however have not been shown to equal the sensitivity and specificity of FFR[60].

DISCUSSION

The integration of invasive coronary physiology measurements into the routine management of patients presenting to the cardiac catheterization laboratory with CAD represents a critical adjunctive tool in the optimal management of these patients. The use of FFR can identify patients that would most benefit from revascularisation either by PCI or CABG and importantly also highlights patients that would not gain benefit and therefore reducing the likelihood of adverse outcomes associated with coronary revascularisation. In the setting of acute coronary syndromes, the use of IMR and CFR provides important information with regard to outcome and myocardial salvage, although the clinical value of these measures remains uncertain. The interpretation of the described coronary physiology indices is now essential in current interventional cardiology practice and is represented by current training medical curricula in this sub-specialty field.

The use of newer techniques to derive FFR– both invasively that do not depend on the administration of agents to induce hyperaemia and non-invasive functional imaging may result in coronary physiology parameters playing an even more central role in the future.

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MINIREVIEWS

Review on microbiota and effectiveness of probiotics use in older

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Abstract

The aim of the present systematic review is to summarize the existing knowledge about the human microbiota in the elderly and the effects of probiotics in elderly population. The elderly subjects, compared to adult population, show a reduction in the diversity of the microbiota, characterized by a large interindividual variability, with lower numbers of *Firmicutes*, *Bifidobacteria*, *Clostridium cluster* XIV, *Faecalibacterium Prausnitzii*, *Blautia coccoides-Eubacterium rectal* and higher presence of *Enterobacteriaceae* and *Bacteroidetes*. These differences of the intestinal microbiota of the elderly may not necessarily be caused by aging, but they could be associated with the decline of the general state of health with malnutrition and with increased need for medication, such as antibiotics and nonsteroidal anti-inflammatory drugs, situations that occur frequently in the elderly. Differences have been demonstrated in the composition of the microbiota between healthy elderly subjects and hospitalized or institutionalized elderly subjects. These findings which further indicates that the living conditions, health status, nutrition and drugs have a significant effect on the composition of the microbiota. According to the available knowledge, the use of probiotics is safe and could represent an useful intervention to prevent or treat antibiotic-associated diarrhea, in addition to reducing the severity of symptoms, other than to help the management of constipation.

Key words: Microbiota; Elderly; Probiotics; Antibiotic-associated diarrhea; Constipation

Core tip: The intestinal microbiota of elderly manifested a reduction in the diversity, characterized by a large interindividual variability, with lower numbers of *Firmicutes*, *Bifidobacteria*, *Clostridium cluster* XIV, *Faecalibacterium Prausnitzii*, *Blautia coccoides-Eubacterium rectal* and higher in *Enterobacteriaceae* and *Bacteroidetes*. These derangements may not necessarily

aging-correlated, but they can be consequent to the decline of general state of health, malnutrition and increased use of drugs. As regards probiotics, the main double-blind studies in the elderly have shown that use is safe and could represent an interesting support to reduced frequency and/or duration of antibiotic-associated diarrhea, other than to help for constipation.

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INTRODUCTION

Differences in the composition of the microbiota have been shown in the literature, when healthy elderly and adult have been compared, but differences in the composition of the microbiota have been also shown when healthy elderly and hospitalized or institutionalized elderly patients have been compared. Then, the topic concerning the changes in the composition of the microbiota with age is much debated in the literature. Another issue of great interest is whether the use of probiotics may be effective in the elderly population.

Given this background, the aim of the present review is to summarize the state of the art according to the extant literature about two topics: the changes in the microbiota associated with aging and the activity of probiotics on the microbiota in this age group evaluated with two issues: (1) the effect on the composition of the microbiota after administration of probiotics; and (2) the efficacy of intake of probiotics on symptoms of major gastrointestinal diseases, including the iatrogenic ones, that frequently affect elderly subjects, including constipation, diarrhea secondary to the intake of antibiotics, particularly when linked to the presence of *Clostridium difficile*.

RESEARCH

The present systematic review was performed following the steps by Egger *et al*[1] as follows: configuration of a working group: three operators skilled in clinical nutrition in the geriatric age, of whom one acting as a methodological operator and two participating as clinical operators. Formulation of the revision question on the basis of considerations made in the abstract: "microbiota in elderly, use of probiotics during aging". Identification of relevant studies: a research strategy was planned, on PubMed [Public MedIine run by the National Center of Biotechnology Information (NCBI) of the National Library of Medicine of Bathesda (United States)], as follows: (1) definition of the key words (microbiota, elderly, probiotics), allowing the definition of the interest field of the documents to be searched, grouped in inverted commas ("…") and used separately or in combination; (2) use of: the Boolean AND Operator, that allows the establishments of logical relations among concepts; (3) research modalities: advanced search; (4) limits: time limits: papers published in the last 20 years; humans; languages: English; and (5) manual search performed by the senior researchers experienced in clinical nutrition through the revision of reviews and individual articles on microbiota in elderly published in journals qualified in the Index Medicus. Analysis and presentation of the outcomes: the data extrapolated from the revised studies were collocated in tables; in particular, for each study we specified: the author, the name of the journal where the study was published and year of publication, study characteristics. The analysis was carried out in the form of a narrative review of the reports.

MICROBIOTA IN ELDERLY POPULATION

This research has been carried out based on the following keywords: "microbiota" AND "elderly"; 1040 articles were found. Among them, 6 case control studies, 1 Randomized Controlled Trial (RCT), 6 cross sectional researches, 5 observational studies, 6 reviews, 1 prospective and 1 population based studies have been selected and discussed.

The changes in the microbiota associated with aging are still far from being clarified with certainty, but there are numerous studies that suggest that aging has a significant effect on the microbiota.

First of all, it has to be taken into account that changes in the intestinal microbiota of the elderly may not necessarily be caused by aging: they can be influenced by the decline of the general state of health, by malnutrition and increased need for medication, such as antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs)[2,3], that occur frequently in the elderly. Differences in the composition of the microbiota have been shown when healthy elderly and hospitalized or institutionalized elderly patients have been compared[4,5], thus proving that the living conditions, health status, nutrition and drugs have a significant effect on the composition of the microbiota.

Moreover, the colonic transit has a great influence on the function of the large bowel and increased transit time is related to a reduced fecal bacterial cell mass[6]. Due to a lack of exercise and long periods of bed rest[7,8], intestinal transit times are often significantly increased in hospitalized elderly patients[7], and this may be a factor influencing the changes in the intestinal microbiota in hospitalized or institutionalized elderly compared to healthy

subjects. Moreover, modified diets, parenteral and enteral artificial nutrition and different eating habits during hospitalization[9] may contribute to these variations.

The normal intestinal microbiota provides an important natural defence mechanism against invading pathogens and prevents the overgrowth of opportunistic microorganisms (colonization resistance). Therefore, alterations in the composition of the microbiota that occur in the elderly may lead to negative consequences, such as a decreased efficacy of in the immune system and a higher incidence of gastrointestinal infections, which is more frequent in the elderly than in the young[10]. The immunological changes associated with aging involve reductions of efficiency of the responses mediated by B and T cells[11]. In addition, the increase of circulating antibodies against commensal intestinal bacteria in the elderly has been associated with age-related changes, such as the reduction of gastric acid secretion and increased mucosal permeability[12].

The elderly subjects, compared to the young adult population, show a reduction in the diversity of the microbiota[13], characterized by a large interindividual variability, with a lower number of Bifidobacteria and a higher number of Enterobacteriaceae[14,15]. In addition, the *Bacteroidetes* are more numerous, while the *Firmicutes* appear to be fewer than in the elderly compared to younger adult controls[16]. The elderly population also shows decreased levels of *Clostridium cluster* XIV and *Faecalibacterium Prausnitzii*, which are known as major producers of butyrate[17,18]. Moreover, the levels of *Blautia coccoides - Eubacterium rectal* (formerly known as *Clostridium coccoides - E. Rectale*) are lower in the elderly than in adults[19]. Finally, aging has been associated with an increase in the diversity of species not yet identified[20]. In an interesting recent study[21], a cohort of 178 (non on antibiotic treatment) elderly subjects (mean age 78, range 64-102 years) were recruited by taking into account their place of residence (a group of healthy elderly were resident in a community and a group of frail elderly institutionalized in a long-term care center) and were compared with 13 young adults (mean age 36 years, range 28-46 years), who were used as a control group. The data were acquired through the reading of more than 5 million sequences generated from 16S rRNA amplicons of the gene. The results revealed that the composition of the intestinal microbiota of the elderly considered in the study was correlated with the place where they live. The elderly community residents had a greater number of *Firmicutes* and lower incidence of *Bacteroidetes* when compared the long-term care residents. Considering the division according to the enterotype, six co-abundance groups were detected. The dominant genera were *Bacteroides, Prevotella, Ruminococcus, Oscillibacter, Alistipes* and *CAG Odoribacter*. The transition from healthy elderly living in the community to elderly and frail institutionalized in a long-term care center is accompanied by the dominance of a CAG distinctive, with a significantly greater number of *Prevotella* and *Ruminococcus CAG* in the cohort residing in the community and *Alistipes* and *CAG Oscillibacter* in the cohort of elderly subjects institutionalized in a long-term care center. This study also demonstrated a correlation between alterations of the microbiota and the state of fragility of the elderly, confirming the results of previous study[22]. In addition, the study demonstrated a correlation with increased inflammation (as assessed by the determination of C-reactive protein and interleukin 6 and 8), thus confirming the hypothesis that there is a close association between the presence of the so-called "inflammaging" and alterations of the microbiota[23]. Finally, a clear association between diet and microbiota has been outlined in this study: thus confirms the results of many other studies[24-26].

A recent study by Biagi *et al*[15] evaluated, by means of "Human Intestinal Tract Chip" and quantitative PCR of the 16S rRNA genes of Bacteria and Archaea, the microbiota of centenarians and compared these data with the microbiota of young and not centenarians elderly subjects. The results show that *Firmicutes* and *Bacteroidetes* dominate the intestinal microbiota of centenarians (representing over 93% of total bacteria). Compared to adults and centenarians, in pre centenarian elderly subjects changes were observed in the relative proportion of specific subgroups of *Firmicutes*. A decrease in the contribution of *Clostridium cluster* XIV, an increase in Bacilli, and a rearrangement of *Clostridium cluster* IV, and of *Clostridium cluster* XIVa were found. *Clostridium cluster* XIVa is one of the main bacteria that produce methane, a short chain fatty acid, which is a source of energy for the enterocytes and has been implicated in the protection against intestinal inflammatory diseases. A lower number of several producers of butyrate was observed in centenarians when compared with other age groups, including *Ruminococcus obeum et rel*, *Roseburia intestinalis et rel*, *E. ventriosum et rel*., *E. rectale et rel*., *E. hallii et rel.* (all belonging to the *Clostridium cluster* XIV), and *Papillibacter cinnamovorans et rel*., and *F. Prausnitzii et rel*. (*Clostridium cluster* IV). Conversely, other butyrate producers, such as *Anaerotruncus colihominis et rel*. (*Clostridium cluster* IV), and *Eubacterium limosum et rel*. (*Clostridium cluster* XV) were increased in centenarians. The increase of *E. limosum* is high (about 15 times), and may indicate a group of bacteria characteristic of centenarians. Also the decrease of *F. prausnitzii* in centenarians is of interest, as this species is known to affect inflammation of the intestine. Finally, the intestinal microbiota of centenarians is more

rich in proteobacteria, a group containing many of those bacteria recently defined as "patobionti". These are considered minor and opportunistic components of human intestinal ecosystem that, in some circumstances (for example in the presence of inflammation) can get out of control and cause a disease.

Many therapeutic substances frequently taken by elderly subject[27], such as NSAIDs, are associated with alterations in the microbiota[3]. Mäkivuokko, thanks to the sequencing of the 16S rDNA, demonstrated in a group of 18 elderly people taking NSAIDs, that there are changes in all the major microbial phyla, such as a lower number of *Firmicutes* and an increase number of *Bacteroidetes*. In addition, it was reported a reduction in the number of the known butyrate producers belonging to *Clostridium cluster* XIV, as *Roseburia* and *Ruminococcus*, and, in the *Actinobacteria* cluster, a lower number of *Collinsella* spp. compared to both the young adults and the elderly subjects not taking NSAIDs.

EFFECTIVENESS OF THE USE OF PROBIOTICS IN THE ELDERLY POPULATION

The studies carried out in the elderly population to test the activity of probiotics on the microbiota in this age group, has been evaluated with two topics: the effect on the composition of the microbiota after administration of probiotics; the efficacy of intake of probiotics on symptoms of major gastrointestinal diseases, including the iatrogenic ones, that frequently affect elderly subjects, including constipation, diarrhea secondary to the intake of antibiotics, particularly when linked to the presence of *Clostridium difficile*.

This research has been carried out based on the keywords: "probiotics" AND "elderly" AND "aging"; 56 articles were sourced. Among them, as far as variations in the composition of the microbiota in the elderly after use of probiotics are concerned, 3 randomized double blind clinical trials and 1 observational research have been selected and discussed. Concerning the efficacy of use of probiotics on symptoms of major diseases that affect the elderly, 2 RCT, 7 double blind studies, 3 reviews and 1 cross sectional research have been selected and discussed.

Variations in the composition of the microbiota in elderly after use of probiotics

Regarding changes in the composition of the microbiota following the intake of probiotics, in the elderly population, three double-blind studies versus placebo were selected: (1) the study of Lahtinen *et al*[28] that considered the effect of a fermented oat beverage containing 10^9 cfu/mL *Bifidobacterium longum* 46 (DSM 14583) and *B. longum* 2C (DSM 14579) given daily for 6 mo; (2) the study by Ahmed *et al*[29] that considered the effect of a drink made of reconstituted skim milk containing 3 different doses (5 x 10^9 CFU/die, 1.0 x 10^9 CFU/die and 6.5 x 10^7 CFU/die) of *Bifidobacterium lactis* HN019 (DR10TM) administered daily for 4 wk; and (3) the study of Bartosch *et al*[4] that considered the effect of *Bifidobacterium bifidum* and *B. lactis* in combination with inulin.

Table 1 shows the changes in the composition of the microbiota of the treated group when compared to the placebo group.

Efficacy of use of probiotics on symptoms of major diseases, including iatrogenic, that affect the elderly

In a large controlled study conducted in 360 subjects older than 60 years, the effect of a 3-wk intervention of a fermented milk containing cultures of yogurt and the probiotic casei DN-114001 showed that the incidence of winter infections was not different than in the placebo group, but the duration of all pathologies was significantly lower in the intervention group (7.0-3.2 d) when compared to the control group (8.7-3.7 d)[30].

One double-blind study, which involved 24 elderly patients who had undergone artificial enteral nutrition, evaluated the effects of a 12-wk administration of fermented milk containing *Lactobacillus johnsonii* LA1. The group who took the probiotic had significantly fewer days with infections at the end of the intervention: a decrease from 15.4% of days with infection to 5.7% was observed, and this reduction was significantly greater than that recorded for the control group[31].

Numerous studies conducted in the elderly population have shown that the intake of probiotics determines a reduced frequency and/or duration of episodes of antibiotic-associated diarrhea (AAD), in addition to reducing the severity of symptoms. Probiotics have been used in combination with antibiotics as therapy for *Clostridium difficile*, which represents 20% to 25% of cases of AAD, causing more than 95% of cases of pseudomembranous colitis[32]. A study of Hickson *et al*[33] evaluated 135 hospitalized patients, with an average age of 74 years, before and after 1 wk of consumption of 100 g (97 mL) of a drink containing *Lactobacillus casei*, *L bulgaricus* and *Streptococcus thermophilus* taken twice per day during a course of antibiotics. The placebo group received a sterile milkshake. As a primary outcome the appearance of antibiotic-associated diarrhea was considered, while a secondary outcome, the presence of *Clostridium difficile* toxin and diarrhea were identified. The results showed that 7/57 (12%) of those taking the probiotic drink developed diarrhea associated with

Table 1 Changes in the composition of the microbiota of the treated group when compared to the placebo group

Design of the study	Subjects	Age	Probiotics	Results in intervention *vs* placebo	Ref.
Double blinded controlled trial	*n* = 33 placebo group;	83 ± 7 yr	Oat drink fermented with Bifidobacter um longum and *B. longum*	↑*B.catenulatum* ↑*B. bifidum* ↑*B. breve*	Lahtinen *et al*[28]
	n = 33 control group	84 ± 8 yr			
Double blinded controlled trial	*n* = 20 placebo; *n* = 20 low dose of probiotics; *n* = 20 medium dose of probiotics; *n* = 20 high dose of probiotics	> 60 yr	Reconstituted skim milk containing *Bifidobacterium lactis*	↑*Bifidobatteri* ↑*Lactobacilli* ↑*Enterococci* ↓*Enterobatteri*	Ahmed *et al*[29]
Double blinded controlled trial	*n* = 9 placebo	Mean 71 yr	*Bifidobacterium bifidum* and *B. lactis*	↑*Bifidobacteria*	Bartosch *et al*[4]
	n = 9 symbionts (mixture of probiotics and prebiotics)	Mean 73 yr	together with inulin	↑*Lactobacilli* ↓*B. bifidum*	

antibiotic use, compared with 19/56 (34%) of the placebo group (P = 0.007). Logistic regression for control of other factors gave an odds ratio of 0.25 (95%CI: 0.07-0.85) for the use of probiotics. The absolute risk reduction was 21.6% (6.6%-36.6%). No one in the group that received the probiotic and 9/53 (17%) in the placebo group had diarrhea due to *Clostridium difficile* (P = 0.001). The absolute risk reduction was 17% (7%-27%).

A further study on the use of probiotics as adjuvants to antibiotic therapy for the preventing of gastrointestinal disorders was conducted by Beausoleil in 89 elderly men with a mean age of 72 years[34]. The preparation employed was a fermented milk containing at least 50 × 10^9 colony-forming units of *L acidophilus* CL1285 and *L casei*. The scheme of administration was 49 g once a day for two days, followed by 98 g once a day to cover the entire duration of antibiotic treatment. The antibiotic-associated diarrhea occurred in 7 out of 44 patients (15.9%) in the group that received *lactobacilli* and in 16 out of 45 patients (35.6%) in the placebo group (OR = 0.34, 95%CI: 0.125-0.944, P = 0.05). The median length of hospital stay was eight days in the group that received the probiotics, compared to 10 d in the placebo group (P = 0.09). The prevention of CDAD is an important result to be considered in the elderly population, because this condition has been associated with increased mortality and morbidity[35].

In the elderly, constipation is a common condition characterized by a constellation of symptoms defined by the criteria "Rome Ⅲ criteria"[36]. A review published in 2010[37], included 3 double-blind, placebo-controlled studies conducted by Koebnick *et al*[38], Möllenbrink *et al*[39], and by Yang *et al*[40]: as a whole 266 patients were evaluated and the most of them were elderly patients. This review confirmed the efficacy of treatment with *Bifidobacterium lactis* DN-173010, *Lactobacillus casei Shirota*, and *E. coli Nissle* 1917 on the frequency of defecation and stool consistency. This improvement is secondary to the decrease of the colonic pH value that follows the probiotics intake, thanks to the production of short chain fatty acids (butyric acid, propionic acid and lactic acid). A lower pH enhances peristalsis in the colon, and thereafter, it may decrease the intestinal transit time[37].

