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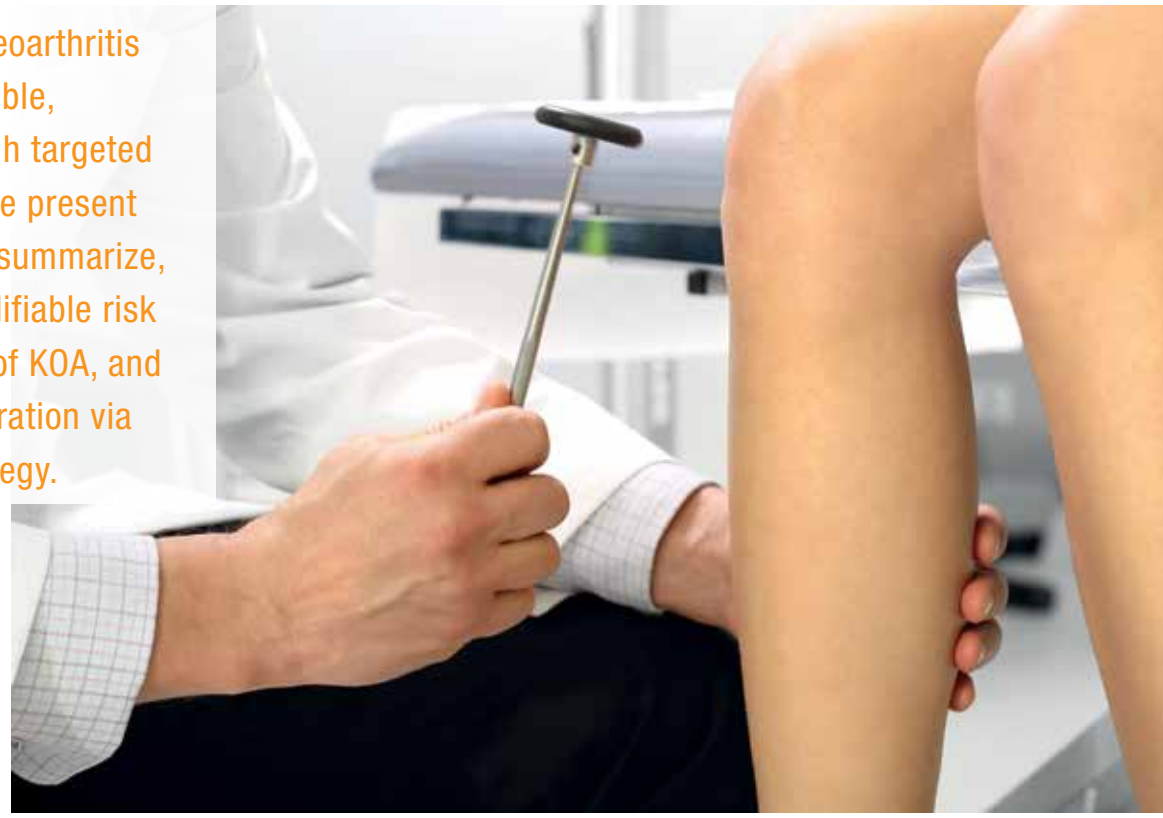
Optimal management of knee osteoarthritis (KOA) should include, where possible, modification of risk factors through targeted interventions. The objectives of the present narrative review were to identify, summarize, and cluster all the potentially modifiable risk factors that influence the course of KOA, and discuss their susceptibility to alteration via personal, clinical, and public strategy.



MODIFIABLE RISK FACTORS IN KNEE OSTEOARTHRITIS: TREATMENT IMPLICATIONS

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Osteoarthritis (OA) is a highly heterogeneous disorder characterized by progressive cartilage loss, remodeling of adjacent bones and concomitant local low-grade inflammation. From a concept of mechanical wear and tear process, the idea of OA has evolved through the last few years to a whole organ disease affecting different joint structures and functions, being in interaction with the human body as a whole [1, 2]. OA affects people of all ages with different levels of physical activity and the knee is among the joints most commonly affected [3, 4].

To date, every single detail of the complex structural changes and the processes of articular remodeling in knee OA (KOA) are easily recognized thanks to the high-resolution imaging modalities and innovative biomarkers, respectively. The area with the most unsatisfactory progress seems to remain the non-surgical treatment of the disease. Although we already have a greater understanding of the pathogenetic mechanisms behind the scenes of OA development and progression, modern conservative management approaches serve mainly to relieve pain rather than to influence the biochemical environment of the joint and to impact the disease progression. In the last few years, a ray of hope is emerging on the research front as orthobiotics, stem cell-based approaches and gene therapy look promising. However, they may never be applicable or accessible for the majority of patients with KOA and their efficacy and safety is still in question. What if there are safe and potent conservative, non-pharmacological treatment options right before our eyes? They may often be overlooked by researchers and clinicians due to the temptation of investigating only innovations and presenting them to patients.