A double blind *vs* placebo study conducted by Ouwehand *et al*[41] studied the effects of a symbiotic combination of lactitol and *Lactobacillus acidophilus* NCFM (total daily dose of 10 g lactitol and 2 × 10^{10} cells probiotic bacteria) taken twice a day for 2 wk, in a group of elderly subjects. The results of the study showed a higher frequency of evacuation in the group that received the probiotic, as well as significantly higher levels of PGE2, as well as a changes of IgA level and spermidine, thus demonstrating positive effects on the function of the intestinal mucosa.

The same working group[42] recently assessed by means of a double- blind, placebo-controlled trial, the efficacy of the same combination of *Lactobacillus acidophilus* NCFM and lactitol in 51 elderly people who followed NSAIDs treatment. Before, during and after the intervention period, the amount of six stool bacterial phylogenetic groups was determined using quantitative PCR, and variations in the composition of total microbiota were assessed by percent profiling guanine-plus-cytosine. The results of the study showed an increase of lactobacilli and bifidobacteria and also a possible stabilizing effect on the levels of *B. coccoides-E.* XIVab and *Clostridium cluster*.

CONCLUSION

The changes in the microbiota associated with aging are still far from being clarified with certainty, but there are numerous studies that suggest that aging has a significant effect on the microbiota.

Alterations in the intestinal microbiota of the elderly may not necessarily be caused by aging, but they can be consequent to conditions that occur frequently in the elderly, such as the decline of the general state of health or malnutrition or increased need for medication (*i.e.*, antibiotics and nonsteroidal anti-inflammatory drugs). Differences in the composition of the microbiota have been

found when healthy elderly and hospitalized or institutionalized elderly subjects were compared. This further indicates that the living conditions, health status, nutrition and drugs have a significant effect on the composition of the microbiota.

When compared to young adult populations, elderly subjects show a reduction in the diversity of the microbiota, which is usually characterized by a large interindividual variability, with a lower number of *Firmicutes*, *Bifidobacteria*, *Clostridium cluster* XIV, *Faecalibacterium Prausnitzii*, *Blautia coccoides-Eubacterium rectal* and a higher number of *Enterobacteriaceae* and *Bacteroidetes.* In the elderly, the intake of and NSAIDs is followed by a significant change on the composition of the microbiota. A reduction in the proportion of the known butyrate producers belonging to *Clostridium cluster* XIV, as *Roseburia* and *Ruminococcus*, and, in the *Actinobacteria* group, a lower number of *Collinsella* spp. has been reported in elderly subjects taking NSAIDs when compared to both young adults and elderly subjects who are not taking NSAIDs.

The use of probiotics in elderly population is safe and could represent an interesting support to prevent or treat AAD, in addition to reducing the severity of symptoms, other than to help the management of constipation.

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MINIREVIEWS

Conservative strategy for treatment of stable coronary artery disease

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Abstract

Patients with coronary artery disease vary widely in terms of prognosis, which is mainly dependent on ventricular function. In relation to the major outcomes of death and myocardial infarction, it is not clear in the literature if an invasive strategy of myocardial revascularization is superior to a conservative strategy of optimized medical therapy. Moreover, with the exception of patients with left main coronary disease, this similarity in prognosis also occurs in different subgroups of patients.

Key words: Coronary artery disease; Angina pectoris; Myocardial revascularization; Coronary angioplasty; Myocardial infarction; Prognosis; Disease-free survival

Core tip: Despite the evolution of myocardial revascularization techniques, the mainstay of treatment of stable coronary artery disease is optimal medical therapy. With the better understanding of the mechanisms underlying atherosclerosis, medical therapy develops and shows similar results in terms of survival and freedom from myocardial infarction compared to coronary interventions. Moreover, clinical trials have also demonstrated similar results between conservative and invasive strategies in various subgroups of patients, previously found to benefit from coronary interventions. In this review article, the authors discuss the results from main trials on specific groups of coronary artery disease patients which compared conservative and invasive strategies.

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INTRODUCTION

The first studies on the evolution of patients with stable coronary artery disease (CAD) and preserved left systolic ventricular function demonstrated a low incidence of major cardiac events, death or myocardial infarction, in non-revascularized patients, despite their anatomical complexity. Moreover, retrospective studies that compared optimized medical therapy (OMT) alone with coronary artery

bypass surgery (CABG) demonstrated similar rates of death or myocardial infarction in patients both with single-vessel or multivessel disease, in the presence of preserved systolic ventricular function.

In clinical conditions like diabetes mellitus or in elderly patients, the literature demonstrates that the conservative strategy of OMT is as safe as invasive strategies are, for the majority of CAD patients.

Although sub analyses from important studies have suggested surgery would be a safer strategy in patients with CAD and impaired ventricular function, this information has been questioned by a recent important prospective randomized clinical trial, which demonstrated similar results of medical therapy compared to bypass surgery.

Despite the evolution of CABG and percutaneous coronary intervention (PCI) in the last 20 years, with the widespread use of arterial grafts and surgery without the use of extra-corporeal circulation, and the emergence of pharmacological stents, the improvement in medical therapy also occurred substantially with the use of antiplatelets, beta-blockers, angiotensin-converting enzyme inhibitors and statins. Currently, these are the basis of pharmacological CAD treatment, but other options with specific mechanisms of action as ranolazine and ivabradine have also emerged as potential adjunct therapy. In addition, technical problems of invasive strategies, such as graft failure and restenosis of stents, deserve attention in this matter. Moreover, clinical complications of interventions also carry risks, especially related to cerebrovascular accidents after surgery and the possible need for future interventions with PCI. On the other hand, some specific subgroups of CAD patients do benefit by invasive strategies.

Thus, a conservative OMT strategy with multi-factorial control is a safe option for the treatment of the majority of CAD patients, especially those with well-preserved ventricular function. Invasive strategies are important tools for the management of CAD patients, and should be reserved particularly for patients with refractory symptoms, for those who develop acute coronary syndromes, and possibly for select patients with ischemic heart failure.

In this review article, the authors discuss the major findings of studies, especially clinical trials, comparing medical therapy with invasive coronary interventions, in terms of major outcomes, death and MI, in different clinical settings.

EVOLUTION OF CORONARY ARTERY DISEASE PATIENTS

The natural history of patients with CAD is impossible to observe in epidemiological studies for ethical reasons. Even if patients refuse coronary interventions, they still receive medical therapy and instruction on lifestyle modifications, which result in changes in their clinical evolution. Consequently, the evolution of CAD patients may be observed in prospective studies, and especially in randomized groups that include patients receiving medical therapy alone.

The evolution of patients with chronic, stable CAD was demonstrated in an important study published in 1989[1]. In this study, from 1977 to 1983, 150 stable CAD patients, including 92% with multivessel disease and also patients with left main coronary disease or equivalent (39.3%) with a formal indication for coronary surgical revascularization refused the procedure. They were followed for two to eight years until 1985, and medically treated with beta-blockers, nitrates, calcium-channel blockers, aspirin, and dipyridamole. Differently from modern treatment, at that time, they were not treated with angiotensin-converting enzyme inhibitors or with statins, important medications of current therapy. Despite anatomic complexity, the estimated overall survival in eight years was 89%, which represents an average annual mortality rate of 1.37%. Of note, only 10% of patients had myocardial infarction and 4% requested surgical revascularization during follow-up.

One of the first randomized studies that compared medical therapy alone with coronary bypass surgery in stable CAD patients was the Coronary Artery Surgery Study (CASS) trial[2], published in 1983. In this study, 780 CAD patients were randomized to one of the two strategies and followed for 5 years. Interestingly, in this study, the average annual mortality rate for patients assigned to medical therapy was 1.6% and to surgery 1.1% (P = 0.34). Analyzing only the patients with an ejection fraction ≥ 0.50 (75% of the entire population of the trial), those assigned to medical therapy had annual mortality rates of 1.1%, 0.6%, and 1.2%, respectively, for single-, double-, and triple-vessel disease. Patients with an ejection fraction $\geqslant$ 0.50 assigned to surgery had similar mortality rates 0.8%, 0.8%, and 1.2%, respectively, for single-, double-, and triple-vessel disease. There were no statistical differences between the two treatment strategies.

Analysis of ten-year follow-up of patients from the CASS trial[3] demonstrated an overall survival of 79% and 82% in medical and surgery groups, respectively, or an average annual mortality rate of 2.1% and 1.8% (P = 0.25).

The results of these studies demonstrate that annual mortality rates for stable CAD patients with normal ejection fraction is low and range from 0.8% to 2.1%, even in those with multivessel disease. In addition, these studies were performed during a time when patients did not receive statins or angiotensin-converting enzyme inhibitors, which are medications with the potential to lower this risk. Although great numbers of patients in these studies had a low-risk profile (preserved systolic ventricular function, stable non-limiting symptoms, and young patients), their

prognostic information is essential for understanding the results of studies on invasive strategies.

SINGLE-VESSEL CAD PATIENTS

As mentioned previously, the CASS trial as well as other trials have demonstrated that single-vessel CAD patients have low annual mortality rates, especially in the presence of preserved ventricular function (1.1% and 0.8%, respectively, for medical therapy and bypass surgery). Moreover, this good prognosis is similar among different treatment strategies.

One of the studies that addressed the comparative results of different strategies in this scenario of single-vessel CAD patients was the Medical, Angioplasty or Surgery Study Ⅰ trial[4]. This study evaluated 214 CAD patients with an isolated severe lesion > 80% at the proximal portion of the left anterior descending coronary artery. Patients with stable symptoms and well-preserved ventricular function were selected and randomized to medical therapy alone (n = 72), balloon angioplasty (n = 72), or CABG (n = 70) with an internal thoracic artery. After an average of 3-year follow-up, the primary end-point of cardiac death, myocardial infarction, or refractory angina requiring revascularization was 12%, 17%, and 3%, for medical therapy, angioplasty, and CABG. This difference was mainly dependent on new revascularizations, because mortality and myocardial infarction were similar in the 3 treatment strategies.

Another important study on single-vessel CAD patients was published in 1992[5] and compared medical therapy alone with angioplasty with the use of stents. Patients with severe stenosis in one coronary artery were randomized and followed for 6 mo. In that period, myocardial infarction occurred in 5 patients who underwent angioplasty and in 3 patients in the medical therapy group. However at the end of the follow-up, a higher number of patients assigned to angioplasty were free of angina (64% × 46% in angioplasty and medical therapy, respectively, P < 0.01), and performed better on exercise treadmill tests, despite higher costs and complications in the angioplasty group.

Thus, in the subset of single-vessel CAD patients, unless limited by refractory symptoms, the strategy of optimal medical therapy poses a similar prognosis in terms of survival and myocardial infarction compared to invasive strategies. However, patients with severe symptoms, especially if refractory to medical interventions may benefit in terms of alleviation of symptoms with angioplasty.

MULTIVESSEL CAD PATIENTS

The three most important studies conducted in the 1970's and 1980's that compared the strategy of medical therapy alone with bypass surgery were the Veterans Affairs (VA) Cooperative Study[6], the European Coronary Surgery Study (ECSS)[7], and CASS[2].

Most of the patients enrolled in these trials had multivessel CAD, and the European Study only enrolled such patients.

The VA Cooperative Study included 686 CAD patients with stable angina, electrocardiographic signs of previous infarction or ischemic changes in exercise, and at least one major coronary artery with ⩾ 50% stenosis. Patients were randomized to medical therapy alone or bypass surgery and were followed for 18 years. This study demonstrated similar rates of overall survival (33% and 30% for MT and CABG, respectively, P = 0.60), and similar rates of myocardial infarction (41% and 49% for MT and CABG, respectively). Importantly, in patients with preserved ventricular function, irrespective of the number of diseased coronary arteries, patients assigned to medical therapy had similar rates of death and myocardial infarction as those assigned to bypass surgery. On the other hand, the group with left main disease or with a high angiographic risk, characterized as triple-vessel disease associated with impaired left ventricular function, had better survival associated with bypass surgery. Of note, 41% of medical therapy patients underwent surgery during the entire 18-year follow-up.

Consistent with the findings of the VA Study, the CASS trial also showed that patients with single-, double-, or triple-vessel coronary disease had similar rates of overall survival and myocardial infarction in medical therapy and bypass surgery, if they had preserved systolic ventricular function (defined as an ejection fraction ⩾ 0.50). CASS also showed that in patients with impaired ventricular function and triple-vessel disease, surgery was a better survival option. Of note, these 5-year results were confirmed by a 10-year follow-up study[8].

Another important study, the ECSS demonstrated some differences compared to the two previous studies. This trial included 767 men with normal left ventricular function and multivessel disease and randomized them to bypass surgery or medical therapy. Differently from VA and CASS, ECSS showed higher survival rates after 5- and 12-year follow-up for surgically treated patients, but the difference between treatments in the 5-year follow-up decreased in the 12-year results (70.6% ± 5.8% *vs* 66.7% ± 5.3%, P = 0.04). However, this better survival with bypass surgery only occurred in triple-vessel disease patients. Survival of double-vessel disease patients was similar in the two strategies.

After these 3 studies, the only study that compared an invasive with a conservative strategy of OMT and included three groups of treatments was the Medical, Angioplasty or Surgery Study (MASS-Ⅱ)[8]. In this study, 611 patients with multivessel proximal CAD, preserved systolic ventricular function and stable

symptoms were randomized to receive OMT alone (n = 203), CABG surgery (n = 203), or PCI (n = 205) with the use of conventional stents. After 5-year follow-up[8], the combined primary end-points of death, myocardial infarction, and additional revascularization favored the patients assigned to bypass surgery (21.2%, 32,7% and 36.0%, respectively, for CABG, PCI and MT, P = 0.0026), especially due to a significant reduction in the rates of new revascularizations (3.9%, 11.2%, and 9.4%, respectively for CABG, PCI, and MT). However, mortality and myocardial infarction rates were statistically similar between the 3 groups. After 10-year follow-up[9], overall survival was similar between the 3 treatment groups (74.9%, 75.1%, and 69%, respectively, for CABG, PCI, and MT, P = 0.089). However, the incidences of myocardial infarction and cardiac deaths favored the surgical group. Importantly, after 10 years about 40% of MASS Ⅱ trial patients assigned to medical therapy did not develop any complications. In addition, combined and isolated end-points were similar between medical therapy and angioplasty groups.

Compared to the first studies (VA, ECSS, and CASS), the MASS trial was a more contemporary study, in which medical therapy included the use of statins, angiotensin-converting enzyme inhibitors, and dual antiplatelet therapy after PCI. However, the higher annual mortality in this trial compared to the previous ones may be due to a higher-risk profile, as patients were older at study entry, had a higher proportion of diabetics, and more complex and diseased coronary arteries (higher frequency of triple-vessel disease and lesions at the proximal portion of the left anterior descending artery). Thus, this higher-risk profile of patients from the MASS trial seemed to benefit from surgery, information similar to that of the VA and ECSS trials. The high-risk profile patients from the CASS trial also demonstrated the benefits of bypass surgery, but in this study this profile included patients with impaired ventricular function.

The MASS trial showed that medical therapy had similar outcomes when medical therapy was compared to angioplasty. However, this was not the primary objective of this study.

However, this was the major finding of another important study published in 2007, the COURAGE trial[10]. This study aimed at evaluating the clinical significance of PCI in stable CAD patients. With this purpose, 2287 patients with objective evidence of myocardial ischemia and significant CAD were randomized between 1999 and 2004 to OMT alone (n = 1138) or PCI with OMT (n = 1149). After a median 4.6-year follow-up, the primary end-point of overall death and myocardial infarction occurred in 19.0% in the PCI group and 18.5% in the medical therapy group (P = 0.62). Other isolated end-points such as myocardial infarction or hospitalization for acute coronary syndromes had similar rates in both groups. On the other hand, symptoms were better controlled by PCI, but still with a modest reduction in these rates compared to OMT.

Some meta-analysis of studies comparing PCI with medical therapy alone[11,12] demonstrated similar results, even when only patients with objective myocardial ischemia were included in the analysis[13].

Thus, the information from these trials shows that even for multivessel patients, with preserved ejection fraction, stable non-limiting symptoms, medical therapy is a safe alternative. The groups of patients who benefit from bypass surgery are those with a higher anatomical or clinical risk profile, such as patients with left main disease or limiting symptoms. The option for bypass surgery should also consider peri-procedural risks and the possibility of recent graft failure, which is mainly dependent on the surgeon's technical ability but also by anatomic characteristics, especially the coronary bench that will receive the graft. The option for PCI in stable CAD patients should also be carefully evaluated because it does not protect patients from myocardial infarction, hospitalizations, and or from the risk of death. PCI could be indicated for those patients with limiting symptoms despite optimized medical therapy and with an anatomy favorable to the procedure.

IMPAIRED VENTRICULAR FUNCTION AND CAD

As already mentioned, the CASS trial[2] was one of the first randomized trials to demonstrate that bypass surgery is superior in terms of overall survival compared to medical therapy alone in patients with triple-vessel CAD and impaired ventricular function. Interestingly, in this context, only patients with a great percentage of jeopardized ischemic myocardium had the benefits of revascularization, because single- and double-vessel disease patients with impaired ventricular function had similar survival rates with bypass surgery compared to medical therapy. However, one should consider that the CASS trial enrolled only 160 patients with left ventricular dysfunction, so that it could not have power enough to demonstrate potential differences between treatment groups. On the other hand, medical therapy at that time was quite different from current medical therapy for heart failure. For the entire population of the CASS trial, 64% of the medical group received beta-blockers at 60 mo after randomization, while only 34% of the surgical group received beta-blockers at the same follow-up period. Besides, angiotensin-converting enzyme inhibitors were not disposable at that time, nor were aldosterone blockers, which are also current essential medications for the treatment of heart

failure patients. Similarly, anesthesia, cardioplegia methods, and surgical technique have also improved since CASS trial.

Interestingly, an analysis from the CASS registry[14] with patients with severe left ventricular dysfunction, manifested by an ejection fraction below 0.36, demonstrated that the group of patients assigned to surgery had an improvement in survival compared to medical therapy patients, despite a high operative mortality of 6.9%. Moreover, a higher benefit of surgery over medical therapy was observed in patients with ejection fraction below 0.26 (5-year survival of 63% *vs* 43%, respectively, for surgery and medical therapy, $P = 0.005$) and in patients with predominantly anginal symptoms. The patients in whom heart failure symptoms predominated did not receive benefits from surgery over medical therapy. Thus, surgery probably benefited heart failure patients who had some extent of viable and ischemic myocardium, and probably did not benefit those with non-viable, fibrotic myocardium.

The findings from the CASS trial and registry were the basis for cardiology guidelines recommendations and cardiology practice supporting CABG in this scenario in the following decades.

Recently, the STICH (Surgical Treatment for Ischemic Heart Failure) trial[15], published in 2011, questioned the superiority of CABG for CAD patients with impaired ventricular function. This was a multicenter, randomized, clinical trial, in which CAD patients amenable to surgery who had an ejection fraction of 0.35 or less were randomized to OMT or CABG plus OMT. During the 56-mo follow-up, the primary end-point of overall death occurred in 41% of the medical therapy group and in 36% of the CABG group ($P = 0.12$). Of note, 17% of medical therapy group patients underwent CABG during follow-up.

In this contemporary trial, the hypothesis tested in previous studies, including CASS, that bypass surgery would be superior to medical therapy in terms of survival was contradicted by the results of such a well-designed study. Some reasons might be pointed out for this interesting finding. First, medical therapy for heart failure has improved continuously during the last 20 years. The better knowledge of the physiopathology of heart failure lead to the development and use of classes of medications directed to neurohormonal cascades[16,17] related to the progression of ventricular dysfunction. In many clinical trials[18-20], these medications were proven to positively influence survival, and currently beta-blockers, angiotensin-converting enzyme inhibitors, and aldosterone blockers are the main stain of modern treatment. On the other hand, despite its higher initial risk of complications, bypass surgical treatment of ischemic heart failure may benefit patients with jeopardized ischemic myocardium, amenable to revascularization. Of note, 52% of the population of the STICH trial had Canadian Cardiac Society (CCS) angina class 0 or 1, and 37% had dyspnea New York Heart Association (NYH) class Ⅲ or Ⅳ. However, subgroup analysis did not show differences when angina or dyspnea groups were compared. Thus, a great percentage of patients might have fibrotic ischemic scars not amenable to improving its function by bypass surgery. Thus, on the one hand, medical therapy improved substantially over time and changed the outcomes of heart failure patients. On the other hand, surgery was performed in patients with a great variability of ischemic heart disease. The patients with the highest likelihood of benefitting from CABG would be those with a higher percentage of hibernating myocardium (potential to improve function with revascularization), and especially if suitable to be revascularized (good distal benches to receive an arterial or venous grafts).

DIABETES AND CAD

In stable CAD patients, diabetes mellitus confers higher rates of complications and a worse prognosis[21]. Considering that some previous trials have demonstrated that CABG was superior to medical therapy alone in high-risk groups of patients, the BARI 2D trial[22] proposed studying the comparative results of a strategy of OMT *vs* a strategy of coronary revascularization (PCI or CABG) for type-2 diabetic CAD patients. After 5 years, the primary end-point of overall survival was similar between the 2 groups (survival rates of 88.3% and 87.9%, respectively, for revascularization and medical therapy alone, $P = 0.97$). Moreover, the rates of freedom from cardiovascular events (death, myocardial infarction, or stroke) were also similar between groups (77.2% and 75.9%, respectively, for revascularization and medical therapy groups, $P = 0.70$). When patients were stratified by the choice of PCI or CABG as the appropriate intervention, in the PCI stratum, survival and composite end-points were similar between medical therapy and PCI. In CABG stratum, survival was similar between medical therapy and CABG, although the rates of cardiovascular events were higher in medical therapy than in CABG.

Contrary to results of the BARI 2D trial, a substudy of 10-year results of the MASS Ⅱ trial[23] analyzed diabetic CAD patients in terms of comparative outcomes among medical therapy, PCI, and CABG in a long-term follow-up. Among diabetic patients ($n = 232$), mortality rates were 37.5%, 31.3%, and 27.5%, respectively, for medical therapy, PCI, and CABG ($P = 0.015$ for CABG *vs* medical therapy). Cardiac mortality also favored CABG-assigned patients, as the rates were 26.1%, 18.8%, and 12.5%, respectively ($P = 0.005$ for CABG *vs* medical therapy).

The strong evidence from BARI 2D is not con-

Table 1 Main randomized clinical trials comparing medical therapy alone with coronary interventions in stable coronary artery disease patients

Clinical scenario	Clinical trial	Randomization period	*n*	Study groups	Annual mortality	Main findings
Single-vessel CAD	MASS I (3.5 yr)	1988-1991	214	MT 72 PCI 72 CABG 70	MT 0 PCI 0.4% CABG 0.4%	Similar mortality and MI among the 3 groups
Multivessel CAD (majority of trials' patients)	VA (18 yr)	1972-1974	686	MT 354 CABG 332	MT 3.7% CABG 3.9%	Similar mortality and MI rates in the 2 groups
	ECSS (12 yr)	1973-1976	767	MT 373 CABG 394	MT 2.7% CABG 2.4%	Mortality higher in MT group in 3-vessel disease patients
	CASS (10 yr)	1975-1979	780	MT 390 CABG 390	MT 2.1% CABG 1.9%	Similar mortality in 1, 2 or 3-vessel with EF ⩾ 0.50. CABG was superior in 3-vessel with EF < 0.50
	MASS II (5 yr)	1995-2000	611	MT 203 PCI 205 CABG 203	MT 2.4% PCI 2.3% CABG 1.6%	Similar mortality in the 3 groups. Similar events in MT and PCI. CABG superior in terms of reinterventions
	COURAGE (4.6 yr)	1999-2004	2287	MT 1138 PCI 1149	MT 1.8% PCI 1.65%	Similar mortality and events in the 2 groups
Impaired ventricular function	STICH (4.6 yr)	2002-2007	1212	MT 602 CABG 610	MT 8.8% CABG 7.7%	Similar mortality rates. CABG superior in terms of hospitalization for cardiac causes
Diabetes mellitus	BARI 2D (5.3 yr)	2001-2005	2368	MT 1192 CABG/ PCI 1176	MT 2.3% CABG/PCI 2.2%	Similar mortality and MI rates in the 2 strategies
Elderly	TIME (3.1 yr)	1996-2000	282	MT 142 CABG/PCI 140	MT 7.2% CABG/PCI 6.8%	Similar mortality and MI rates between the 2 strategies

CAD: Coronary artery disease; MASS: Medical, Angioplasty or Surgery Study; VA: Veterans Affairs; ECSS: European Coronary Surgery Study; STICH: Surgical Treatment for Ischemic Heart Failure; TIME: Medical Therapy in Elderly patients; MT: Medical therapy; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass surgery.

firmed by other substudies like the MASS trial. A higher risk profile in the MASS trial, as well as the intensity of treatment in BARI 2D may explain in part such differences.

ELDERLY PATIENTS AND CAD

With the aging of the world population in recent decades, CAD has become more frequent. In addition, in the elderly, the likelihood of severe and diffuse CAD is higher than in younger populations[24]. Moreover, due to higher rates of procedure-related complications[25,26] and a lack of clinical trials comparing treatments in patients older than 65 years, the treatment of this specific population becomes even more challenging.

A sub analysis from the CASS registry[27] showed that in 1985 older CAD patients surgically treated had better survival rates compared to medically treated patients, during a 6-year follow-up (adjusted 6-year survival 79% and 64%, respectively, for surgical and medical therapy groups, $P < 0.0001$). However, this study should be carefully analyzed as this was a non-randomized study, and there were important baseline differences between the two treatment groups.

Another prospective, observational study published in 2002 analyzed clinical data and outcomes of all patients who underwent catheterization and revascularization in the province of Alberta, Canada[28]. This study showed that in 3 age cohorts (< 70 years, 70-79 years, and ⩾ 80 years), CABG was superior to PCI and medical therapy alone in terms of overall survival during 4-year follow-up. However, this study has also to be analyzed carefully because its design was observational, non-randomized, and included a great range of risk profiles, such as acute coronary syndrome patients as well as patients with impaired ventricular function, which may have favored surgical results.

One of the few studies designed to compare a conservative *vs* an invasive strategy for the treatment of elderly CAD patients was the Trial of Invasive *vs* Medical therapy in Elderly patients (TIME), published in 2004[29]. In this study, patients age 75 years or older, with Canadian Cardiac Society (CCS) class Ⅱ or greater angina, despite taking at least 2 classes of anti-anginal drugs, were randomized to medical therapy alone or to angiography and appropriate coronary revascularization (PCI or CABG). Despite their high-risk profile (mean age at entry 80-year-old, 82% with CCS class Ⅲ or Ⅳ angina), survival was similar between patients in the two strategies (91.5% *vs* 95.9% after 6 mo, 89.5% *vs* 93.9% after 1 year, and 70.6% *vs* 73.0% after 4.1 years, respectively, for medical therapy and revascularization strategies, P = NS). However, late revascularizations were more frequent in the medical therapy than in the revascularization group (45% *vs* 12%, $P < 0.0001$).

Post-hoc analysis of elderly CAD patients from the COURAGE trial[30] also demonstrated similar survival rates between conservative and invasive

strategies.

A recent post-hoc analysis of patients 65 years or older from the 10-year follow-up of the MASS Ⅱ trial[31] also showed similar overall survival rates comparing the three treatment strategies, medical therapy, PCI with conventional stents or CABG (63%, 69% and 66%, P = 0.93). The rates of myocardial infarction were also similar among the three groups. However, as demonstrated in the TIME trial, the rates of additional revascularizations were lower in the CABG group (Table 1).

EXTENSION OF MYOCARDIAL ISCHEMIA

Although ESC guidelines[32] and some retrospective studies[33,34] have suggested that patients with myocardial ischemia extension greater than 10% benefit from myocardial revascularization, no prospective study have confirmed this finding. Currently, the on-going International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial, which aims at randomizing 8000 coronary artery disease patients with moderate or severe ischemia to an invasive or a conservative strategy, should help to bring some reliable information in this matter.

CLINICAL IMPLICATIONS AND CONCLUSION

Despite the strength of several study findings, significant developments in aggressive MT and lifestyle prescriptions with comprehensive risk factor modification have continued to occur since trials were conducted, and this may impact the outcomes of an MT-based strategy, even in the long-term follow-up. Further evidence in this long-running debate will be provided by the results of current trials of the initial MT strategy in patients with stable multivessel disease and preserved ventricular function. Moreover, results of studies on drug-eluting stents demonstrating the superiority of CABG over PCI have been questionable, and some might argue that this procedural refinement makes the present results obsolete. However, data from randomized and nonrandomized trials show that this new type of stent has no advantageous effect on death and nonfatal MI relative to bare-metal stents despite yielding striking reductions in rates of restenosis and repeat revascularization procedures. Thus, we believe that the observations reported herein with respect to death and MI remain applicable to contemporary practice.

In summary, several trials strongly show the benefits of PCI and CABG over MT in regard to some end points at long-term follow-up, although with similar rates of overall mortality. Additionally, CABG surgery is associated with higher rates of event-free survival.

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ORIGINAL ARTICLE

Observational Study

Correlation between hypertension and hyperglycemia among young adults in India

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Informed consent: All study participants, provided informed written consent prior to study enrollment.
Conflict-of-interest: There are no conflicting interests (including but not limited to commercial, personal, political, intellectual, or religious interests) to declare.
Data sharing: Technical appendix, statistical code, and dataset available from the corresponding author at tanumidha2001@gmail.com. Participants gave informed consent for data sharing.

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Abstract

AIM: To assess the correlation between blood pressure levels and fasting plasma glucose levels among young adults attending Chatrapati Shahuji Maharaj University, Kanpur, India.

METHODS: The present study was cross-sectional in nature, conducted among students in the Institute of Paramedical Sciences, Chatrapati Shahuji Maharaj University, Kanpur. Study subjects included 185 young adults. Among them, 94 were males and 91 were females, in the age group 17 to 19 years.

RESULTS: Mean age among males was 18.5 ± 1.5 years and among females was 17.9 ± 1.8 years. Of the total 185 study subjects, 61 (32.9%) were classified as pre-diabetic and 20 (10.8%) as pre-hypertensive. Mean waist circumference, systolic blood pressure and serum high density lipoprotein did not vary significantly between normoglycemic and pre-diabetic subjects. However, the mean diastolic blood pressure of pre-diabetics (82 ± 5 mmHg) was significantly higher than normoglycemics (79 ± 6 mmHg). Mean

serum cholesterol, serum triglycerides, serum low density lipoprotein (LDL) and serum very low density lipoprotein was also higher among pre-diabetic subjects in comparison to normoglycemic subjects and the difference was statistically significant. Upon multiple linear regression analysis, it was observed that body mass index (BMI) (β = 0.149), diastolic blood pressure (β = 0.375) and serum LDL (β = 0.483) were significantly associated with fasting plasma glucose. Multiple linear regression with diastolic blood pressure as the outcome variable showed that BMI (β = 0.219), fasting blood glucose (β = 0.247) and systolic blood pressure (β = 0.510) were significantly associated.

CONCLUSION: A significant prevalence of pre-diabetes and pre-hypertension in young adults is a matter of concern therefore all young adults need to be targeted for screening of diabetes and hypertension and lifestyle modification.

Key words: Adolescent; Hypertension; Diabetes; Co-prevalence; India

Core tip: In the present study, 32.9% young adults were pre-diabetic whereas 10.8% were pre-hypertensive. Around 2.7% young adults had both pre-diabetes and pre-hypertension. Among the pre-hypertensives, 25% also had pre-diabetes. However among the pre-diabetics, 8.2% had pre-hypertension. The correlation between systolic blood pressure and fasting plasma glucose was not statistically significant. However, the correlation between diastolic blood pressure and fasting plasma glucose was significant. The mean diastolic blood pressure of pre-diabetics (82 ± 5 mmHg) was significantly higher than normoglycemics (79 ± 6 mmHg). Upon multiple linear regression analysis, it was observed that body mass index (β = 0.149), diastolic blood pressure (β = 0.375) and serum LDL (β = 0.483) were significantly associated with fasting plasma glucose.

Midha T, Krishna V, Shukla R, Katiyar P, Kaur S, Martolia DS, Pandey U, Rao YK. Correlation between hypertension and hyperglycemia among young adults in India. *World J Clin Cases* 2015; 3(2): 171-179 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i2/171.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i2.171

INTRODUCTION

Diabetes and hypertension is the twin epidemic, rapidly on the rise in the developing countries[1]. Diabetes mellitus or chronic hyperglycemia is a metabolic disorder which results from defects in carbohydrate, fat and protein metabolism that occur as a consequence of deranged insulin secretion or action. Long term hyperglycemia is associated with the development of cardiovascular disease, renal disease, neuropathy, retinopathy, peripheral vasculopathy, and stroke[2]. World Health Organization (WHO) has estimated that globally the number of adults with diabetes will increase from 171 million in 2000 to 366 million in the year 2030[3]. In 2004, worldwide, around 3.4 million people died as a result of hyperglycemia[4]. Of the total deaths among diabetics, around 80% occur in developing countries[5]. According to WHO, diabetes will be the 7th leading cause of global mortality in 2030[6]. India has been declared as the capital of diabetes because approximately 41 million Indians have diabetes to date and every fifth diabetic in the world is an Indian[7].

Worldwide, hypertension or high blood pressure has caused around 7.5 million deaths, which accounts for 12.8% of the global mortality. Around 57 million disability adjusted life years (DALYS) or 3.7% of total DALYS have been attributed to hypertension[8]. The global prevalence of hypertension in adults more than 25 years of age, averaged around 40% in 2008[8]. The WHO has estimated that hypertension is directly responsible for about 62% of stroke and 49% of coronary artery disease, worldwide[9]. In a meta-analysis of prevalence studies on hypertension in India, from January 2000 to June 2012, it was observed that the prevalence of hypertension in the urban population was 40.8% whereas that in the rural population was 17.9%[10]. Hypertension leads to cardiovascular disease, peripheral vasculopathy, cerebrovascular disease, and nephropathy[11].

It has been observed that diabetes and hypertension often exist together in the population. The risk of developing hypertension is 1.5-2.0 times higher in diabetics as compared to non-diabetics, whereas around one-third of the hypertensives develop diabetes[12]. These co-morbidities hasten the progress of vascular complications[13-15].

Diabetes and hypertension both can be prevented and managed by lifestyle modification and medical intervention. Moreover, screening and early management of diabetes and hypertension, through periodic surveillance, will slow down the progress of the disease and prevent complications[16]. American Diabetic Association has described a new entity of impaired glucose metabolism as prediabetes in which two categories are included-Impaired Fasting Glucose, when fasting plasma glucose is between 100 and 125 mg/dL and Impaired Glucose Tolerance, when 2-h result following oral glucose tolerance test is between 140 and 199 mg/dL[17]. Persons with prediabetes, are at greater risk for the future development of diabetes as well as cardiovascular disease[18]. According to JNC-7,

systolic blood pressure 120-139 mmHg and/or diastolic blood pressure 80-89 mmHg was classified as pre-hypertension[19]. Similarly, individuals with pre-hypertension are pre-disposed to developing hypertension in the later years of life.

Though the manifestation of cardiovascular disease occurs in middle age and later, it has now been proved that the initiation of cardiovascular disease occurs in childhood and adolescence[20]. The known risk factors of cardiovascular disease such as hypertension, raised blood glucose, raised serum cholesterol, tobacco consumption, high fat diet and obesity start early in childhood and adolescence and then continue into adulthood[20]. Screening and early identification of these risk factors and their progenitors like pre-diabetes and pre-hypertension may go a long way to prevent cardiovascular morbidity and mortality in adults.

The overall prevalence of glucose intolerance among adolescents in South India was reported to be 3.7%[21]. Prevalence of hypertension among children and adolescents in north India was observed to be 9.4%[22].

The rising prevalence of diabetes and hypertension in India, their beginning in the adolescent age group, and the co-occurrence of the two disease entities, is a cause of concern, therefore this study was planned to study the association between hypertension and hyperglycemia in Indian young adults.

MATERIALS AND METHODS

Study design and sample size

It was a cross-sectional study. The minimum sample size required (n = 89) was calculated taking a prevalence of glucose intolerance of 3.7%, as reported in the ORANGE-2 study, with a precision of 4% and a confidence level of 95%[21]. The formula used was, $n = Z_{(1-\alpha/2)}{}^2 pq/d^2$ (where $Z_{(1-\alpha/2)}$ was taken at 95%CI; P = prevalence of obesity, q = 100-p; d = absolute precision). For this study, P = 3.7%; q = 96.3%; d = 4%. Adding a 10% for incomplete answers, the total number came out to be 98. A design effect of 2 was included to minimize any error due to inherent variation in the population. The calculated sample size was multiplied by 2 to obtain the sample size of 196.

Sampling

The study was conducted among students in the Institute of Paramedical Sciences, affiliated to Chatrapati Shahuji Maharaj University, Kanpur. The Institute of Paramedical Sciences provides a course of 4 years in Paramedical Sciences and enrols around 100 students annually. A list of all the students enrolled in the Institute in the first, second and third year was obtained. Systematic random sampling technique was applied to identify the required number of study subjects. Written informed consent was taken from the students and their parents/guardians. In case a student refused to participate in the study, the next consecutive student was included. The data was analyzed for 185 subjects only whose laboratory test results were available. Among the study subjects thus selected, 94 were males and 91 were females, in the age group 17 to 19 years.

Methodology

A standard mercury sphygmomanometer, Diamond Co., Industrial electronics and Allied Products, Pune, Maharashtra, India, was used for recording blood pressure. Blood pressure (BP) was measured on the left arm, in the sitting position, using appropriate size cuffs. Before the measurement was taken, the subject was seated for at least 5 min. Care was taken that the arm muscles were relaxed and the arm was placed at heart level. The cuff was applied to the left upper arm and was inflated until the manometer reading was 30 mmHg above the level at which the radial pulse disappeared, and thereafter the cuff was slowly deflated. The Korotkoff sounds were monitored using a stethoscope applied over the brachial artery. The first (appearance) and the fifth (disappearance) Korotkoff sounds were noted as the systolic and diastolic blood pressure, respectively. Blood pressures were measured twice and their mean was recorded. Subjects were categorized into normotensive, pre-hypertensive and Stage I and Stage II hypertensive based on the blood pressure classification for adolescents for subjects of age 17 years and according to JNC-7 for subjects $\geqslant$ 18 years[19,23]. JNC-7 has classified systolic blood pressure (SBP) < 120 mmHg and a diastolic blood pressure (DBP) < 80 mmHg as normal blood pressure; SBP 120-139 mmHg and/or DBP 80-89 mmHg as pre-hypertension; SBP 140-159 mmHg and/or DBP 90-99 mmHg as Stage I hypertension and SBP $\geqslant$ 160 mmHg and/or DBP $\geqslant$ 100 mmHg as stage II hypertension[19]. For adolescents upto 17 years of age, normal BP was defined as systolic and diastolic blood pressure < 90th percentile, Prehypertension as systolic or diastolic blood pressure 90th percentile to < 95th percentile or blood pressure > 120/80 mmHg to < 95th percentile, Stage 1 Hypertension (HTN) as systolic and/or diastolic blood pressure 95th percentile to 99th percentile plus 5 mmHg and Stage 2 HTN as systolic and/or diastolic blood pressure > 99th percentile plus 5 mmHg[23].