As has already been emphasized, OA is a multifactorial disease that affects the whole joint. Therefore, the expectations for the optimal treatment strategy are very high, since it has to impact a large number of

tissues and functions. Modern management of KOA should be based on an individualized approach, including not only palliative pharmacological relief of pain but also identifying and managing risk factors contributing to the patient's condition, resulting in improvement of the metabolic and biomechanical environment of the joint. In the search for the optimal treatment strategy, clinicians should aim at affecting where possible risk factors that could be potentially intervened.

The objectives of this narrative review were to identify, summarize, and cluster all the modifiable risk factors that influence the course of KOA, and discuss their susceptibility to intervention via personal, clinical and public strategy.

Search Methodology

We adhered to the previously published recommendations for writing a narrative review [5]. PubMed and Scopus databases were queried for studies that reported risk factors of clinical and structural progression for KOA to January 2019. The initial search started with the terms "knee osteoarthritis", "risk factors" and "improvement". After the identification of potentially modifiable risk factors, the search was extended using each modifiable factor as a keyword. MeSH terms and relevant free-text terms were used, accordingly. The full-search strategy of biomedical literature in PubMed database is presented in Supplementary Appendix 1. References of retrieved studies and relevant reviews were hand-searched for a further supplement. The final search was carried out on 7 Feb 2019. A priority was given for studies in the last 5 years, which included more than 100 participants, had a control group and the duration of the trial was at least 3 months. In our quest for presenting a wider range of evidence-based knowledge, relevant data from observational studies, systematic reviews, and meta-analyses were also included. In accordance with the Osteoarthritis Research Society International (OARSI) recommendations, greater emphasis was put on publications related to symptomatic, physical function, and disability improvement; however, also discussing modifiable risk factors as potential structure-modifying interventions [6,–8]. In this review, only exposures considered to be positively or negatively associated with clinical improvement or structural progression of KOA are addressed as potentially modifiable. Studies reporting associations of KOA with age, race, gender, family history of genetic disease, biomarkers and anthropometric indices (such as body height, knee height, and arm span) were not included as, to the best of our knowledge, these exposures are not a subject to an intervention. Trials of drug exposures were also excluded. Current recommendations of the leading OA societies were identified based on the prior knowledge of the authors.

Risk Factor Categories and Current Recommendations

The identified modifiable exposures were grouped into six main categories, based on their nature, as follows: (1) obesity and overweight, (2) comorbidity, (3) occupational factors, (4) physical activity, (5) biomechanical factors, (6) dietary exposures. In comparison, most of the current recommendations for non-pharmacological treatment mainly emphasize weight reduction, promotion of physical activity, and use of assistive devices for modifying the biomechanics of the knee joint, e.g., braces and insoles (Table 1) [9–14]. Less attention is paid on comorbidities, occupational factors, and diet exposures, although their alteration might produce a significant size effect on KOA progression.

Overweight and Obesity

The majority of patients with KOA are overweight or obese [15]. The risk of developing OA is twice higher in overweight individuals compared to those with normal body mass index (BMI) (< 25) [odds ratio (OR) 1.98]. Obesity (BMI ≥ 30) further increases this risk (OR 2.66) [16]. The high body mass promotes development and progression of KOA via two possible mechanisms: mechanical stress beyond the physiological capabilities of the weight-bearing knee joint, on the one hand, and altered metabolic and humoral profile, resulting in elevated adipocytokine levels and associated pro-inflammatory response, on the other [17] (Fig. 1).

There is a strong evidence that weight loss is an effective treatment modality for KOA, resulting in pain alleviation, improvement of physical function, mobility, and quality of life [18–21]. These benefits are independent of structural damage severity [22]. In terms of structure-modifying capability of weight loss, the literature is divergent, with some investigators reporting that intensive diet-induced weight loss was not beneficial for slowing down structural damage progression in comparison with exercise-alone program in patients with KOA who did not significantly reduce their weight [19, 23] with a lack of decrease in markers of cartilage breakdown [24]. In contrast to these findings, an observational trial found out that 7% weight loss was associated with reduced medial femoral cartilage thickness loss [25]. Weight reduction is already included as a core treatment in the management of patients with KOA in most of the current guidelines and recommendations [9–14]. Nevertheless, under real-world conditions weight loss is recommended by physicians in a suboptimal number of overweight or obese patients [26].

Table 1: Modifiable risk factors addressed in the current non-pharmacological treatment recommendations of the leading organizations.

Organization (issue date)	Recommendations/guidelines					
	OO	Comorbidity	OF	PA	BF	DE
AAOS (2013) [9]	✓			✓	✓	
ACR (2012) [10]	✓			✓	✓	
ESCEO (2014) [11]	✓			✓	✓	
EULAR (2013) [12]	✓		✓	✓	✓	
NICE (2014) [13]	✓		✓	✓	✓	
OARSI (2014) [14]	✓			✓	✓	

AAOS American Academy of Orthopaedic Surgeons, *ACR* American College of Rheumatology, *BF* biomechanical factors, *DE* diet exposures, *ESCEO* European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, *NICE* National Institute for Health and Care Excellence, *OARSI* Osteoarthritis Research Society International, *OF* occupational factors, *OO* overweight and obesity, *PA* physical activity

Fig. 1: The vicious circle of the complex cause-and-effect relationship between knee osteoarthritis and obesity.

Dose- and Time-dependent Effect of Weight Reduction

For each kilogram of body weight lost, the knee experiences a fourfold reduction in load during daily physical activity [27]. In a recent study investigating the dose–response relationship between weight loss and symptomatic improvement, the group with the largest amount of weight loss (> 10%) showed the greatest improvement in clinical scores, independently of age, sex, baseline weight, and baseline physical function. On average, minimal clinical improvement was achieved when 7.7% of body weight was reduced [28]. It seems that the more drastic the weight loss is, the better the outcome may be: 25% less pain and better function experienced by patients who reduced more than 20% weight compared to patients with more than 10% of weight reduction [29].

Diet, Exercise or a Combination of Both?

The way the weight loss is achieved may be of particular interest for investigators and clinicians, influencing the preservation of muscle mass, inflammatory response and long-term maintenance of body weight. Although fasting was found out efficient in a small uncontrolled German study where pain, mobility, and joint function were improved significantly after a significant reduction in weight [30], there may be more favorable weight reduction programs in the long term. Theoretically, based on the anti-inflammatory effect of Mediterranean-like diets rich in fibers, polyphenols, and omega-3 fatty acids [31], healthy diet-based weight loss programs may provide additional benefits to patients suffering from low-grade inflammatory conditions [32] such as KOA. On the other hand, this may be true for patients performing habitual physical activity for weight reduction [33]. A recent meta-analysis showed that diet-induced weight loss alone or combined with exercise in overweight or obese people results in improvement of physical function, but moderate pain relief is achievable only with a combination of diet and physical activity, and not with diet-only strategies [20]. In terms of weight loss effect on structural progression, Henriksen *et al.* observed an increased number of bone marrow lesions in KOA patients allocated to the physical activity group compared to the diet-only and no-attention groups, with no significant difference in cartilage loss, synovitis or effusion [34]. A diet creating an energy-intake deficit of 800–1000 kcal/day from a ration 15–20% from protein, less than 30% from fat, and 45–60% from carbohydrates showed a significant reduction in serum biomarkers for KOA [19, 35]. The importance of these findings still remains unclear. Overall, patient preferences appear to be detrimental for the prescription of weight loss regimen. Real-world data show that physical training programs alone or in combination may have slightly worse adherence compared to diet-only programs [36]; obese patients with KOA may not be induced to exercise as instructed [37].

Bariatric surgery should be considered in refractory cases of morbidly obese patients (BMI ≥ 40) [12]. Better symptomatic relief after the surgery is expected in younger patients and those without prior knee injury or other OA involvement [38].

Weight Maintenance

The list of randomized controlled trials for the effect of weight maintenance on KOA symptoms after achieved weight reduction is short, consisting, to the best of our knowledge, of a single trial. According to Christensen *et al.*, benefits of weight reduction remain if weight maintenance is promoted with physical exercise or diet over a 12-month period, irrespective of the maintenance program. Nevertheless, patients who underwent only dietary interventions regained less weight than did those allocated to the exercise-based program [37]. Furthermore, an increased number of bone marrow lesions were observed in the exercise-based group, although no greater cartilage loss has been reported [34]. A structured formula diet strategy in combination with dietary counseling was successful for weight and symptoms maintenance over the long term in KOA patients [39].

Comorbidity

Diabetes

Both in healthy and OA joint, metabolism plays a crucial role in the physiological turnover and remodeling of synovial joint tissues, including articular cartilage [40]. In the setting of persistent hyperglycemia, the formation of oxidants is promoted, resulting in increased matrix catabolism of the osteoarthritic cartilage [41]. Cartilage was shown to be softer in diabetics [42]; thus, more prone to damage. Although there is still little evidence to conclude with certainty that impaired glucose metabolism increased the risk of KOA, independent of obesity and advanced age [43], a recent study of a relatively large cohort of KOA patients from the Osteoarthritis Initiative found that diabetics exhibited a significantly greater increase in

cartilage and meniscus lesions when compared to diabetes-free controls over a period of 4 years. The more severe the course of diabetes was, the greater the structural progression was observed [44]. Whether stringent glycemic control, in addition to cardioprotective, is also chondroprotective is yet to be determined.