According to American Diabetic Association, subjects were classified as normoglycemic when fasting plasma glucose was less than 100 mg/dL after 8 h fasting, prediabetic when fasting plasma glucose was between 100 and 125 mg/dL and diabetic when fasting plasma glucose was more than

Table 1 Bio-social characteristics of study subjects

Determinant	Total	Male (n = 94)		Female (n = 91)		P value[1]
		n	%	n	%	
Place of residence						
Urban	119	56	47.1	63	53.9	0.17
Rural	66	38	57.6	28	42.4	
Religion						
Hindu	164	84	51.2	80	48.8	0.084
Muslim	15	6	40	9	60	
Sikh	4	4	100	0	0	
Christian	2	0	0	2	100	
Type of family						
Nuclear	100	36	36	64	64	< 0.001[2]
Joint	85	58	68.2	27	31.8	
Physical activity						
Sedentary	69	28	40.6	41	59.4	0.056
Moderate	92	50	54.3	42	45.7	
Heavy	24	16	66.7	8	33.3	
Smoking habit						
Non-smoker	173	82	47.3	91	52.7	0.001[2]
Smoker	12	12	100	0	0	
Alcohol intake						
Non-alcoholic	183	92	50.3	91	49.7	0.162
Alcoholic	2	2	100	0	0	
Eating habit						
Vegetarian	110	52	47.3	58	52.7	0.013[2]
Mixed	75	42	56	33	44	
Diabetic status						
Normoglycemic	124	60	48.4	64	51.6	0.347
Pre-diabetic	61	34	55.7	27	44.3	
Hypertensive status						
Normotensive	165	86	52.1	79	47.9	0.306
Pre-hypertensive	20	8	40	12	60	

[1]Pearson's χ^2 test; [2]P value < 0.05 is significant.

126 mg/dL[17].

Body weight was estimated, using Krup's weighing machine, with a least count of 0.5 kg. The subject was made to stand on the weighing scale, feet around 15 cm apart, and weight distributed on both the legs. Zero setting was done before each measurement. Height was estimated, with the subject standing upright against the wall such that the roof of the external auditory meatus was in line with the lower margin of the orbit. A hard board was placed on the wall, just over the head and height was marked on the wall and measured with a measuring tape with a least count of 0.5 cm. Waist circumference was measured, at the level of the umbilicus, with the subject in the erect position, breathing silently.

Fasting blood samples were drawn on the day subsequent to the interview. A total of 10 mL blood was collected from each subject: 4 mL in EDTA tube and 6 mL in plain tube. The samples were immediately sent to the laboratory in the Department of Biochemistry, Chatrapati Shahuji Maharaj University, Kanpur. The samples were centrifuged without any delay. The samples were analyzed for glucose on the same day. Remaining plasma and serum was aliquoted and stored at -70 deg C. Lipid

Table 2 Co-prevalence of diabetes and hypertension

	Prediabetes		Normoglycemia		Total
	n	%	n	%	
Pre-hypertension	5	25	15	75	20
Normotension	56	33.9	109	66.1	165

estimations were done in batches in serum samples. Standard internal quality control procedures for laboratory were followed. Fasting plasma glucose was estimated using the Enzymatic colorimetric GOD-PAP method, Serum Cholesterol using Enzymatic Colorimetric High Performance CHOD-PAP method, Serum HDL using Enzymatic Colorimetric High Performance CHOD-PAP method, and Serum triglycerides using colorimetric method[24].

Data was compiled using Microsoft Excel and analysed using SPSS 17.0. Pearson's Chi square test was applied to study the difference between categorical variables. Student's t-test was used to analyse the difference between continuous variables. Two-tailed P-value less than 0.05 was considered significant. Pearson's correlation coefficient was applied to determine the association between fasting plasma glucose and systolic and diastolic blood pressure. Multiple linear regression analysis was done to analyse the association of various determinants with fasting plasma glucose.

Statistical analysis

The statistical methods are adequately and appropriately applied to the best of the authors' knowledge.

RESULTS

Data was analyzed for 185 subjects, 94 males and 91 females. Mean age among males was 18.5 ± 1.5 years and among females was 17.9 ± 1.8 years. Among the subjects living in urban area, 47.1% were males whereas among those living in rural areas 57.6% were males (Table 1). Subjects predominantly belonged to Hindu religion. Among those who were sedentary, 40.6% were males, whereas among heavy workers, 66.7% were males. However, there was no statistically significant association between physical activity and gender. Of all the study subjects, 12 (6.4%) were smokers and all were male (100%). The association between smoking and gender was statistically significant.

Among the total study subjects, 61 (32.9%) were pre-diabetic whereas 20 (10.8%) were pre-hypertensive. Five (2.7%) subjects had both pre-diabetes and pre-hypertension. Among the pre-hypertensives, 25% also had pre-diabetes (Table 2). However among the pre-diabetics, 8.2% had pre-hypertension.

The correlation of systolic blood pressure with fasting plasma glucose was not found to be stati-

Table 3 Correlation between fasting plasma glucose and systolic and diastolic blood pressure among study subjects

Fasting plasma glucose	Pearson's correlation coefficient	*P* value[1]
Systolic blood pressure	0.045	0.546
Diastolic blood pressure	0.301	< 0.001[2]

[1]Pearson's Correlation coefficient; [2]*P* value < 0.05 is significant.

stically significant. However, the correlation of diastolic blood pressure with fasting plasma glucose was significant ($P < 0.001$) (Table 3).

Among the normoglycemic subjects, mean BMI was 20.6 ± 42.0 kg/m^2 whereas among the pre-diabetic subjects the BMI was 21.8 ± 3.0 kg/m^2 and the association was found to be significant (Table 4). There was no significant association between the waist circumference, systolic blood pressure and serum HDL of normoglycemic and pre-diabetic subjects. However, the mean diastolic blood pressure of pre-diabetics (82 ± 5 mmHg) was significantly higher than normoglycemics (79 ± 6 mmHg). Mean serum cholesterol, serum triglycerides, and serum VLDL was also higher among pre-diabetic subjects as compared to normoglycemic subjects and the association was found to be significant. Mean serum LDL was also significantly higher in prediabetics (104.1 ± 22.7 mg/dL) than in normoglycemics (92.7 ± 23.6 mg/dL).

Multiple linear regression analysis for the determinants of fasting plasma glucose was done and the adjusted R^2 was 23.5% (Table 5). Waist circumference, systolic blood pressure, serum cholesterol, serum triglycerides, serum HDL, serum VLDL were not significantly associated with fasting plasma glucose. For every 1 mmHg increase in diastolic blood pressure, the fasting plasma glucose was expected to rise by 0.375 mg/dL ($\beta = 0.375$) and this association was found to be significant ($P < 0.05$). Similarly, BMI ($\beta = 0.149$), and serum LDL ($\beta = 0.483$) were also significantly associated with fasting plasma glucose.

Multiple linear regression analysis was done for systolic blood pressure as the outcome variable and the adjusted R^2 was 43.7% (Table 6). Diastolic blood pressure and serum LDL were observed to be significantly associated. Multiple linear regression analysis for diastolic blood pressure as the outcome variable showed an adjusted R^2 of 49.6% (Table 7). BMI ($\beta = 0.219$), fasting plasma glucose ($\beta = 0.247$) and systolic blood pressure ($\beta = 0.510$) were found to be significantly associated.

DISCUSSION

In this study, the overall prevalence of pre-diabetes was 32.9%. In another study from Dhaka, Bangladesh, around 20% subjects aged 11-18 years, with BMI $\geqslant$ 95th percentile for age and sex using CDC growth chart, were reported to have impaired glucose tolerance as detected after two hours oral glucose tolerance test[25]. A study from United States revealed that 21 percent of obese adolescents between 11 and 18 years had impaired glucose tolerance following two hours oral glucose tolerance test[26]. The difference from our study may be due to the criteria used for impaired glucose tolerance as we have considered fasting plasma glucose, whereas the other studies have considered the plasma glucose after a two hours oral glucose tolerance test which may have greater specificity in labelling impaired glucose tolerance. In a study from South India, the prevalence of impaired glucose tolerance was 3.7% in children and adolescents 6-19 years following oral glucose tolerance test[21]. The low prevalence as compared to our study may be due to the large age range of study subjects and the criteria used for impaired glucose tolerance.

In our study, the prevalence of pre-hypertension was 10.8%. The prevalence of pre-hypertension among adolescents from Wardha, in central India, was reported as 10.6%, which was very similar to our results[27]. This was also in concordance with the results of another study from Shimla, in north India wherein the prevalence of prehypertension was found to be 12.3%[28].

The present study revealed that 5 (2.7%) subjects had both pre-diabetes and pre-hypertension. However, the multi-center Screening India's Twin Epidemic (SITE) survey revealed that 20.6% of the study subjects had co-existent diabetes and hypertension[16]. In our study, among the pre-hypertensives, 25% also had pre-diabetes whereas in the SITE study, among 7212 hypertensives, 3227 (44.7%) had diabetes. The present study showed that among the pre-diabetics, 8.2% had pre-hypertension whereas in the SITE study, among 5427 diabetics, 59.5% were hypertensive.These differences may be because only adult subjects more than 18 years were studied in the SITE survey whereas our study included subjects in the 17 to 19 years age group.

Hypertension is responsible for acceleration of the vascular complications of diabetes, including coronary artery disease, renal disease, and retinopathy[29]. The pathophysiology of hypertension occurs at the cellular level in the intima of the arteries, which involves the function of the endothelial cells. Hypertension and diabetes both alter the endothelial cell structure and function. In large and medium size vessels and in the kidney, endothelial dysfunction causes proliferation of vascular smooth muscle cells and vasoconstriction of mesangial cells[29]. These alterations in the smooth muscle cells lead to atherosclerosis and glomerulosclerosis. Similarly, proliferation of retinal capillary endothelial cells causes retinopathy. Therefore, endothelial

Table 4 Determinants of impaired fasting plasma glucose

Determinant	Normoglycemic (n = 124)		Impaired fasting glucose (n = 61)		P value[1]
	Mean	SD	Mean	SD	
BMI	20.6	4.2	21.8	3	0.026[2]
Waist circumference	76	9.3	76.7	20.1	0.794
SBP	121	12	122	8	0.238
DBP	79	6	82	5	0.003[2]
S.Cholesterol	155.9	31.6	174.2	34.5	0.001[2]
S.Triglycerides	128.1	55.9	154.7	55.6	0.002[2]
S.HDL	39.3	8.6	41.4	7.3	0.095
S.LDL	92.7	23.6	104.1	22.7	0.002[2]
S.VLDL	25.6	11.2	32.8	12.3	< 0.001[2]

[1]Student's *t*-test; [2]*P* value < 0.05 is significant. BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein.

Table 5 Multiple linear regression analysis of determinants of fasting plasma glucose

Determinant	Unstandardized coefficients		Standardized β	P value[1]
	β	SE		
(Constant)	24.067	17.964		0.182
Smoking	3.075	8.899	0.023	0.730
BMI	0.530	0.263	0.149	0.046[2]
Waist circumference	0.049	0.070	0.050	0.483
SBP	0.121	0.113	0.094	0.285
DBP	0.844	0.200	0.375	< 0.001[2]
Cholesterol	0.092	0.126	0.224	0.467
Triglycerides	0.008	0.038	0.033	0.830
HDL	0.060	0.154	0.036	0.696
LDL	0.279	0.141	0.483	0.040[2]
VLDL	0.151	0.146	0.132	0.301

[1]Multiple linear regression analysis. R^2 = 48.5%, adjusted R^2 = 23.5%; [2]*P* value < 0.05 is significant. BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein.

Table 6 Multiple linear regression analysis of determinants of systolic blood pressure

Determinant	Unstandardized coefficients		Standardized β	P value
	β	SE		
(Constant)	65.983	10.961		< 0.001
Smoking	1.276	5.939	0.012	0.830
BMI	0.241	0.177	0.087	0.174
Waist circumference	0.057	0.047	0.074	0.225
DBP	0.997	0.118	0.571	< 0.001[2]
Cholesterol	0.018	0.084	0.056	0.831
Triglycerides	0.009	0.025	0.048	0.715
HDL	-0.135	0.103	-0.104	0.188
LDL	0.085	0.095	0.189	0.025[2]
VLDL	0.218	0.096	0.245	0.053
FPG	0.054	0.050	0.069	0.285

[1]Multiple linear regression analysis. R^2 = 66.1%, adjusted R^2 = 47.3%; [2]*P* value < 0.05 is significant. BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein; FPG: Fasting plasma glucose.

cell damage is responsible for the complications of diabetes and this damage is accelerated by co-existing hypertension[29].

Co-occurrence of hypertension in diabetics increases the risk of development of macrovascular and microvascular complications[30,31]. Diabetic

Table 7 Multiple linear regression analysis of determinants of diastolic blood pressure

Determinant	Unstandardized coefficients		Standardized β	*P* value[1]
	β	SE		
(Constant)	21.387	6.314		0.001
Smoking	0.682	3.214	0.012	0.832
BMI	0.347	0.093	0.219	< 0.001[2]
Waist circumference	0.013	0.025	0.030	0.602
Cholesterol	0.053	0.045	0.288	0.249
Triglycerides	0.014	0.014	0.125	0.311
HDL	-0.090	0.055	-0.121	0.105
LDL	0.064	0.051	0.250	0.212
VLDL	0.062	0.053	0.121	0.242
FPG	0.110	0.026	0.247	< 0.001[2]
SBP	0.292	0.035	0.510	< 0.001[2]

[1]Multiple linear regression analysis. R^2 = 70.4%, adjusted R^2 = 49.6%; [2]*P* value < 0.05 is significant. BMI: Body mass index; SBP: Systolic blood pressure; HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein; FPG: Fasting plasma glucose.

individuals with coexisting hypertension have a much higher occurrence of cerebrovascular accidents as compared to diabetics with normal blood pressure[30,32,33]. The risk of peripheral vasculopathy also increases in case of co-existence of hypertension in diabetics[33]. Both hypertension and diabetes lead to coronary artery disease[34]. It has been observed that in hypertensive diabetics, the risk of death due to cardiovascular disease is almost doubled[34]. Hypertension accelerates the progress of diabetic retinopathy and nephropathy[35,36]. Hypertension in diabetics hastens the occurrence of microalbuminuria and the progress of nephropathy after the development of proteinuria[36].

In our study, mean waist circumference, systolic blood pressure and serum HDL did not vary significantly between normoglycemic and pre-diabetic subjects. However, the mean diastolic blood pressure of pre-diabetics (82 ± 5 mmHg) was significantly higher than normoglycemics (79 ± 6 mmHg). Correlation between systolic blood pressure and fasting plasma glucose was not statistically significant. However, the correlation of diastolic blood pressure with fasting plasma glucose was significant ($P < 0.001$).

In the present study, upon multiple linear regression analysis for fasting plasma glucose, BMI (β = 0.149) diastolic blood pressure (β = 0.375) and serum LDL (β = 0.483) were found to be significantly associated. However, in the study from South India, on multiple regression analysis, only family history of diabetes (OR 4.11) and HOMA-IR (insulin resistance assessed by homeostasis model assessment) (OR 11.22) were found to be significant in girls and only HOMA-IR (OR 5.19) was associated with glucose intolerance in boys[21]. Due to financial constraints, HOMA-IR assessment was not included in our study. Upon multiple linear regression for diastolic blood pressure, it was observed that BMI (β = 0.219), fasting plasma glucose (β = 0.247) and systolic blood pressure (β = 0.510) were significantly associated.

The present study reveals that prediabetes and pre-hypertension begin to occur in young adults. It is well known that the prevalence of cardiovascular disease is increasing among Indians, occurring especially at a younger age[12]. Therefore it is imperative that policies and programs be developed for identifying and successfully managing hypertension and diabetes at an early age.

Given the risk associated with co-prevalence of diabetes and hypertension, it is important to identify young adults with pre-diabetes and pre-hypertension who are prone to develop full blown disease as adults, and it is the need of the hour that guidelines be formulated under the National Program for Prevention and Control of Cancer, Diabetes, CVD and Stroke (NPCDCS) for primordial and primary prevention efforts through evidence-based screening and health education initiatives. Health education programs among young adults regarding lifestyle modification to curb diabetes and hypertension in their incipient stage may be considered as a cost-effective public health approach in dealing with the morbidity attributed to consequent cardiovascular diseases.

COMMENTS

Background

As per World Health Organization estimates, globally the number of adults with diabetes will rise from 171 million in 2000 to 366 million in the year 2030. India has been declared as the capital of diabetes because approximately 41 million Indians have diabetes till date and every fifth diabetic in world is an Indian.The global prevalence of raised blood pressure or hypertension in adults aged 25 and over was around 40% in 2008. A meta-analysis of prevalence studies on hypertension in India, from January 2000 to June 2012, revealed a high prevalence of hypertension in the urban (40.8%) as well as rural population (17.9%). The co-prevalence of diabetes and hypertension is strongly associated with cardiovascular disease. Prevalence of cardiovascular disease

is on the rise among Indians, especially at a younger age, therefore early detection and management of hypertension and diabetes may hold the key to reducing cardiovascular mortality in India. Prevalence of glucose intolerance among adolescents in South India was reported to be 3.7%. Prevalence of hypertension among children and adolescents in north India was observed to be 9.4%. The high prevalence of diabetes and hypertension in India with their beginning in the adolescent age group, and the co-occurrence of the two disease entities leading to cardiovascular diseases, is an area of concern. Screening and health education programs regarding lifestyle modification may be considered as a cost-effective public health approach in dealing with the morbidity attributed to cardiovascular diseases. Therefore, a precise estimate of the prevalence of diabetes and hypertension among Indian young adults is required to assess the magnitude of the problem that has to be addressed and to design programs and policies for prevention and control.

Research frontiers

Pre-diabetes and pre-hypertension have a high degree of co-prevalence among Indian young adults and this knowledge will help in shaping primordial and primary level preventive programs for our country.

Innovations and breakthroughs

In India, very few studies are available on the prevalence of diabetes and hypertension among young adults and none have analysed the association between the two co-morbidities. Given the risk associated with co-prevalence of diabetes and hypertension, it is important to estimate their prevalence among Indian young adults to provide evidence-based guidelines for preventive efforts through screening and health education initiatives.

Applications

Very few studies on the prevalence of diabetes and hypertension among young adults are available in India; and this study reveals their co-prevalence in the indigenous population and emphasizes the need to develop a strategy for prevention of these co-morbidities to bring down the consequent cardiovascular morbidity and mortality in India.

Terminology

Regression analysis is a statistical process for estimating the relationships among variables. It includes many techniques for modeling and analyzing several variables, when the focus is on the relationship between a dependent variable and one or more independent variables. More specifically, regression analysis helps one understand how the typical value of the dependent variable changes when any one of the independent variables is varied, while the other independent variables are held fixed. In statistics, linear regression is an approach for modeling the relationship between a scalar dependent variable y and one or more explanatory or independent variables denoted X. The case of one explanatory variable is called simple linear regression. For more than one explanatory variable, the process is called multiple linear regression. The beta (β) regression coefficient is computed to assess the strength of the relationship between each predictor variable and the dependent variable.