Depression

Since every fifth patient with OA experiences depressive symptoms, a clearly higher prevalence of patients with OA suffered from depressive disorders compared to age-matched non-OA individuals [45]. Greater disability, mortality rate, and medical costs are associated with OA patients with concomitant depression [46, 47]. Furthermore, the persistence of depressive symptoms is significantly associated with worsening of knee pain in patients with KOA, although their cause-and-effect relationship is still in question [48]. Depression also does not significantly affect changes in radiographic disease severity over time [49]. Nevertheless, since depression is a modifiable exposure, its management in the routine clinical practice may extensively contribute to symptom alleviation in KOA patients. Decreasing the levels of depression is also beneficial for patients undergoing total knee arthroplasty [50] and should be a part of the complex disease management in the broader context.

Cardiovascular Diseases

Both KOA and cardiovascular diseases are strongly associated with sedentary behavior and obesity. A dual association thus was previously suggested with comorbidity and KOA accelerating the progression of each other, resulting in a non-causal correlation [16].

Occupational Factors

One in every seven cases of KOA is attributable to work [51]. Occupation is one of the strongest modifiable exposures for developing and subsequent progression of KOA. It exerts its effect via two possible mechanisms: first, force exertion, repetitive physical movements or demanding posture at work may result in non-physiological stress on the knee joint structures and increase the patellofemoral joint reaction, and secondly, specific occupational activities (mainly among professional athletes) may lead to higher incidence of knee and ACL injury. The latter is being confirmed in a study among current and retired professional footballers who are nearly twice as likely to suffer from KOA and the risk increases with a knee injury or surgery accumulation [52]. However, a history of knee trauma is hardly modifiable, as opposed to occupational activities that may be intervened via vocational rehabilitation. Professional activities that increase the risk for KOA are kneeling, squatting, lifting heavy weight and climbing, with OR ranging from 1.55 to 1.7 [53].

> *The persistence of depressive symptoms is significantly associated with worsening of knee pain in patients with knee osteoarthritis.*

Vocational Rehabilitation

Although to the best of our knowledge there are no cohort studies to support the effect of vocational rehabilitation on symptom alleviation, there is a wide range of interventions that could theoretically help relieve pain and improve physical function in patients with KOA and slowing down the progression of the disease. This includes alteration of occupational behavior, change of work tasks or working hours, use of assistive technology, workplace modification [12] and neuromuscular education.

Occupational activities requiring deep flexion such as kneeling and squatting have a dose-dependent effect on KOA risk contributing for 26% risk elevation per 5000 h increase of kneeling or squatting [53]; thus, the most simple and effective measure is to reduce the working hours of activities demanding for kneeling or squatting. Use of assistive technology may also help, since the duration of kneeling in the sand–cement-bound screed floor layers is shorter using electrical screed leveling machines (particularly manually moved) [54]. Incorporating proper knee pad and posture in a work environment could reduce the risk of knee injuries and favorably redistribute the load forces unloading the knee joint to a varying degree [55]. Education for lumbopelvic-thigh muscle co-contraction while squatting may improve functional performance and reduce patellofemoral joint crepitus, showed a single case report [56]. The use of a low assemble seat on wheels may also help reducing the time spent in a forced working posture by alternating kneeled or squatted work with seated work [57]. Occupational disease surveillance should be of utmost importance in the prevention of work-related KOA.

Physical Activity

Supervised individualized exercise therapy is clinically and cost-effective; thus, it should be integrated as a central part in the treatment of every patient with KOA [58]. After adjusting for BMI, better physical performance was associated with a higher percentage of lean mass and a lower percentage of fat [59]. Patients should aim at being physically active at least 180 min per week for optimal pain reduction and functional improvement [60]. Nevertheless, up to 70% of patients with KOA do not achieve the recommended levels of physical activity, especially females; therefore, new strategies should be developed to encourage KOA patients' engagement in exercise [61]. To optimize patient outcome, a tailored regimen should be prescribed using proper dosage, progression, and behavioral modulation techniques, accounting for individual differences and comorbid conditions [62].

Prejudice

Underutilization of physical activity interventions due to fear of disease acceleration is a common problem. Nevertheless, the notion of putting aside preconceived ideas will allow the clinician to trust high-quality evidence-based data that moderate exercise is safe and improves pain and knee function if trauma is avoided [63]. Loading the knee joint with exercise seems not to damage the articular cartilage [64]. Notwithstanding, patients with advanced radiographic disease (Kellgren–Lawrence grade 4) should be approached with caution since greater daily physical activity is associated with symptom aggravation [65]. For patients with BMI over 35, psychological support and lifestyle changes promote their participation in physical activities, but orthopedic consultations should preferably not be delayed [66].