Peer review

This a well written report from a useful study.

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Use of steroids for facial nerve paralysis after parotidectomy: A systematic review

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Abstract

AIM: To systematically review the literature to assess the efficacy of corticosteroids in treating post-parotidectomy facial nerve palsy (FNP).

METHODS: We searched the Cochrane library, EMBASE and MEDLINE (from inception to 2014) for studies assessing the use of corticosteroids in post-parotidectomy FNP. Studies were assessed for inclusion and quality. Data was extracted from included studies.

RESULTS: Two randomised controlled trials met the inclusion criteria. One study assessed the use of dexamethasone and the other prednisolone. None of the studies demonstrated a significant difference in the outcome of FNP post-parotidectomy with the use of corticosteroids *vs* no therapy. The majority of FNP post-parotidectomy is transient. Preoperative factors (size of tumour and malignancy), intraoperative factors (extent of parotidectomy and integrity of facial nerve at the end of the operation) are important in determining prognosis of FNP if it does occur.

CONCLUSION: Corticosteroids do not appear to improve FNP prognosis post-parotidectomy. Further studies assessing patients by cohort and with long term follow-up are required to increase scientific evidence.

Key words: Adrenal cortex hormones; Facial paralysis; Parotid diseases; Steroids

Core tip: Parotidectomy is a common operation performed to treat benign and malignant parotid lesions. Facial nerve palsy (FNP) is a well documented complication of parotidectomy that can significantly impair quality of life. Steroids have been proposed as a treatment option for post-parotidectomy FNP. In this systematic review of randomised controlled trials, we found minimal evidence to suggest steroids improve the prognosis of FNP after parotidectomy. However, more trials are required to assess the effectiveness of steroids in specific cohorts of patients.

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INTRODUCTION

Parotid surgery remains a key surgical intervention for the treatment of both benign and malignant parotid tumours. Facial nerve palsy (FNP) is a potential complication that can occur as a consequence of a parotidectomy.

When post-parotidectomy FNP occurs it is usually transient. The incidence of temporary FNP post-parotidectomy has a reported range of 12% to just over 40%[1-6]. Permanent FNP is less common with a reported incidence of 0%-6%[1-5]. Key factors linked to increased risk of postoperative FNP include: the extent of the parotidectomy[1,3,6,7], revision surgery[3,7], proximity of the tumour to the facial nerve[5,7], malignancy[6] and inflammatory conditions (*e.g.*, sialadenitis)[4,5,7].

FNP can significantly affect quality of life[8], leading to distress for the patient[9] in addition to the potential for ocular complications[10]. Reducing the risk of FNP is therefore paramount. Intraoperatively this includes the use of key anatomical landmarks[11] and a facial nerve monitor as an adjunct[12].

As most cases of post-parotidectomy FNP are temporary there is a paucity of evidence assessing interventions to improve recovery of FNP. The use of corticosteroids significantly improves chance of complete recovery of FNP in Bell's palsy, with a reduction in neural oedema of the FN as a postulated mechanism[13]. Although Bell's palsy is a distinct entity to post-parotidectomy FNP, it is thought that corticosteroids could improve FNP prognosis through a similar mechanism[14].

To date there has been no systematic review assessing the efficacy of corticosteroids in ameliorating post-parotidectomy facial nerve paralysis. We sought to assess the effectiveness of corticosteroids versus no treatment in patients with post-parotidectomy FNP.

MATERIALS AND METHODS

Inclusion Criteria for considering studies

Types of studies: Well-designed randomised control trials that compared the use of steroids with no steroids for post-parotidectomy facial nerve paralysis were included.

Types of participants: Patients undergoing parotidectomy (superficial and deep) for benign parotid lesions and malignant parotid lesions.

Types of interventions: We included trials that utilised corticosteroids of any type for post-parotidectomy facial nerve paralysis.

Outcome measures: The primary outcome measure was facial nerve function monitored at increments after parotidectomy. Objective assessment of the facial nerve function is undertaken utilising the House Brackmann scale, and further classified based upon the location of the facial muscle.

Search strategy

We developed a search strategy to identify randomised controlled trials in the following databases: MEDLINE, EMBASE, Cochrane Library and NHS Evidence (from inception until August 2014). Search terms were as follows: "steroids" AND "parotidectomy", "dexamethasone" AND parotidectomy and "prednisolone" AND "parotidectomy". Relevant articles were then selected and their references screened to identify further articles.

Data collection and analysis

Study selection: Two review authors (KV and IB) assessed abstracts for relevant articles and the full text of these was obtained. The review authors (KV and IB) independently assessed these full-text articles, and any disagreements on inclusion were resolved by discussion with a third author (ND).

Data extraction: Two review authors (KV and IB) extracted data from included studies with standardised forms. Data extracted included: authors, year of publication, participants (sample size, demographics, type and extent of parotid lesion, type of parotid surgery performed, *etc.*), intervention (type of steroid used and duration) and results (primary and secondary outcome measures, effect size, statistical significance, adverse effects).

Quality assessment: To assess the risk of bias in included studies we utilised the Cochrane risk of bias tool[15].

Statistical analysis

Due to a variation in the type of corticosteroids utilised in included studies (with regards to potency and duration of action) and variations in the protocol of administration, a meta-analysis was not appropriate and thus not carried out.

RESULTS

Description of studies

The original search produced 46 abstracts, from which 11 duplicate studies were excluded. The remaining 35 articles were screened for relevance. 33 articles were rejected as they did not meet the inclusion criteria. A total of two papers met the

eligibility criteria[14,16].

Reasons for exclusion included the study having no relevance to the research question (n = 32) and not being a randomised controlled trial (n = 1). Table 1 summarises included studies.

Interventions

Of the two included studies the interventions used to assess corticosteroid efficacy in post-parotidectomy FNP were dexamethasone[14] and prednisolone[16].

Dexamethasone was administered in two doses intravenously (stratified based on extent of parotid surgery with superficial receiving 0.51 mg/kg and deep receiving 1.41 mg/kg) administered at 8 and 16 h postoperatively[14].

Prednisolone was administered orally as a 10-d reducing course (50 mg/d for 5 d, 30 mg/d for 3 d and 10 mg/d for 2 d)[16].

The control groups received intravenous saline[14] and oral lactose[16] administered with the same protocol as their respective interventions.

Participants

The participant cohort varied slightly between both trials. One included all patients undergoing parotid surgery[14], whilst the other only included those who developed a postoperative FNP[15]. Parotid operations ranged from superficial to total (or deep) parotidectomy in both trials and both studies included only adult patients[14,16].

Outcomes and follow-up

Both trials assessed facial nerve function through clinical assessment. One assessed four facial nerve muscle groups and graded percentage function[14]. The other utilised the House Brackmann scale[17] [grading facial from 1 (normal function) to 6 (total paralysis)][16]. Duration of postoperative follow-up ranged from 6 mo[16] to 12 mo[14].

Risk of bias in included studies

Both included studies were assessed for quality focusing particularly on: randomisation methods, concealment of allocation, effectiveness of blinding, follow up and attrition rates, comparability of groups at baseline and adherence to treatment.

Neither trial described the methods of randomisation, but both had adequate allocation concealment and effective blinding from both the patients and clinicians[14,16].

Both trials had some limitations with regards to comparability of control and intervention groups at baseline. Neither trial made reference to comparability with regards to tumour factors [type of tumour (malignant or benign) or size of the tumour][14,16]. With regards to use of a single surgeon allowing prevention of technique confounding the results, one trial utilised more than one surgeon (including surgeons in training)[14], whilst the other did not specify if a single surgeon undertook the operations[16].

One trial made no reference to extent of compliance and adherence to treatment[15], whilst the other administered treatment intravenously in the immediate postoperative period allowing total compliance[14].

Effects of interventions

Dexamethasone: A variety of analyses were undertaken due to the varying doses within the treatment protocol. Overall, no therapeutic advantage was found with the use of dexamethasone[14]. A higher dose of dexamethasone conferred no functional advantage[14]. Interestingly, early postoperative facial nerve function was better in the placebo group (overall and in superficial and deep parotidectomy cohorts) although not statistically significant; median time to complete recovery of facial nerve function was shorter in the placebo group (150 d in the dexamethasone group *vs* 60 d in the control group)[14].

Prednisolone: There was minimal difference in extent of recovery from FNP in prednisolone *vs* placebo treated patients at 1, 3 and 6 mo ($P > 0.10$)[16]. Eighty-four percent of patients with FNP had full recovery at 3 mo, increasing to 98% by 6 mo[16]. One patient that had a total parotidectomy had a permanent FNP that persisted at 18 mo[16].

Adverse effects: No adverse effects from short term dexamethasone therapy were noted[14]. One patient was found to have "minor symptoms" from the use of prednisolone (although the precise symptoms were not stated)[16].

DISCUSSION

Overall, there appears to be no benefit conferred by corticosteroids for FNP recovery post-parotidectomy. However, this systematic review demonstrates that there is a paucity of evidence assessing the use of corticosteroids in treatment of FNP post-parotidectomy.

Two corticosteroid preparations have been assessed in RCTs with slightly varying mechanisms and durations of actions[14,16]. Prednisolone has mixed glucocorticoid and mineralocorticoid properties, whilst dexamethasone only has glucocorticoid properties (albeit much more potent than prednisolone) and a longer duration of action[18]. This variation in the mechanisms of action allowed different dosing regimens in the two included trials. Despite the variation in types of steroids and dosing regimens, there was no evidence to demonstrate an improved chance of full recovery nor improve recovery

Table 1 Characteristics of included studies

Roh and Park[16]	
Methods	Randomised controlled trial
Participants	Patients undergoing parotidectomy (superficial, partial, total) ± neck dissection 44 patients Exclusion: 1 Direct FN invasion of FN requiring FN sacrifice and reconstruction 2 Incidental cutting of the facial nerve
Interventions	Started day 1 or day 2 postoperatively Reducing dose of oral prednisolone (50 mg/d for 5 d, 30 mg/d for 3 d and 10 mg/d for 2 d) Placebo group received lactose with similarly formulated doses
Outcomes	House Brackmann grading of FN by two blinded experts Assessed postoperatively: immediately, 1 wk, 1 mo, 3 mo and 6 mo
Results	Overall recovery times from FNP: At 3 mo: 84% had fully recovery At 6 mo: 98% had full recovery Prednisolone *vs* placebo recovery at 1, 3 and 6 mo (minimal difference) ($P > 0.10$)
Notes	One patient was lost to follow-up and excluded from the analysis (prednisolone group)
Risk of Bias	
Method of randomisation	Not specified
Allocation concealment	Adequate
Other confounding factors	Groups comparable demographically and extent of postoperatively FNP, however tumour size, type or type of parotid surgery not compared in between intervention and placebo groups
Lee *et al*[14]	
Methods	Randomised controlled trial
Participants	Patients undergoing superficial or total parotidectomy 49 patients Exclusion criteria: Diabetes, age < 18, peptic ulcer disease, previous adverse reaction to steroids and any other contraindication to steroids Prior parotid surgery, anticipated section of FN and pre-existing FNP
Interventions	Two doses of dexamethasone (0.51 or 1.41 mg/kg) depending on type of surgery (superficial or total parotidectomy respectively) at 8 and 16 h postoperatively Placebo group received saline at the same intervals
Outcomes	Facial nerve function in the four major regions was assessed (frontal, orbital, midface, upper lip and lower lip) at a percentage 0-100 depending on extent of function Assessed postoperatively: immediately and every month for 12 mo (or until facial nerve function returned to normal)
Results	Average early postoperative facial nerve function: All patients ($n = 49$): 75.4% Overall: Dexamethasone (69.5%) *vs* placebo (81.3%) ($P = 0.239$) Dose of dexamethasone: High (63.9%) *vs* low (74.7%) ($P = 0.118$) Type of surgery: Superficial ($P = 0.637$) and deep ($P = 0.465$) Time to full recovery of facial nerve (median): Placebo (60 d) *vs* Dexamethasone (150 d) (no *P* value stated)
Notes	As intervention administered intravenously, total compliance can be ensured
Risk of Bias	
Method of randomisation	Not specified
Allocation concealment	Adequate
Other confounding factors	Initial power calculation required 120 patients, however a nationwide shortage of the intervention drug (dexamethasone) allowed only 52 patients to be enrolled in the trial No comparison of the type of parotid lesion excised within the trial groups (*i.e.*, malignant or benign and tumour size) Operations were conducted by more than one surgeon (including junior residents)

times[14,16].

The use of corticosteroids is thought to reduce neural oedema, a proposed mechanism for their excellent efficacy in treating Bell's Palsy[13]. One postulated mechanism of FNP in parotidectomy is stretch of the FN[4,19] leading to neural degeneration[20]. This may explain the lack of efficacy of corticosteroids in treating FNP post-parotidectomy.

There is compelling evidence to suggest that most cases of FNP post-parotidectomy are transient. Moreover, the risk of FNP is associated with a plethora of tumour and intraoperative factors (deeper parotidectomy[1,3,6,7] revision surgery[3,7], the facial nerve being near the tumour[5,7], malignancy[6] and inflammatory conditions[4,5,7]).

Prevention of FNP in parotidectomy is therefore largely linked to operative techniques, including the use of key anatomical landmarks to identify the FN[11]. The use of a facial nerve monitor has been suggested as an adjunct to help prevent postoperative FNP, with reasonable efficacy demonstrated[12,21]. Unfortunately, if FNP does occur its extent may dictate likelihood of full recovery, with a FNP preventing closure of the eyes being a predictor of permanent dysfunction[22].

Nonetheless, when FNP does occur it can significantly reduce quality of life[8]. It is therefore

key to ascertain interventions that can improve time to recovery. Unfortunately, both RCTs included in this trial did not account for the variety of tumour factors that can increase of postoperative FNP. The need for a high quality RCT assessing the use of corticosteroids in specific cohorts of patients is highlighted (particularly low risk patients, *e.g.*, patients with benign parotid tumours undergoing superficial parotidectomy, in whom the perceived risk of FNP should be lower).

Few adverse effects were reported by both randomised controlled trials, highlighting the relative safety of their use.

Limitations

The randomised trials included in this study had some limitations. Most importantly, statistical assessment of confounding factors in control and treatment groups did not specifically assess tumour factors[14,16]. Moreover, one trial did not achieve the power calculation sample size[14], limiting interpretation of its statistical analysis. The methods of randomisation were also unclear in both trials[14,16].

Implications for practice

Based upon current best evidence the use of corticosteroids to ameliorate postoperative FNP cannot be recommended. It is likely that preoperative and intraoperative factors play a more important role in the risk of permanent FNP. Moreover, the majority of cases of FNP are likely to recover, an important factor to consider in preoperative counselling of patients.

Implications for research

Given the extensive effect of FNP on quality of life, it is in the interest of patients to ascertain methods of improving recovery times. Future research should focus on assessing the cohort of patients in whom permanent FNP is more likely, allowing better preoperative counselling. Moreover, well-designed randomised controlled trials that assess the use of corticosteroids in more statistically comparable groups (*i.e.*, with regards to the type of parotid operation and tumour factors), that will allow assessment of specific cohorts of patients in whom corticosteroids may provide benefit.

COMMENTS

Background

Facial nerve palsy (FNP) is a potential complication that can occur after parotidectomy. FNP can be temporary or permanent, and can significantly affect quality of life. Corticosteroids have been proposed as a treatment for post-parotidectomy FNP. A systematic review of clinical trials is needed to provide scientific evidence for the efficacy of the use of corticosteroids for post-parotidectomy FNP.

Research frontiers

Parotidectomy, facial nerve palsy.

Innovations and breakthroughs

Both studies in this systematic review demonstrated no evidence that corticosteroids improve the prognosis of FNP after parotidectomy. Preoperative factors including the size of tumour and presence of malignancy, as well as intraoperative factors including the extent of parotidectomy (superficial or deep) and facial nerve integrity at the end of the operation are key in determining prognosis of FNP when it occurs.

Applications

There is no convincing evidence to propose the routine use of corticosteroids for post-parotidectomy FNP. Further clinical trials are needed to assess the efficacy of corticosteroids in ameliorating FNP in specific cohorts of patients.

Terminology

Parotidectomy is a commonly performed operation for the treatment of both benign and malignant parotid gland pathology. The facial nerve is at risk during parotidectomy.

Peer review

This study is well conducted and written.

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CASE REPORT

Complete remission of primary hepatic lymphoma in a patient with human immunodeficiency virus

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Abstract

Diffuse large B cell primary hepatic lymphoma is a rare disease with limited available information regarding treatment strategy. Although the liver contains lymphoid tissue and is an important site for lymphocytes activation, primary hepatic lymphoma is rare. Host factors make the liver a poor environment for malignant lymphoma development. Its coexistence with human immunodeficiency virus (HIV) infection increases morbidity and mortality risks. Additionally, jaundice increases chances of developing adverse effects from chemotherapy. Here, we report a case of diffuse large B cell primary hepatic lymphoma in a 32-year-old HIV positive man. Due to elevated liver enzyme levels and jaundice, the patient was initially treated with an R-DHAP regimen, which was replaced with an R-CHOP regimen. Restaging images with a positron emission tomography scan after the latest chemotherapy cycle confirmed remission. This is the first report of complete remission of primary hepatic diffuse large B cell lymphoma in an HIV positive patient in the English literature.

Key words: Primary hepatic lymphoma; Diffuse B cell lymphoma; Human immunodeficiency virus; R-DHAP; R-CHOP

Core tip: There are limited reports related to successful management of primary hepatic lymphoma in human immunodeficiency virus (HIV) patients. This case report is not only considered as the first report of complete remission of primary hepatic diffuse large B cell lymphoma in an HIV positive patient in the English literature, but also describes the use of R-DHAP as an induction regimen in the setting of significant impaired liver function and severe immunocompromised status. The use of R-DHAP as an induction regimen in management of primary hepatic lymphoma in HIV patients was never reported.

Widjaja D, AlShelleh M, Daniel M, Skaradinskiy Y. Complete remission of primary hepatic lymphoma in a patient with human immunodeficiency virus. *World J Clin Cases* 2015; 3(2): 186-190 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i2/186.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i2.186

INTRODUCTION

Primary hepatic lymphoma (PHL) is a rare disease associated with immunodeficiency diseases and chronic viral hepatitis. From 1981 to 2003, only 358 cases of primary hepatic lymphoma were reported[1]. Data surrounding disease managements in patients with human immunodeficiency virus (HIV) infection is lacking. Here, we present a case of an HIV positive man whose PHL subsided into complete remission after chemotherapy.

CASE REPORT

A 32-year-old man with no known significant chronic medical problems was admitted to the hospital due to severe right upper quadrant abdominal pain, fever, night sweats, and unintentional weight loss. There was no history of recent heavy alcohol consumption. The patient appeared jaundiced and had a tender and firm hepatomegaly with a liver span of 19 cm. The lymph node was not enlarged. An abdominal ultrasound revealed multiple small hypoechoic lesions throughout the liver, common bile duct of 3.2 mm and normal gallbladder without gallstones. A computed tomography (CT) scan of the abdomen and pelvis with intravenous contrast revealed hepatomegaly with multiple small low attenuation nodules throughout the liver parenchyma, normal common bile duct and small ascites in the pelvis (Figure 1). Magnetic resonance imaging of the abdomen with intravenous contrast confirmed CT scan findings. All imaging studies showed no extrahepatic lymphadenopathies. A liver biopsy of lesions revealed diffuse large B cell lymphoma with non-specific lobular hepatitis (Figure 2). Immunohistochemical stains of the liver specimen revealed $CD20^+$, $CD79^+$, $CD79a^+$, $CD4^-$, and $CD3^-$ cells (Figure 3). The patient also tested positive for HIV infection. Tests for hepatitis B and C were negative. Additional tests results are shown in Table 1.

The patient was diagnosed with Stage 1BE primary liver large B cell lymphoma, and started on anti retroviral therapy along with chemotherapy during in-patient care. The initial anti retroviral medications were efavirenz, emtricitabine, and tenofovir. On the 7th day of the treatment, efavirenz was changed to raltegravir due to the presence of G190A mutation on HIV genotyping testing which confers resistance to non-nucleoside reverse transcriptase inhibitor mutation. Eight cycles of chemotherapy were administered together with anti retroviral therapy. In view of elevated liver enzymes and jaundice, chemotherapy with a platinum based regimen (R-DHAP) was initiated. The regimen of this first cycle consisted of 1.5 mg/kg of oral prednisone, 375 mg/m^2 of rituximab, 100 mg/m^2 of cisplatin, and 2000 mg/m^2 of cytarabine. As the co-administration of cisplatin and tenofovir might have increased his risk of toxicity to the kidney proximal tubule, serum creatinine was monitored closely. His serum creatinine levels were always less than 1 mg/dL and the calculated creatinine clearance was maintained at the level of 77 mL/min per 1.73 m^2. Nine days after starting the first chemotherapy cycle, he developed significant thrombocytopenia (nadir of 10000 cells/uL) and neutropenia (nadir of 300/uL). When platelet count was 10000/uL, the patient had an episode of epistaxis which was controlled after platelets transfusion. He did not develop fever during the episode of neutropenia. Filgrastim was given for 3 d when neutropenia was 300/uL. Upon the completion of first cycle of chemotherapy, the patient remained afebrile and became less jaundiced. Chemotherapy normalized liver enzymes and bilirubin (Table 1). Next, a CHOP regimen containing cyclophosphamide (600 mg/m^2), adriamycin (50 mg/m^2), vincristine (1.1 mg/m^2), and prednisone was administered. Rituximab (375 mg/m^2) was added to the CHOP regimen to start a third cycle of chemotherapy administered every 3 wk. As there was no known significant drug-drug interaction between the R-CHOP regimen and the anti retroviral regimen (tenofovir, emtricitabine and raltegravir), all medications were given according to the standard doses. After the second cycle, the patient remained anicteric with a body weight improvement of 5 kg from baseline. A CT with positron emission tomography (PET) scan performed after the 4th cycle of chemotherapy showed that the liver had reduced in size from 19.5 cm (prior to treatment) to 16.5 cm without evidence of hypermetabolic foci in the neck, chest, abdomen, or pelvis. Re-staging images with CT-PET after the 6th cycle revealed normal uptake within liver, spleen, adrenal glands, renal cortices, and the collecting system. A CT-PET scan at 5 and 11 mo after the last cycle confirmed remission (Figure 4). He is still in remission 19 mo after the treatment. During the chemotherapy, the CD4 count had improved and HIV viral loads were always undetectable (Table 1).

DISCUSSION

Fifty thousand incident cases of lymphoid neoplasms and 19000 related deaths occurred in the United States in 2005[2]. Diffuse large B-cell lymphoma is the most common non-Hodgkin lymphoma subtype and accounts for approximately 23% of all cases[3]. Chronic hepatitis C and hepatitis B and autoimmune diseases increase the risk of PHL[4,5]. Although the liver contains lymphoid tissue and is an important site for lymphocytes activation[6], PHL is rare. Host factors make the liver a poor environment for malignant lymphoma development[4,7].

Table 1 Laboratory tests prior to the chemotherapy cycles and six months post chemotherapy

	Prior to the 1st	Prior to the 2nd	Prior to the 3rd	Prior to the 4th	Prior to the 5th	Prior to the 6th	Prior to the 7th	Prior to the 8th	6 mo post chemotherapy
Hgb (g/dL)	11.9	11.3	11.1	11.3	12	12.5	11.8	12.3	14.6
Platelet count (× 10^3 /uL)	107	95	107	34	169	132	60	78	70
WBC (× 10^3/uL)	5.9	10.6	1.9	11.9	3.7	4.1	3.3	3.5	5.9
Serum albumin (g/dL)	3.5	4.5	4.4	4.5	4.5	4.5	4.6	4.1	4.9
Serum AST (unit/L)	529	38	26	26	31	23	31	26	24
Serum ALT (unit/L)	270	43	37	30	28	27	39	31	30
Serum alkaline phosphatase (unit/L)	1686	442	146	210	1025	1586	1454	190	117
Serum GGT (unit/L)	872	-	-	-	-	149	-	-	-
Serum LDH (unit/L)	1838	313	-	331	326	263	-	148	124
Total bilirubin (mg/dL)	9.7	0.9	0.6	0.5	0.2	0.2	0.4	0.3	0.7
CD4 lymphocyte count (/mm^3)	155	651	-	265	-	-	173	-	729
HIV viral load (copies/mL)	485127	81	-	< 75	-	-	< 75	-	< 75

HIV: Human immunodeficiency virus.

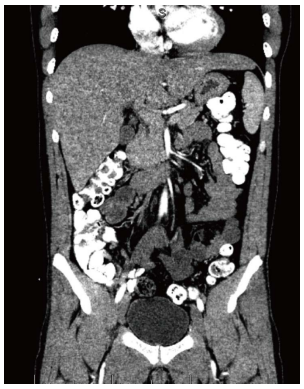

Figure 1 Computed tomography abdomen and pelvis prior to chemotherapy showing multiple small low attenuation nodules throughout the entire liver parenchyma.

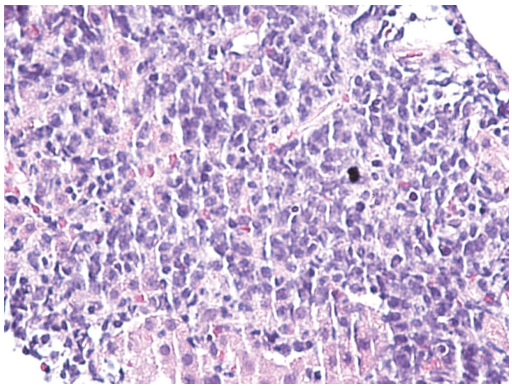

Figure 2 Liver biopsy showing diffuse large B-cell lymphomatous infiltrate.

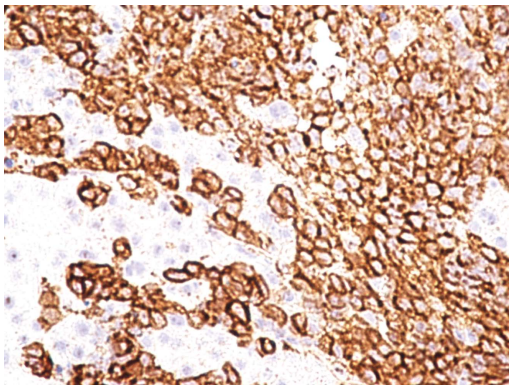

Figure 3 Immunohistochemical stain of liver specimen showing the lymphoma cells are strongly immunoreactive to CD 20.

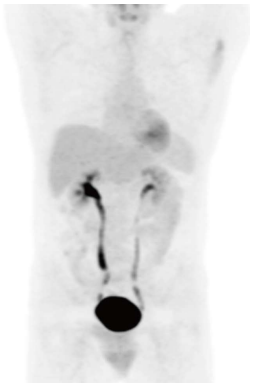

Figure 4 Maximum intensity projection of positron emission tomography/computed tomography scan at 11 mo after the last cycle of chemotherapy showing no hypermetabolic lesions in the liver.

Criteria for establishing the diagnosis of PHL include clinical, histopathological, and radiological findings. Lei *et al*[8] listed the following criteria to establish diagnosis: (1) signs and symptoms related to liver involvement at presentation including laboratory abnormalities and right upper quadrant mass or pain; (2) absence of both palpable adenopathy at presentation and radiologically evident distant lymphadenopathy; and (3) absence of leukemia on a peripheral smear.

A report from Lei[9] showed that among 90 patients with PHL, the most frequent presenting symptoms were upper abdominal pain or discomfort (56%), weight loss (40%), and fever (22%), which

occasionally mimic pyogenic liver abscess. Other symptoms included fatigue (13%), nausea and vomiting (12%), anorexia (8%), night sweats (8%), hemorrhagic diathesis (2%), dysphagia (2%), and rarely, immune thrombocytopenic purpura (1%) and hepatic encephalopathy (1%). In this particular report, 10% of patients were diagnosed incidentally without preceding symptoms. Physical examinations frequently revealed a modest hepatomegaly (82%), but jaundice infrequently presented only as a late manifestation of disease progression or related to underlying cirrhosis (13%)[9]. Lactate dehydrogenase and alkaline phosphatase are sometimes elevated[10]. Alpha-fetoprotein and carcinoembryonic antigen are often normal[4,10]. Radiologically, the presentation of multiple well-defined liver masses is more common than single lesions or diffuse hepatic involvement[11]. On ultrasound imaging, PHL is usually hypoechoic relative to a normal liver. CT scans of PHL usually show hypoattenuating lesions[4,11]. FDG-PET studies are extremely useful in evaluating treatment responses in PHL[12]. Histologically, primary diffuse large B cell lymphoma shows demarcated tumors with no intrasinusoidal invasion, atrophic reactive lymph follicles, and tests positive for the following antigens: CD10, Bcl2, Bcl6, MUM1, and CD25[5].

The United States National Comprehensive Cancer Network recommends managing diffuse large B cell lymphoma with rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone (R-CHOP protocol)[13]. Other regimens include CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high dose methotrexate alternating with ifosfamide, etoposide, high dose cytarabine with or without rituximab), dose adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), dose adjusted EPOCH with rituximab, CDE (cyclophosphosphamide, doxorubicin and etoposide), CDE with rituximab, and hyperCVAD (cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with high-dose methotrexate, and cytarabine with or without rituximab)[13]. Serrano-Navarro *et al*[1] highlighted a patient with PHL who developed complete response to R-CHOP treatment regimen, remaining symptom free for more than two years. Others also reported complete response to R-CHOP in non-HIV infected patients with diffuse large B cell type primary hepatic lymphoma[14-17]. Besides the R-CHOP regimen, a regimen contains rituximab, dexamethasone, high dose cytarabine, and cisplatin (R-DHAP) has been used as a salvage therapy in patients with CD20+ diffuse large B cell lymphoma who develop first time relapse or failure with first line therapy[18]. In addition, R-DHAP, given as remission induction chemotherapy, improved progression free survival and failure free survival in patients with aggressive CD20+ non-Hodgkin lymphomas[19].

In an article in French literature, Walter *et al*[17] reported the only favorable response to an R-CHOP treatment regimen for diffuse large B cell type PHL in an HIV infected patient. The case report described a 34-year-old man whose abdomen CT scan showed multiple liver masses, the largest of which was 14 cm. After four cycles of R-CHOP treatment, the masses markedly regressed with only a residual 5 cm hypodense lesion. Our patient developed complete remission without residual hepatic lesions. To our knowledge, this is the first report of PHL treatment in an AIDS patient that resulted in a complete response. After initial treatment with an R-DHAP regimen, serum levels of liver enzymes and bilirubin, very important in preventing the prolonged half-life of cyclophosphamide and neurotoxicity of vincristine[20], decreased. This may have facilitated further remission from the R-CHOP regimen. Further studies in HIV positive patients may confirm these findings.

COMMENTS

Case characteristics

A 32-year-old man with recent history of unintentional weight loss presented with right upper quadrant pain.

Clinical diagnosis

Patient appeared jaundiced and had a tender and firm hepatomegaly with a liver span of 19 cm.

Differential diagnosis

Acute ascending cholangitis, alcoholic hepatitis and infiltrative liver disease.

Laboratory diagnosis

WBC 5.9 K/μL; ALT 270 unit/L; AST 529 unit/L; serum alkaline phosphatase 1686 unit/L; serum GGT 872 unit/L; serum total bilirubin 9.7 mg/dL; human immunodeficiency virus (HIV) viral load 485 K copies/mL.

Imaging diagnosis

Computed tomography (CT) scan of the abdomen and pelvis with intravenous contrast revealed hepatomegaly with multiple small low attenuation nodules throughout the liver parenchyma, normal common bile duct and small ascites in the pelvis. Magnetic resonance imaging confirmed CT scan findings.

Pathological diagnosis

A liver biopsy of lesions revealed diffuse large B cell lymphoma with non-specific lobular hepatitis. Immunohistochemical stains of the liver specimen revealed $CD20^+$, $CD79^+$, $CD79a^+$, $CD4^-$, and $CD3^-$ cells.

Treatment

Eight cycles of chemotherapy were administered. R-DHAP regimen was given in the first cycle. CHOP regimen was started in the second cycle. R-CHOP regimen was started in the third cycle.

Related reports

In view of elevated liver enzymes and jaundice, chemotherapy with a platinum based regimen (R-DHAP) was given in the first cycle of chemotherapy. Upon completion of the first cycle, the patient became less jaundiced.

Term explanation

Cluster of differentiation (CD) of immunohistochemical stain is referred to a group of antibodies recognizing an antigen. For example, the T-helper cell antigen is called CD4 antigen and the various antibodies reacting with this antigen are called CD4 antibodies.

Experiences and lessons

This case report is not only considered as the first report of complete remission of primary hepatic diffuse large B cell lymphoma in an HIV positive patient in the English literature, but also describes the use of R-DHAP as an induction regimen in the setting of significant impaired liver function and severe

immunocompromised status. The use of R-DHAP as an induction regimen in management of primary hepatic lymphoma in HIV patients was never been reported.

Peer review

This case report well written overall.

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CASE REPORT

Survival in unresectable sinonasal undifferentiated carcinoma treated with concurrent intra-arterial cisplatin and radiation

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Abstract

We report the successful use of RADPLAT to treat a patient with an unresectable T4N0 sinonasal undifferentiated carcinoma. This patient received 4 cycles of weekly intra-arterial cisplatin together with thiosulfate infusion with concurrent radiation therapy. Radiation therapy was given in 28 daily fractions to 54 Gy using intensity-modulated radiation therapy followed by a hypofractionated stereotactic boost of 3 fractions to 13 Gy to a total dose of 67 Gy in 31 fractions to the nasal sinus and bilateral neck. Intra-arterial cisplatin was administered using a bilateral approach due to the midline site of this tumor. Within days of the first intra-arterial cisplatin, there was an obvious decrease in tumor size. She has been followed with magnetic resonance imaging and positron emission tomography, and remains disease-free 47 mo post-treatment. Centers with expertise in intra-arterial chemotherapy could consider the RADPLAT approach for patients with unresectable sinonasal undifferentiated carcinoma.

Key words: Sinonasal undifferentiated carcinoma; Radiation; Intra-arterial cisplatin; Survival; RADPLAT

Core tip: Our patient with unresectable sinonasal undifferentiated carcinoma has enjoyed nearly 4 years disease-free survival after concurrent intra-arterial cisplatin and radiation.

Noticewala SS, Mell LK, Olson SE, Read W. Survival in unresectable sinonasal undifferentiated carcinoma treated with concurrent intra-arterial cisplatin and radiation. *World J Clin Cases* 2015; 3(2): 191-195 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i2/191.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i2.191

INTRODUCTION

Sinonasal undifferentiated carcinoma (SNUC) is a

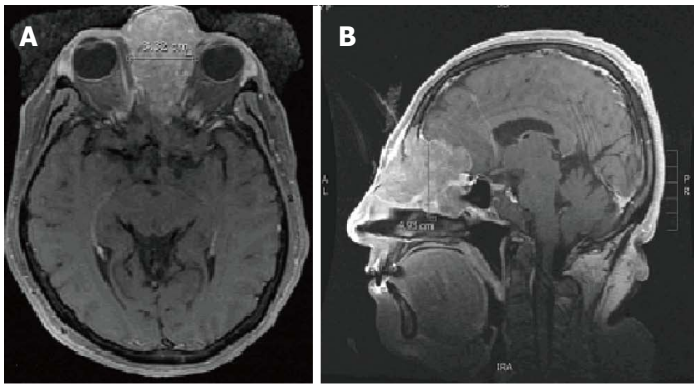

Figure 1 T1 magnetic resonance imaging of sinonasal undifferentiated carcinoma neoplasm prior to treatment. A: Axial T1 magnetic resonance imaging (MRI) and B: Sagittal T1 MRI show an avidly enhancing mass centered in the left ethmoid air cells with extension into the left frontal sinus with adjacent retained fluid and maxillary sinus with erosion of the medial orbital walls bilaterally, left greater than right. The majority of the ethmoid air cells are replaced by the neoplasm. Extension through the cribriform plate is noted with involvement of the left olfactory lobe, predominantly along the gyrus rectus. There is extensive surrounding edema in the left frontal lobe, extending back to the frontal horn of the left lateral ventricle.

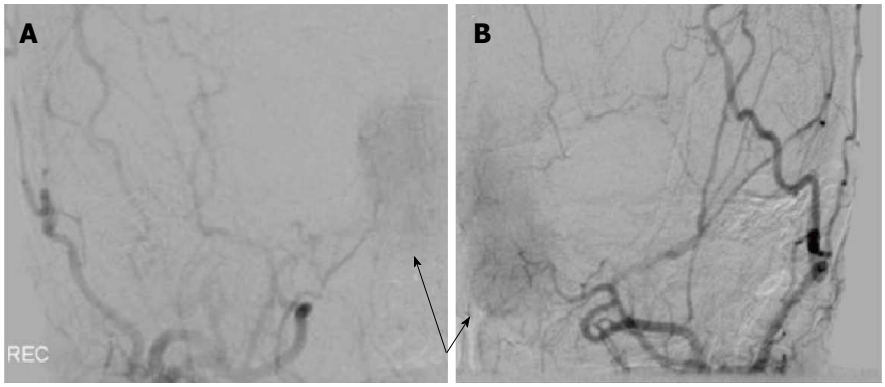

Figure 2 Right and left external carotid artery angiography injections. A: Right and B: Left external carotid angiographic injections demonstrate the tumor blush (arrows) at the first chemo treatment.

rare and highly aggressive neoplasm of the nasal cavity and paranasal sinuses[1]. Thus far, there have been less than 200 reported cases of SNUC[2]. SNUC has a poor prognosis and high mortality with one meta-analysis of 167 cases finding that the disease-free survival was only 26.3%[2]. Currently, there is not a standard treatment of care for SNUC. Treatment for SNUC typically involves a multimodal approach involving surgery (if feasible) and radiation therapy (RT) with concurrent chemotherapy[2-4]. A phase Ⅱ clinical trial in inoperable stage Ⅳ head and neck cancer previously found that the RADPLAT protocol (radiation and intra-arterial cisplatin) achieved an initial tumor response in 91% of patients with 1 and 2 years locoregional control of 82% and 69%, respectively[5]. Here, we describe the successful use of RADPLAT to treat a patient with an unresectable T4N0 SNUC.