Types of Exercise

The remarkable heterogeneity of study protocols leads to poor reproducibility of the data, making a direct comparison of various exercise programs difficult [67]. A distinct and significant difference between aquatic and land-based exercise in terms of symptomatic improvement has not been established so far [68]. Nevertheless, aquatic activities with their high relative load and optimal speed were hypothesized to be superior for addressing power deficits while avoiding pain in elderly adults [69]. While thigh-muscle strengthening may alleviate pain and ameliorate function alone, adding electrical stimulation seems to improve the outcomes [70]. Patients with KOA may benefit additionally from a combination of resistance hip exercises with quadriceps strengthening [71].

A training strategy involving the use of cuffs for venous blood flow restriction during exercise may induce quadriceps muscle hypertrophy and improve strength in patients with weakness and atrophy related to knee pathology while appearing safe when properly performed [72]. Tai Chi and other physical exercise have a dose-dependent effect on the improvement of pain and physical function [73]. Backward walking with conventional physiotherapy treatment is effective in treating gait impairment [74]. A combination of diet- and exercise-induced weight loss is thought to be an optimal treatment for reducing pain and improving physical function in overweight adults with knee OA [75].

Motivation

Engaging and maintaining a physically active lifestyle is a challenge for people with KOA. Factors associated with a good outcome include having positive exercise experience, attitude and beliefs, proper education, adjusting and prioritizing physical activity, and presence of professional and social support. Some of the common barriers in the implementation of physical activity in daily life are the presence of pain and physical limitations, negative experience, beliefs and information, a resigned attitude, and lack of motivation and professional support. There is a complex interplay of individual, psychological and socio-environmental factors for the successful activity intervention; therefore, a personalized approach should be considered for every patient [76].

Exercise and physical activity promotion according to the American College of Sports Medicine guidelines is effective for aerobic and resistance training in patients with OA [69, 77]. Healthcare providers should actively encourage patients to engage in muscle-strengthening and aerobic exercise as there is a strong evidence that it can delay the onset and improve outcomes [78]. Sedentary behavior is strongly influenced by environmental and social factors [79]. Adherence, competence, and motivation should be assessed to identify patients in need of social support and exercise behavior modulation [80].

> *"Varus deformity in combination with medial meniscal extrusion may be the reference to perform an advanced intervention to slow down knee osteoarthritis progression.*

Biomechanical Factors

In recent years, strong evidence has emerged that mechanical forces play an important role in the predisposition to complaints and the development of structural damage. Biomechanics of the knee joint may be modified by intervening intrinsic factors like muscle strength and lower extremity axis or using helping aids.

Thigh Muscle Strength

Acting as a shock-absorber and patellar stabilizer, quadriceps femoris muscle plays a major role in the knee biomechanics and its strengthening should also be an integral part of the treatment regimen, where possible, in patients with KOA [12]. The atrophy of quadriceps femoris is not only a risk factor but also a consequence due to the inactivity and disuse of the "diseased" limb [81]. The latter may explain the fact that concurrent loss in muscle strength is associated with symptomatic KOA progression [82], probably causing a vicious circle of cause and effect. Increasing the muscle mass of the quadriceps femoris improves pain and function in the KOA [83, 84], stabilizing the patella and the knee joint during gait [85]. A study investigating the effect of strength training on KOA progression shows that it reduces the progression of structural changes [86]. Strengthening exercises improve pain and physical function with no apparent superiority between different types of activities, at least in the short term [70].

Lower-extremity Alignment

Varus and valgus malalignment increase the medial and lateral stress distribution of the tibiofemoral joint and are associated with pain aggravation and cartilage loss progression of the medial and lateral compartment, respectively [87, 88]. Varus deformity in combination with medial meniscal extrusion may be the reference to perform an advanced intervention to slow down KOA progression [89]. Shifting the axis with the greatest load away from the injured cartilage to the stronger compartment of the knee by slightly over-correcting to valgus may reduce pain, delay or completely postpone total knee arthroplasty [90, 91].

Orthoses and Other Assistive Devices

Orthoses and assistive devices exert their curative effects mainly by affecting the pathomechanics of the osteoarthritic joint. Although often underestimated in clinical practice, they may be no less effective than the routinely used pharmacologic therapeutic modalities [84].

There are currently a large number of assistive devices including shoe insoles, braces, splints, canes, crutches, walkers that may potentially modify mechanical forces acting at the knee joint. Although some of the current recommendations for the treatment of osteoarthritis advocate the use of specific insoles [13, 14], resulting in a reduction of the knee adduction moment, a recent meta-analysis found no benefit in terms of pain and joint function over placebo (flat) insole [92]. Medial unloading (valgus) knee brace and medial knee taping may provide short-term improvement in pain when compared with sham [93, 94]. Assistive devices such as canes, crutches and walkers may minimize disability when individually tailored to patient's height, weight, and joint alignment.