CASE REPORT

A 60-year-old woman presented with nasal congestion and a prominence on the left side of her nose. Computed tomography (CT) revealed a tumor arising from the ethmoid sinus extending through the cribriform plate and into the anterior cranial fossa without metastasis to the chest and neck. Magnetic resonance imaging (MRI) of the face showed edema in the left frontal lobe, interpreted as suspicious for brain invasion (Figure 1). Biopsy revealed large pleomorphic tumor cells with a high nuclear to cytoplasm ratio, prominent nucleoli and focal areas of necrosis. Immunohistochemistry was positive for pancytokeratin and CD56 and weakly positive for chromogranin. She was diagnosed with a T4N0 SNUC. Since the tumor was deemed unresectable due to brain involvement, the RADPLAT protocol was chosen in hopes of maximizing her chance for local control. She received concurrent 4 cycles of weekly intra-arterial (IA) cisplatin at 150 mg/m^2, administered as a divided dose through left and right-sided feeding arteries for this midline tumor (Figure 2). With the IA cisplatin, she received intravenous (IV) thiosulfate bolus followed by thiosulfate infusion. Radiation therapy was given in 28 daily fractions to 54 Gy using intensity-modulated radiation therapy (IMRT) followed by a hypofractionated stereotactic boost of 3 fractions to 13 Gy to a total dose of 67 Gy in 31 fractions to the nasal sinus and bilateral neck. The biologically effective dose for the radiation treatment is equivalent to 82 Gy_{10} and 117 Gy_3.

Response to RADPLAT

After the first administration of intra-arterial cisplatin, there was an obvious and rapid decrease in tumor size, suggesting response to the chemotherapy. There was marked tumor size reduction after the final cycle of chemotherapy (Figure 3). She tolerated treatment well, with no toxicity from chemotherapy and expected acute sequelae including grade 2 mucositis, grade 2 dermatitis, and grade 1 conjunctivitis. Collagenase and polysporin powder with Xeroform

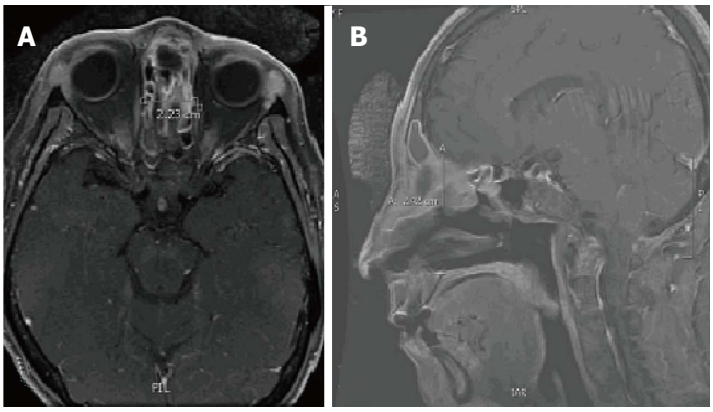

Figure 3 T1 Magnetic resonance imaging after completing fourth dose of chemotherapy. A: Axial T1 magnetic resonance imaging (MRI) and B: Sagittal T1 MRI show the mass had decreased in size as compared to the prior to treatment MRI. The mediolateral dimension is 2.23 cm which is decreased in size from the prior examination at which time it measured 3.32 cm. The AP appears to have decreased in size to 2.42 cm as compared to 4.93 cm on the prior MRI. There appears to be residual enhancing tissue in the right posterior ethmoid. The intracranial enhancement and edema within the inferior left frontal lobe is significantly decreased.

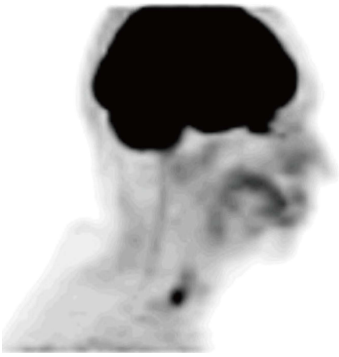

Figure 4 Positron emission tomography performed at four months post-treatment. The Positron emission tomography shows no definite or abnormal fluorodeoxyglucose (FDG) activity to suggest the presence of metabolically active tumor with special attention to the ethmoidal region adjacent to the cribriform plate. Linear FDG activity in the distal esophagus likely represents esophagitis.

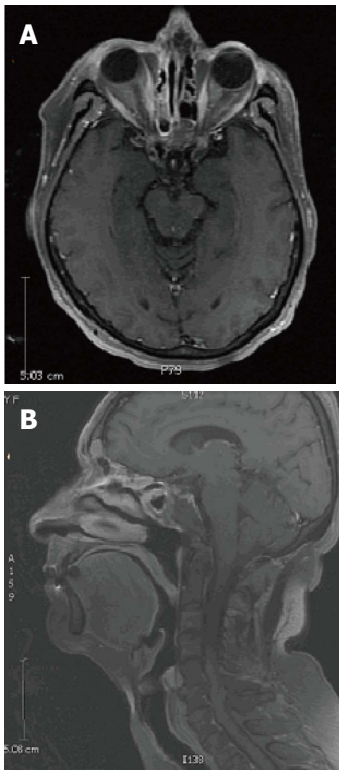

Figure 5 T1 magnetic resonance imaging 30 mo post-treatment. A: Axial T1 magnetic resonance imaging (MRI) and B: Sagittal T1 MRI show no evidence of recurrent disease. There is a decrease of the previously noted inflammatory changes in the sinuses. There is retained fluid in the bilateral frontal and left sphenoid sinuses, without bony destruction or expansion.

was used to treat radiation conjunctivitis. Positron emission tomography (PET)/CT four months post-treatment showed persistent soft tissue density in the anterior ethmoid sinuses, without fluorodeoxyglucose (FDG) uptake (Figure 4). Thirty months post treatment, MRI revealed no evidence of recurrent disease and a decrease in the previously noted inflammatory changes in the sinuses (Figure 5). The patient continues to be disease-free 47 mo post-treatment.

DISCUSSION

This case report presents long survival in a patient with an inoperable SNUC treated with concurrent intra-arterial cisplatin and radiation therapy.

Similar to our case, 84% to 92% of patients with SNUC present with T4 disease[4,6-9]. In many cases, the cancer can extend beyond the nasal and paranasal sinuses to involve the orbit and/or brain[5].

Currently there is no standard of care available for SNUC. Unresectable SNUC is generally treated with radiation or concurrent chemoradiation. Because the interventional radiologists and treating oncologists were familiar with RADPLAT, we opted to utilize this protocol in hopes of maximizing local control. In 213 patients with stage Ⅲ-Ⅳ head and neck squamous cell cancer (SCC) treated with RADPLAT, Robbins *et al*[10] reported a 5 year overall survival of 38.8% and locoregional control of 74.3%[10]. Similarly, Rabbani *et al*[11] reported locoregional control in 78% and four year overall survival in 57% in a study of 35 patients with stage Ⅲ head and neck cancer. Homma *et al*[12] evaluated the efficacy of RADPLAT for untreated advanced cancers (T3, T4a, and T4b) of the nasal and paranasal sinuses in 47 patients. During the median follow-up period of 4.6 years, the 5-year local progression-free survival rate was 78.4% for all patients[12]. Furthermore, the 5-year overall survival rate was 69.3% for all patients[12].

This study indicates that the RADPLAT protocol can not only effectively treat SCC of the head and neck, but also provide locoregional control and long-term survival in cancers specific to the paranasal and nasal sinuses.

The RADPLAT protocol involves intra-arterial infusion of cisplatin with intra-venous systemic neutralization using thiosulfate. The rapid infusion of cisplatin enables high doses of the drug to directly reach the tumor bed while the thiosulfate infusion prevents the systemic toxicity of large doses of cisplatin[10,11]. The cytotoxic effects of cisplatin are potentiated by radiation[13]. This effect was first demonstrated in murine models of tumors[14]. Studies have found that tumor resistance to cisplatin can occur within 2-4 cycles[15,16]. However, resistance can be overcome by increasing doses of cisplatin as demonstrated by *in vitro* and *in vivo* studies[17,18]. Elevated doses are not well-tolerated in patients because they can lead to undesirable side-effects such as neurotoxicity, nephrotoxicity, mucositis, and other systemic effects[19]. To circumvent the high-dose toxicity of the cisplatin, the intra-arterial infusion of cisplatin with concomitant thiosulfate enables high doses of cisplatin to reach the tumor bed without systemic toxicity. With the RADPLAT protocol, it is possible to deliver doses 10 times higher than can be delivered intravenously[17,18].

Many studies highlight the importance of surgery in improving survival in patients with SNUC[2,6,20,21]. In our case, brain involvement of the patient's SNUC made her a poor candidate for surgery, so she was treated with radical chemoradiotherapy to the primary site and bilateral neck. Elective neck irradiation for node negative SNUC is important for regional control[3,20]. Chemoradiation has previously been shown to be a viable treatment option for advanced SNUC. In one study, the 2-year progression-free survival and overall survival were 43% and 64%, respectively, with three cycles of platinum and 5-fluorouracil followed by radiation with two cycles of concurrent platinum, suggesting that induction chemotherapy followed by concurrent chemoradiation is effective[22]. This study found that among patients with SNUC treated to 50-60 Gy, all 4 patients treated with at least 60 Gy were alive without local progression at last follow-up[22]. Another study found that all patients that achieved cause-specific survival when treated with doses greater than 62.5 Gy[3]. Thus, doses of at least 60-70 Gy_2 to the primary site are recommended, if feasible.

In conclusion, our patient was effectively treated with RADPLAT with minimal toxicity and lasting disease control for nearly 4 years. Centers with expertise in intra-arterial chemotherapy could consider this modality for patients with unresectable SNUC.

COMMENTS

Case characteristics

A 60-year-old woman presented with nasal congestion and a prominence on the left side of her nose is diagnosed with unresectable T4N0 sinonasal undifferentiated carcinoma (SNUC).

Clinical diagnosis

Dullness to percussion and decrease breath sounds over the upper lobe of the right lung.

Differential diagnosis

Esthesioneuroblastoma, rhabdomyosarcoma, squamous cell carcinoma, adenocarcinoma, adenoid cystic carcinoma, lymphoma, melanoma, other soft tissue sarcoma.

Laboratory diagnosis

Labs were drawn but were found to be unremarkable.

Imaging diagnosis

Computed tomography revealed a tumor arising from the ethmoid sinus extending through the cribriform plate and into the anterior cranial fossa without metastasis to the chest and neck. Magnetic resonance imaging of the face showed edema in the left frontal lobe, extending back to the left lateral ventricle.

Pathological diagnosis

Biopsy of the mass revealed large pleomorphic tumor cells with a high nuclear to cytoplasm ratio and prominent nucleoli and focal areas of necrosis. Immunohistochemistry was positive for pancytokeratin and CD56 and weakly positive for chromogranin.

Treatment

The patient was treated with RADPLAT (concurrent intra-arterial cisplatin with simultaneous thiosulfate and radiation therapy).

Related reports

Sinonansal undifferentiated carcinoma is difficult to treat and there is currently no standard treatment protocol.

Term explanation

The RADPLAT protocol involves intra-arterial infusion of cisplatin with intra-venous systemic neutralization using thiosulfate and concurrent radiation therapy. The rapid infusion of the cisplatin enables high doses of the drug to directly reach the tumor bed while the thiosulfate infusion prevents the systemic toxicity of large doses of cisplatin.

Experiences and lessons

This case report represents long survival in a patient with an unresectable T4N0 SNUC using RADPLAT. Centers with expertise in intra-arterial chemotherapy could consider this modality for patients with unresectable SNUC.

Peer Review

These data are thorough and convincing.

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CASE REPORT

Sweet syndrome and differentiation syndrome in a patient with acute promyelocytic leukemia

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Author contributions: Solano-López G contributed to manuscript writing and patients data collection; Llamas-Velasco M contributed to main idea, patients data collection; Concha-Garzón MJ contributed to patients data collection; Daudén E contributed to supervision.

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Abstract

The differentiation syndrome is an inflammatory reaction with increased capillary permeability that occurs in up to 25% of patients with acute promyelocytic leukemia treated with all-trans retinoic acid. A 50-year-old man with acute promyelocytic leukemia underwent chemotherapy with idarubicin and all-trans retinoic acid. On day +21 the patient developed pruritic prepatelar papules as well as several 10 mm subcutaneous nodules in both thighs accompanied by persistent fever. On the day +25 the patient presented with bilateral pulmonary crackles, infiltrates in the right lower lobe and severe hypotension which required dopamine infusion. Biopsy of one of the thighs nodules was performed. A Sweet syndrome associated to a differentiation syndrome was suspected. All-trans retinoic acid therapy was discontinued and dexamethasone was administered. In 48 h the patient showed remission of the fever and the infiltrates and the skin lesions acquired a residual aspect. It is debatable whether these two syndromes are distinct entities with common mechanisms or whether they are poles of the same spectrum. Dermatologists and hematologists must be aware of these two syndromes and its pathophysiologic association.

Key words: Differentiation syndrome; Sweet syndrome; Acute promyelocytic leukemia; All-trans retinoic acid

Core tip: It is debatable whether the differentiation syndrome and the sweet syndrome are distinct syndromes with common mechanisms or whether they are poles of the same spectrum. We believe that there may be more cases of differentiation presenting with skin sweet syndrome lesions, which are underdiagnosed, overshadowed by the critical state of these patients. Dermatologists and hematologists must be aware of these two syndromes and its pathophysiologic association. It is very likely that these two specialties are staring the same phenomenon from two different points of view.

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INTRODUCTION

All-trans retinoic acid (ATRA) therapy induces the differentiation of the myelogenous leukemic cells in acute promyelocytic leukemia (APL). The differentiation syndrome (DS) is an inflammatory reaction with increased capillary permeability that occurs in up to 25% of patients with APL treated with ATRA. It is characterized by respiratory distress, fever, pulmonary infiltrates, pleuropericardic effusions, renal failure and hypotension, with a mortality of up to 30% without treatment[1]. The association of sweet syndrome (SS) and DS has been exceptionally described in the literature.

CASE REPORT

A 50-year-old man presented with pancytopenia on a routinal analysis. A bone marrow (BM) aspirate showed 73% of blasts; homogeneous medium to large cells with visible nucleoli in most cases and clasmatosis. Auer rods were also seen. The red series was decreased without megakaryocytes. The BM biopsy showed that the hematopoietic parenchyma was replaced by a proliferation of myeloid cells showing a monomorphic appearance. The neoplastic cells were positive for myeloperoxidase and CD117 and negative for CD34, TdT and Glycophorin. Thirty percent of BM cells were positive for PML-RARa by fluorescence *in situ* hybridization (FISH). Diagnosed of APL the patient underwent chemotherapy with idarubicin 12 mg/m^2 and ATRA 45 mg/m^2. On day +21 of ATRA therapy, the patient developed pruritic erythematous 3-5 mm prepatelar papules as well as several 10 mm subcutaneous nodules in both thighs along with persistent fever (Figure 1). On day +25, the patient presented with bilateral pulmonary crackles, infiltrates in the right lower lobe and severe hypotension which required dopamine infusion. No features of disseminated vascular coagulation were present. The patient did not gain or lose weight and no renal or hepatic dysfunction was observed. Empirical antibiotic and antifungical treatment was started. A cutaneous biopsy of one papule showed moderate edema in the papillary dermis with perivascular infiltrates consisting predominantly of confluent neutrophils, without vasculitis or involvement of the adipose tissue (Figure 2). Blood, urine and biopsy cultures were negative. Skin lesions occurred along with the neutrophil count recovery and the disappearance of the promyelocytes in the BM smears. Based on the data, a diagnosis of SS associated with DS was made. ATRA therapy was discontinued and dexamethasone 10 mg every 12 h was administered. In 48 h the patient showed remission of the fever and the pulmonary infiltrates and skin lesions cleared. On day +29, a new BM aspiration FISH study did not show the PML-RARa translocation.

Haematologists reintroduced ATRA as maintenance therapy for the APL along with corticosteroids without new recurrences.

DISCUSSION

Cases of drug-induced SS associated with ATRA has been exceptionally described in the literature. Although systemic manifestations in SS are uncommon, there are cases of biopsy proven pulmonary involvement[2-4].

As far as we are concerned, there are only 2 cases of SS associated with DS in patients with APL (Table 1)[2,5].

It is debatable whether the DS and the SS are distinct syndromes with common mechanisms or whether they are poles of the same spectrum. They share common features such as fever, infiltration of neutrophils and improvement with steroid therapy. One of the differences between these two syndromes is that in most cases of SS, the involvement is limited to the skin while the main difference is the capillary leakage in the DS which is produced by the cytokine storm released by the promyelocytes as they mature. ATRA induces the differentiation of myelogenous leukemic cells into mature myeloid cells conferring them functional properties with modification of their migratory capability.

We know that these two syndromes are caused by ATRA therapy but we cannot rule out the possibility that they can be the sides of the same phenomenon with common mechanisms. For some authors, the SS and the DS are different inflammatory reactions with common mechanisms induced by ATRA therapy[6] while Ueno *et al*[7] thought that the SS due to ATRA therapy could represent a partial form of the DS.

We believe that there may be more cases of DS presenting with skin SS lesions which are underdiagnosed, overshadowed by the critical state of these patients. Dermatologists and hematologists must be aware of these two syndromes and its pathophysiologic association. It is very likely that these two specialties are staring the same phenomenon from two different points of view.

COMMENTS

Case characteristics

A 50-year-old man with acute promyelocytic leukemia presented with erythematous prepatelar papules as well as several subcutaneous nodules in both thighs along with persistent fever, pulmonary crackles and hypotension.

Clinical diagnosis

Sweet syndrome lesions and systemic symptoms in a patient who underwent chemotherapy with idarubicin and all-trans retinoic acid (ATRA).

Differential diagnosis

Sepsis, drug reaction.

Table 1 Cases of sweet syndrome associated with differentiation syndrome in patients with acute promyelocytic leukemia treated with all-trans retinoic acid

Ref.	Age(yr)/sex	Cutaneous location	Biopsy	Onset of skin lesions after ATRA induction therapy (d)	Onset of the DS after ATRA induction therapy (d)	DS signs and symptoms	Steroid response	Time until improvement
Takada *et al*[5]	49/F	Arms	Yes	18	28	Respiratory distress	Yes	24 h
Astudillo *et al*[2]	46/M	Trunk, arms, lower extremities	Yes	6	uk	Weight gain	Yes	Unknown
This case	50/M	Trunk lower extremities	Yes	21	25	Respiratory distress Hypotension	Yes	48 h

DS: Differentiation syndrome; ATRA: All-trans retinoic acid; M: Male; F: Female.

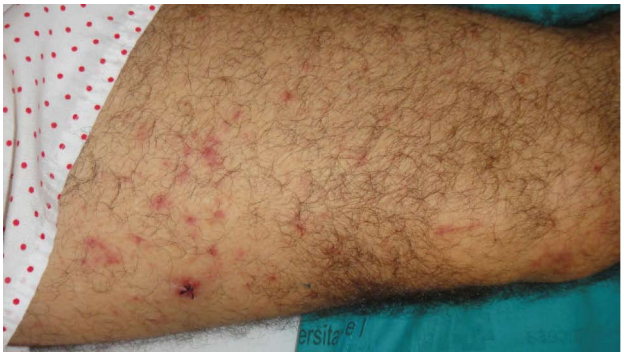

Figure 1 Papules and nodules appeared on day +21 of all-trans retinoic acid therapy.