Dietary exposures

Information on the efficacy of dietary exposures in KOA patients is rather controversial

documented in related trials with highly heterogeneous results. Moreover, most of the studies have a short-term follow-up. High-quality data mostly come from industry-sponsored trials and should be considered in light of the potential positive funding outcome bias. Overall analysis trials showed that dietary supplements provide moderate and clinically meaningful treatment effects on pain and function in patients in the short term, although the quality of evidence is low [95].

Plant-derived Products

Fruits

Results from two longitudinal studies invariably indicated that greater fiber consumption was related to a lower risk of symptomatic KOA, while the relation to the incidence of radiographic KOA remained unclear [96]. Nevertheless, the observational nature of both studies raised concerns about residual confounding. In a small randomized controlled trial, Schell *et al.* observed that dietary strawberries had a significant analgesic effect in obese KOA patients with mild-to-moderate knee pain. A 12-week intake of dietary strawberries results in a reduction of total pain and disability. The authors have hypothesized both effects may be due to dietary polyphenols and other bioactive compounds found in strawberries [97]. Similarly, another recent study showed that pomegranate juice rich in antioxidants decreased significantly Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total, stiffness, and physical function scores over a short-term exposure in a small randomized trial [98].

Herbal Formulations

Supplementation with 500 mg of *Momordica charantia* (bitter melon) for 3 months resulted in reducing pain and improving symptoms among KOA patients. However, when compared to the placebo group, *Momordica charantia* differed significantly only in the analgesics use [99]. Similarly, a trend towards reduced analgesics consumption compared to placebo was observed with a special formulation composed of a mixture of rosehip (*Rosa canina* L.) puree/juice concentrate, nettle (*Urtica dioica* L.) leaf extract, devil's claw root extract, and vitamin D [100]. A low dose of the medicinal plant *Artemisia annua* (150 mg) showed an effect in a randomized control trial of 42 patients, improving pain and WOMAC total score from baseline to 12 weeks. Significant improvement of symptoms was not seen in the placebo group and in the group taking a higher dose of *Artemisia annua*. However, a direct comparison between *Artemisia annua* and placebo was not evaluated [101]. Consumption of spearmint tea with or without high rosmarinic-acid content for 16 weeks improved physical disability and stiffness, while the pain was alleviated only in the rosmarinic-acid group [102].

> ***Orthoses and assistive devices exert their curative effects mainly by affecting the pathomechanics of the osteoarthritic joint. Although often underestimated in clinical practice, they may be no less effective than the routinely used pharmacologic therapeutic modalities.***

In a 12-week randomized double-blind, placebo-controlled, parallel-design trial, KOA symptoms in overweight or obese female patients taking 1000 mg garlic tablets were significantly improved for the study period. However, there was no difference between active and placebo groups [103].

Avocado/soybean Unsaponifiables

Avocado/soybean unsaponifiables have been suggested to possess chondroprotective, anabolic, and anti-inflammatory characteristics. At the clinical level, they seem to reduce pain and stiffness while improving joint function [104, 105]. Although effective for symptomatic treatment more research seems warranted for structural progression inhibition and long-term effects [106].

Animal Products

Fish and Crustacean Extracts

Placebo-controlled trials did not show any significant clinical effect of krill oil and oral salmon calcitonin over placebo [107]. Low- and high-dose fish oil intake improved significantly pain in a randomized non-placebo controlled trial [108]. Nevertheless, this improvement for pain was comparable to the one commonly observed with the 'placebo effect'. Further studies are warranted before any conclusions could be drawn.

Collagen

Van Vijven *et al.* did not find sufficient evidence to recommend the generalized use of collagen hydrolysate in clinical practice [109]. A recent meta-analysis, however, showed a significant reduction in the stiffness subscore of the WOMAC index in patients with OA [110].

Glucosamine and Chondroitin Formulations

Chondroitin and glucosamine supplements are found to be safe, but results of their efficiency are inconsistent, varying among different formulations. Their place in the management of KOA and clinical effectiveness are a frequent topic of debate among researchers, resulting in high heterogeneity of recommendations of the leading organizations: from a first-line "pharmacological" therapy in European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis treatment algorithm [11] with potential structure-modifying effect according to the European League Against Rheumatism [111] to a conditional recommendation of the American College of Rheumatology that KOA patients "should not use the following: Chondroitin sulfate, Glucosamine" [10]. A highly cited meta-analysis by Wandel *et al.* showed no superiority of chondroitin sulfate and/or glucosamine (sulfate or hydrochloride) over placebo for reduction of pain and joint space narrowing [112]. Since its publication, however, numerous criticisms have been raised [11, 113] and in contrast to its results, favorable effects on symptoms were reported in other high-quality studies, especially for glucosamine sulfate in crystalline form [114, 115]. Conclusively, further research, including industry-independent trials, is warranted to assess the proper dosage, the most effective formulation, and the optimal duration of treatment and to identify specific subsets of patients in whom glucosamine and chondroitin, either alone or in combination, may improve prognosis.