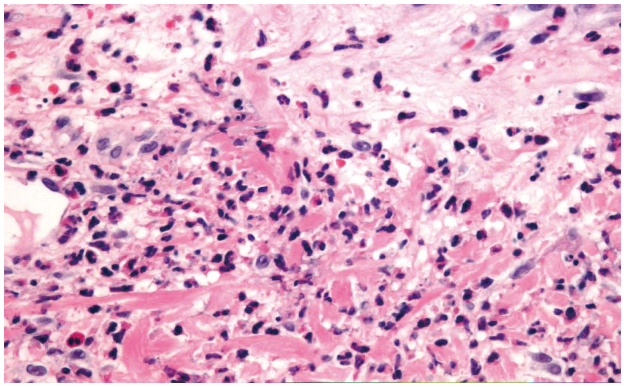

Figure 2 Infiltrates consisting predominantly of neutrophils, without vasculitis (HE, × 20).

Laboratory diagnosis

Blood, urine and biopsy cultures were negative.

Imaging diagnosis

Pulmonary infiltrates in the right lower lobe on a chest radiography.

Pathological diagnosis

A biopsy of a papule showed moderate edema in the dermis with perivascular infiltrates consisting predominantly of confluent neutrophils, without vasculitis or involvement of the adipose tissue.

Treatment

Dopamine infusión, empirical antibiotics, ATRA therapy discontinued and dexamethasone 10 mg every 12 h.

Related reports

As far as the author are concerned, there are only 2 cases of Sweet syndrome associated with differentiation syndrome in patients with acute promyelocytic leukemia.

Term explanation

Sweet syndrome is an inflammatory neutrophilic skin condition characterized by a sterile infiltrate of normal polymorphonuclear leukocytes.

Experiences and lessons

The authors believe that there may be more cases of differentiation syndrome presenting with skin sweet syndrome lesions which are underdiagnosed, overshadowed by the critical state of these patients.

Peer review

In the submitted manuscript the authors described a rare disorder–a drug-induced sweet syndrome associated with ATRA therapy for a patient with acute promyelocytic leukemia (APL). The association of sweet syndrome and ATRA-induced differentiation syndrome is rarely observed in APL. The case in this report is well-described, along with relevant lab results.

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CASE REPORT

Gingival unit transfer using in the Miller Ⅲ recession defect treatment

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Author contributions: Kuru B designed the report; Kuru B performed the surgery; Yıldırım S collected the patient's clinical data and wrote the paper.

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Abstract

The most significant factor for the success in soft tissue grafts is the synergistic relation between vascular configuration and involved tissues. In the soft tissue graft procedures, site specific donor tissue is assumed to have improved potential for function and aesthetic survive at recipient sites. On a clinical level, using site specific gingival unit graft that placed on traditionally prepared recipient site, results in predictable root coverage. In this case report the clinical effectiveness of gingival unit transfer (GUT) technique performed on Miller Ⅲ recession was presented and a similar recession case treated with free gingival graft (FGG) technique for comparison. Probing depth, recession depth, keratinized tissue width and clinical attachment level clinical parameters were measured at baseline and postoperative 8 mo. Percentage of defect coverage was evaluated at postoperative 8 mo. Creeping attachment was assessed at postoperative 1, 3, 6 and 8 mo. The GUT revealed better defect coverage and creeping attachment results than the FGG in the treatment of Miller Ⅲ defects.

Key words: Autografting; Gingiva; Gingival recession; Tooth root; Transplants

Core tip: On a clinical level, using site specific vascular configuration gingival unit graft for donor tissue that placed on traditionally prepared recipient site, results in predictable defect coverage. This report was to evaluate effectiveness of gingival unit transfer technique in comparison with free gingival graft technique on clinical parameters in the Miller Ⅲ recessions treatment.

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INTRODUCTION

Gingival recession is the denudation of root surfaces as a result of the relocation of the gingival margin apical to the cement-enamel junction (CEJ)[1] that causes root hypersensitivity and aesthetic problems[2].

Recession defects can be treated with numerous surgical procedures such as free gingival grafts[3], connective tissue grafts[4], acellular dermal matrix grafts[5], various pedicle flaps[6,7], combinations of

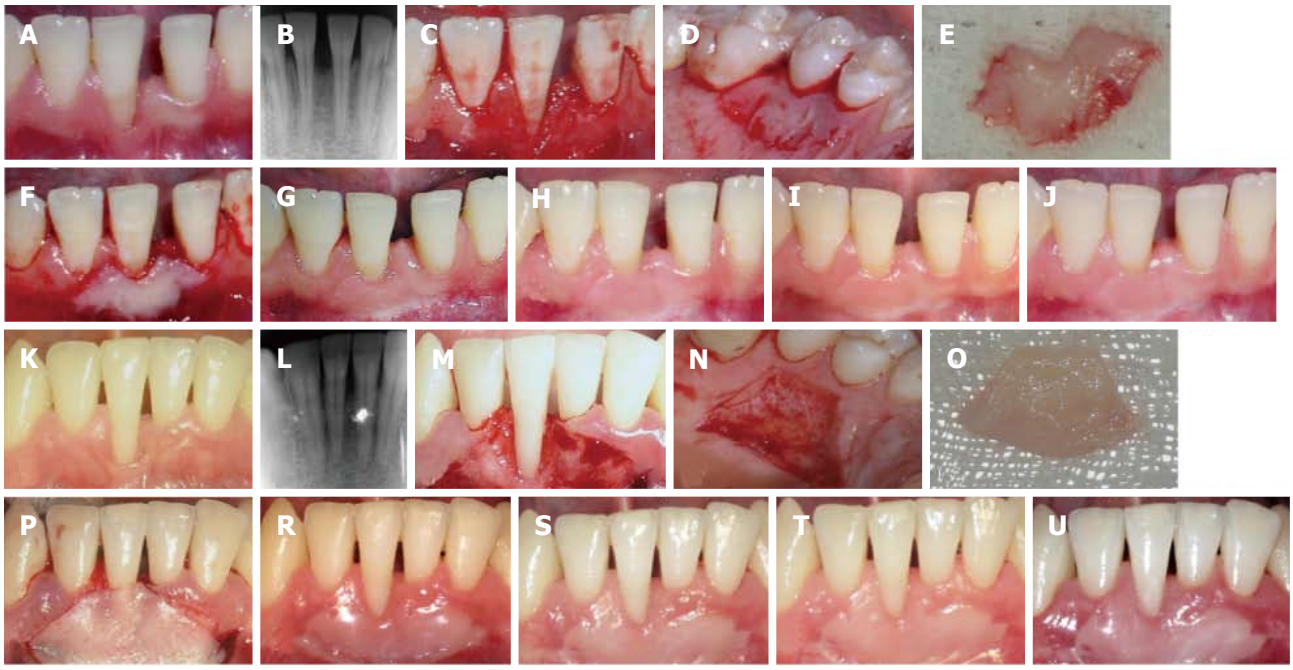

Figure 1 Surgical procedures and follow-ups in treatment with gingival unit transfer and free gingival graft. Surgical procedures and follow-ups in treatment with gingival unit transfer: (A: Initial clinical appearance; B: Radiographic appearance; C: Recipient site; D: Donor site; E: Gingival unit graft; F: Gingival unit graft in place; G: 1 mo after surgery; H: 3 mo after surgery; I: 6 mo after surgery; J: 8 mo after surgery); surgical procedures and follow-ups in treatment with free gingival graft: (K: Initial clinical appearance; L: Radiographic appearance; M: Recipient site; N: Donor site; O: Free gingival graft; P: Free gingival graft in place; R: 1 mo after surgery; S: 3 mo after surgery; T: 6 mo after surgery; U: 8 mo after surgery).

these pedicle flaps and graft techniques[8,9] and guided tissue regeneration[10]. The literature review presents different rates of success and predictability with these surgical procedures[11-13]. Nevertheless, additional clinical studies are needed to define the issues that are in a relation with the predictable and successful results[12].

The synergistic relation between vascular configuration and related tissues is one of the major factors for the success in soft tissue grafts[14,15]. Gingival tissue has complex and unique vascularity[16]. Supracrestal part of gingiva, as well as the donor tissue, is naturally created and specifically designed to function and survive above avascular denude root surfaces[14] in the soft tissue grafts procedures[17]. Gingival unit (GU) graft with site specific vascular supply placed on traditionally prepared recipient area may have capacity for survival on root surfaces and results in predictable root coverage[18].

Most clinical studies about root surface coverage have focalized on Miller Ⅰ-Ⅱ recession treatment[19]. Defect coverage by using gingival unit transfer (GUT) on Miller Ⅰ-Ⅱ recession defects revealed successful results in a previous clinical study[18]. However, there is a lack of success and ability to provide root coverage in Miller Ⅲ recession defects, because of interproximal bone and soft tissue loss[20]. There are different anatomical characteristics when compared with Miller Ⅰ-Ⅱ recession defects, as if prominent and avascular root surfaces, decreased periosteal bed and occasionally deep periodontal pocket depths[21].

The purpose of this case report is to present the clinical results of two cases of Miller Ⅲ localized recessions treated by using GUT and free gingival graft (FGG).

CASE REPORT

In April 2009, a 25-year-old woman (case Ⅰ) and 21-year-old man (case Ⅱ) with single Miller Ⅲ recession defects on mandibular right central incisor were applied to the Periodontology Department of Marmara University (Figure 1A, B, K and L). Case Ⅰ had complaints about aesthetics and tooth loss whereas case Ⅱ about hypersensitivity. Patients were non-smokers, did not have any medical problems and there were no contraindications for periodontal surgery. After clinical examination, oral hygiene motivation and mechanical periodontal treatment were performed.

Recession depth (RD) was recorded from CEJ to margin of the gingiva, probing depth (PD) was recorded from margin of the gingiva to the bottom of the pocket, clinical attachment level (CAL) was recorded from CEJ to bottom of the pocket, keratinized tissue width (KTW) was recorded from the margin of the gingiva to mucogingival junction, at baseline and postoperative 8 mo with a manual probe (PCP UNC-15, Hu-Friedy, Chicago, IL.). Only RD parameter was measured at 1, 3 and 6 mo for the evaluation of soft tissue creeping coronally.

One clinician (BK) performed surgical procedures

Table 1 Clinical parameters at baseline (0 d) and 8 mo

Parameters	Case Ⅰ gingival unit graft technique			Case Ⅱ free gingival graft technique		
	0 d	8 mo	Gain	0 d	8 mo	Gain
Recession depth (mm)	3	0.5	2.5	4	2	2
Probing depth (midbuccal) (mm)	1	1	0	2	1.5	0.5
Clinical attachment level (mm)	4	1.5	2.5	6	3.5	2.5
Keratinized tissue width (mm)	2	7	5	1.5	6	4.5
Defect closure (%)		83			50	

and another clinician (SY) evaluated clinical measurements. Local anesthesia was made and then in both cases, the recipient site was prepared by two vertical beveled incisions that extending apically to adjacent teeth, 3 to 4 mm across to the mucogingival line, and the surfaces of interdental papillae was removed (Figure 1A, C, K and M)[14]. The incisions were divergent therefore the recipient site was trapezoidal. At the mucogingival line, vertical incisions were connected by a horizontal incision. A partial thickness dissection was made apical to the alveolar mucosa. The epithelial surfaces within these incisions were deepithelized. The base of the recipient site was ⩾ 5 mm apical to the apical part of the exposed portion of the root surface. The root planning was made in the exposed portion of the root surface with hand instruments. Then irrigated with saline[18].

In case Ⅰ, the GU graft was harvested from the palatal part of the premolar area (Figure 1D) including the marginal gingival tissue and the papillae. In case Ⅱ, the donor FGG was conventionally dissected from the palate aspect of the premolar area, but ⩾ 2 mm apical from the margin of the gingiva (Figure 1N)[18]. In both cases, thickness of grafts were about 1 mm[22]. Then the grafts were sutured at the level to the CEJ (Figure 1E, F, O and P), and compressed for 2 min[18]. The periodontal dressing was applied to the donor sites for closing the wound. After 1 wk, the dressing and sutures were removed.

At the postsurgical care for infection control, the patients were advised rinse twice daily with 0.2% chlorhexidine solution for 3 wk, avoid brushing and hard chewing. After that, a gentle coronally directed brushing in the surgical area was recommended. During the first 2 mo recall appointments were scheduled every second week, and then patients were called once a month for the postoperative following period[18].

At postoperative period in both patients clinical healing in both the recipient and donor sites was complete and no complications were observed. Pre (0 d) and postsurgical (8 mo) clinical parameters are shown in Table 1. At 8 mo, 2.5 mm defect coverage with a PD of 1 mm, CAL gain of 2.5 mm and KTW gain of 5 mm was observed in case Ⅰ grafted with a GUT. Two millimetre defect coverage with a PD of 1.5 mm, CAL gain of 2.5 mm and KTW gain of 4.5 mm was observed in case Ⅱ grafted with FGG (Table 1). Percentage of defect closure were 83% and 50% in cases Ⅰ and Ⅱ, respectively. The creeping attachment level in case Ⅰ was 1.5 mm between 1 and 8 mo period (Table 2). The margin of the GU graft was moved coronally, and an acceptable colour and configuration harmony with adjacent gingival tissues was seen (Figure 1G, H, I and J). In case Ⅱ, there was no color harmony with the adjacent tissue and 1 mm of creeping was detected at the same follow-up period (Figure 1R, S, T and U) (Table 2).

DISCUSSION

GUT technique, using GU graft as a donor tissue with site specific vascular supply, was evaluated in treatment of a single Miller Ⅲ gingival recession case. GUT is a modification of FGG with the difference of including marginal gingiva and papillae in the conventional palatal tissue graft that vascular supply matches intimately with the recipient site[14,18]. After 8 mo in this case, RD reduction and defect coverage were found in favor of GU graft compared to FGG.

This is the first case reporting the use of GUT technique in the Miller Ⅲ localized gingival recession treatment. There are no clinical studies or case reports with which to compare our clinical outcomes. There is one case report in which gingival unit was used as a FGG[14] and a randomized clinical trial evaluating GUT in comparison with FGG in the Miller Ⅰ-Ⅱ recession defects treatment[18]. In this case report, the GU graft performed in the Miller Ⅲ recession defect treatment, 2.5 mm of RD reduction; 83% defect coverage together with gains in CAL and keratinized tissue (KT) were reported. The reduction in recession was in accordance with the attachment gain. The mean defect coverage was 50% in the FGG case, presenting an obvious difference from the GUT case.

According to our clinical outcomes, GUT resulted in almost indistinguishable texture and colour with neighbouring soft tissues. Creeping defines the postoperative movement of marginal gingiva coronally[23]. Allen[14] presented equivalent results in his case report that the marginal position of the

Table 2 Recession reduction in 1-3, 3-6, 6-8, and 1-8 mo periods

Recession reduction (mm)	Case I	Case II
1-3 mo	0	0.5
3-6 mo	0.5	0
6-8 mo	1	0.5
1-8 mo	1.5	1

GU graft is more coronal than the neighbouring gingival tissue at 3 mo. Creeping has been detected in several clinical studies[24-27]. With an average of 1 mm, creeping can be seen within 1-12 mo after FGG in narrow recessions[25,26]. However, after 8 mo, the coronal ascent of gingival margins in case Ⅰ, treated with a GUT (1.5 mm) was higher than in case Ⅱ (1 mm). The unique vascular supply of GU graft is believed to be of importance for this difference[18]. The present outcomes support the usefulness of GUT for suitable root coverage in aesthetic areas. Although FGG has lost its popularity for aesthetic area[28,29], it may be still the gold standard surgical technique to increased KT[30] especially when it is modified with the inclusion of marginal and papillary gingival tissue.

The GU donor site healed uneventfully. No unacceptable attachment loss or recession were detected at the premolar site where the GU graft was harvested from in case Ⅰ after postoperative 8 mo. Inevitable recession at donor site were reported in laterally positioned flap procedure[6]. This does not possible for GUT procedure. Harvesting donor graft with marginal gingiva is easy, less invasive. Any harmful results can be prevented with cautious manipulation. Before harvesting the GU graft, the depth of gingival sulcus at palatal donor premolar area was measured. Donor tissue was harvested carefully not to cause any attachment loss. If some injury had happened at the attachment, new attachment apparatus would have been developed quickly[31].

In conclusion, the GUT technique performed on case Ⅰ can be successfully used for the Miller Ⅲ recession defect treatment.

COMMENTS

Case characteristics

Twenty-five (female) and 20-year-old (male) patients with Miller Class Ⅲ localized gingival recession defects on mandibular anterior teeth.

Clinical diagnosis

Miller Class Ⅲ recession defect on mandibular anterior teeth.

Treatment

One patient was treated with gingival unit transfer whereas the other with free gingival graft technique.

Term explanation

Gingival unit graft is masticatory palatal tissue involving marginal gingival and papillary tissue.

Experiences and lessons

Surgical treatment of Miller Ⅲ gingival recessions are more challenging, due to loss of interproximal bone and soft tissues. This case report represents the effectiveness of gingival unit transfer technique in comparison with free gingival graft technique on clinical parameters in the treatment of Miller Ⅲ gingival recession.

Peer review

This is an interesting case report.

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Is Takotsubo syndrome in patients receiving chemotherapy drug-specific?

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Abstract

In commenting on a case report of a 55-year-old man who suffered Takotsubo syndrome (TTS), in the setting of receiving chemotherapy with cytarabine and daunorubicin for acute myeloid leukemia, the author expresses his views that TTS in the setting of chemotherapy for malignancies may not be chemotherapeutic drug-specific (like in the chemotherapeutic drug induced-cardiomyopathy), but may be due to the emotional and physical stresses resulting from the realization of having diagnosed with a malignancy, and the diagnostic testing, and therapeutic management which follows.

Key words: Daunorubicin; Radiotherapy; Cardiotoxicity; Takotsubo syndrome; Malignancies; Chemotherapy; Cytarabine; Anthracyclines; Cardiomyopathy; Autonomic sympathetic Nervous system.

Core tip: Is Takotsubo syndrome, in time proximity to chemotherapy, due to the specific chemotherapeutic agent?

Madias JE. Is Takotsubo syndrome in patients receiving chemotherapy drug-specific? *World J Clin Cases* 2015; 3(2): 204-205 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i2/204.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i2.204

TO THE EDITOR

The interesting report by Goel *et al*[1], published in the October, 2014 issue of the Journal, about the 55-year-old man who suffered Takotsubo syndrome (TTS), in the setting of receiving chemotherapy with cytarabine and daunorubicin for acute myeloid leukemia, is well documented and discussed; however it makes one wonder whether we are on the right track in terms of attributing causation of TTS to specific chemotherapeutic agents. A number of cases of patients receiving a variety of chemotherapeutic drugs[2], and radiotherapy[3], have been reported, and their authors, like in the present paper, delved in the issue of cardiotoxicity of the particular drug administered, akin with what is done for cases of drug-specific (*e.g.*, anthracyclines) chemotherapy-induced cardiomyopathy, which certainly should be

differentiated from TTS. The intimate association of TTS with malignancies is intriguing[4-7], and has made some to recommend that patients with TTS should undergo evaluation for an underlying malignancy[4,5]. In terms of mechanisms many have attributed TTS, in the setting of malignancies, to paraneoplastic manifestations[4-6], a heightened autonomic sympathetic nervous system tone, emanating from the emotional stress of patients with a recently made diagnosis of malignancy, and non-specific physical stresses, related to diagnostic procedures, and administered chemotherapy and radiotherapy, without of course discarding the possible cardiotoxic role of the implemented therapies[6,7]. Incidentally, any reader of the present report will be interested in the details of further management of this patient with non M3 acute myeloid leukemia, whether he received more therapy, the specific chemotherapeutic regimen implemented, and the eventual outcome.

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