Probiotics

Skimmed milk containing *Lactobacillus casei* Shirota (LcS) showed greater improvement in pain and function in 6 months than placebo. Serum levels of hs-CRP were found also significantly lower in patients consuming LcS. The authors of the study have hypothesized that probiotic consumption could serve as a novel therapeutic option in the clinical management of knee OA [116].

Minerals

Choline-stabilized orthosilicic acid (a bioavailable form of silicon) was tested in a multicenter, double-blind, placebo-controlled study with 211 patients with KOA for 12 weeks. In the total study population, no differences in clinical parameters were observed between the placebo and the active-treatment groups, but gender interaction was found, where men receiving choline-stabilized orthosilicic acid had a significantly greater improvement in WOMAC total score, stiffness and physical function as well as a lower increase in biomarker levels of cartilage degradation [117]. Lower magnesium intake is associated with worse pain and function in KOA patients [118]. Serum levels may also have an inverse association with radiographic OA, joint space narrowing and hsCRP levels [118, 119].

Vitamins

Vitamin D

A randomized controlled pilot trial of KOA patients with vitamin D insufficiency suggested there was a small but statistically significant clinical benefit of vitamin D on knee pain and knee function over placebo [120]. In addition, an observational study investigating the effect of vitamin D insufficiency on the clinical and structural outcome of the KOA found that the consistently sufficient group had significantly less loss of tibial cartilage volume, less increase in effusion-synovitis volume, and less loss of physical function compared with the consistently insufficient group [121]. However, in a multicenter randomized, double-blind, placebo-controlled vitamin D supplementation, compared with placebo, did not result in significant differences in change of MRI-measured tibial cartilage volume or knee pain over 2 years [122]. Another high-quality 3-year, double-blind, randomized, placebo-controlled trial comparing 800 IU cholecalciferol daily supplementation with placebo confirms the non-efficacy of vitamin D [123]. Therefore, it may be concluded that supplementing with vitamin D does not play a significant role in modifying the progression of KOA and the previously reported small positive effects may be due to residual confounding.

> ***Theoretically, femoral muscle strengthening activities, complemented with proper diet, weight loss, vocational rehabilitation, management of comorbidities (especially diabetes and depression), and biomechanical support may add up to the holistic treatment approach towards the patient with knee osteoarthritis.***

Vitamin K

An increased risk of radiographic knee osteoarthritis and cartilage loss over time was associated with subclinical deficiency of vitamin K [124]. Moreover, very low plasma vitamin K1 levels (< 0.2 nM) were related to cartilage and meniscus damage progression after 3 years of follow-up. Decreased plasma levels of dephospho-uncarboxylated matrix gla-protein, a marker for vitamin K deficiency, were associated with the presence of KOA symptoms but not with progression [125].

Conclusion

The present narrative synthesis of modifiable risk factors does not pretend to cover all aspects of the possible non-pharmacological interventions for KOA management, nor to create recommendations, as there are obviously enough of them. We have rather outlined the main categories of risk factors that could be intervened and pointed out their significant effect size in modifying the symptoms and the course of KOA. In fact, to the best of our knowledge, this is the first review to propose a detailed classification of the modifiable risk factors for KOA and to discuss most of them in terms of therapeutic interventions. In the era of age- and obesity-related diseases, the combined effects of local and systemic risk factors should be managed by combined measures—simple but effective individual interventions on health-altering exposures forming a comprehensive package of care. Theoretically, femoral muscle-strengthening activities, complemented with proper diet, weight loss, vocational rehabilitation, management of comorbidities (especially diabetes and depression), and biomechanical support may add up to the holistic treatment approach towards the patient with KOA. An individual risk factor modification program should be developed in accordance with patient preferences and habits, level of physical activity, workplace, medical history, and overall health condition. Unlike pharmacological treatment, non-pharmacological interventions could be easily combined without any concerns for drug interactions or cumulative side effects. Due to its great impact on a wide range of functions and tissues, risk factor modification seems to be getting really close to the optimal treatment of KOA, capable of improving the metabolic, biochemical, and biomechanical environment of the joint. We have already started thinking of osteoarthritis as a whole; now, it is time to treat it as a whole.

Author contributions: Both TG and AKA took part in the conception and design of the study, data management, analysis, and logical interpretation. TG drafted the introduction, search strategy, overweight and obesity, comorbidity, occupational factors, biomechanical factors, and conclusion sections, while AKA—physical activity and dietary exposures. Both authors revised the manuscript critically for important intellectual content and approved its final version.

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Compliance with ethical standards

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Revision anterior cruciate ligament surgery may be complicated by tunnel malposition and/or tunnel widening and often requires a staged treatment approach that includes bone grafting, a period of several months to allow bone graft incorporation and then definitive revision ACL reconstruction. The purpose of this study was to evaluate the results of a single-staged ACL revision reconstruction technique using a cylindrical dowel bone graft for patients who have existing posteriorly placed and/or widened tibial tunnels in the tibia at a minimum of 2 years follow-up.

SINGLE-STAGE REVISION ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION USING BONE GRAFTING FOR POSTERIOR OR WIDENING TIBIAL TUNNELS RESTORES STABILITY OF THE KNEE AND IMPROVES CLINICAL OUTCOMES

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Reconstruction of the anterior cruciate ligament (ACL) is a very common surgical procedure with an incidence of greater than 200,000 annually with reported rates of success of 75–97% [21]. Regardless of the ACL reconstruction technique utilized, restoring the correct position of the ACL is paramount to achieving functional stability of the knee joint [4, 17]. However, if acceptable tunnel position is not achieved, there is an increased risk for graft failure.

Tunnel malposition is reported to be the most common mechanism for ACL graft failure and recurrent instability. It has been estimated that 70–80% of ACL graft failures are a result suboptimal tunnel placement [3]. Most often, this is a result of failure to restore the anatomic position of the femoral tunnel; however, establishing an anatomic tibial footprint is also critically important [17]. Placement of the ACL graft in a position too anterior on the tibia can result in graft impingement and subsequent limitations of motion and possible graft failure, while a graft placed too posterior can lead to rotatory instability due to a vertical graft position [17].

As with primary ACL reconstruction, the goal of revision ACL surgery is to provide a stable and functional ACL that

most accurately reproduces the kinematics of the native anatomic knee. A variety of factors dictate the surgical strategy in revision ACL reconstruction, including tunnel position, tunnel widening/bone loss, graft type, and fixation method [7, 9, 16]. In situations of significant tunnel malposition and/or tunnel widening, staged bone grafting followed by delayed reconstruction is often required [10]. However, a staged approach requires two separate surgical procedures, a period of several months to allow bone graft incorporation, and increased time to definitive revision ACL reconstruction, which could result in higher risk of cartilage and meniscus injury [13, 14]. As a result, several techniques have been described to perform revision ACL reconstruction in a single-stage procedure.

The purpose of this study was to report the prospective results of a consecutive series of patients with persistent instability following ACL reconstruction secondary to suboptimal tibial tunnel placement, with or without tunnel widening, treated with a single-stage revision ACL reconstruction technique. The hypothesis of this study was that patients would experience an improvement in clinical outcome scores and obtain results similar to two-stage revision for malpositioned tibial tunnels.

Materials and Methods

Eighteen consecutive patients were enrolled between 2010 and 2014. Patients were eligible if they met the following inclusion criteria: age less than 50 years, previous primary ACL reconstruction, persistent or recurrent instability since the primary reconstruction that limited daily and/or athletic activities, physical examination demonstrating instability with both positive Lachman and positive pivot shift testing, MRI imaging demonstrating a posteriorly placed tibial tunnel or tibial tunnel widening, and clinical follow-up greater than 24 months. Exclusion criteria were previous multi-ligamentous reconstruction or current multi-ligamentous instability or greater than or equal to grade 2 Kellgren–Lawrence tibiofemoral joint degenerative changes.

All patients completed standardized questionnaires including Knee Osteoarthritis Outcome Score (KOOS), Lysholm Knee Score, Tegner Activity Level and 12-Item Veteran Rand (VR-12) quality of life scale preoperatively and then again postoperatively at 6, 12, and 24 months.

Clinical and Radiographic Evaluation

The diagnosis of ACL graft failure was based on patient history, physical exam and a MRI documenting graft rupture. The onset of symptoms was noted and defined as follows: "acute" signified a well-defined event precipitating the acute onset of symptoms/instability or "insidious" meant absence of injury or precipitating event but a gradual onset of symptoms/instability. Subjective instability was noted and defined as follows: instability with activities of daily living and change-in-direction sports, instability with change-in-direction sports only, and no sense of instability with any activities. The type of graft used during the primary ACL reconstruction was recorded, as well as the time between the primary and revision surgeries.

> ***"Regardless of the anterior cruciate ligament (ACL) reconstruction technique utilized, restoring the correct position of the ACL is paramount to achieving functional stability of the knee joint."***

Anterior cruciate ligament-specific physical examination was performed at each visit by a fellowship-trained orthopedic surgeon not involved with the study. The exam included the Lachman test, anterior drawer test, and pivot shift test. Preoperative radiographic examination included a standing posterior–anterior (PA) radiograph of bilateral knees, a lateral radiograph, a merchant view of the patella, and a full-length standing hip–knee–ankle radiograph to measure the mechanical alignment axis.

Magnetic resonance imaging of the knee was performed both preoperatively and at 12 months postoperatively. MRI measurements included preoperative and postoperative sagittal tibial tunnel position, maximum tibial tunnel width at the tibial aperture, and sagittal and coronal tibial tunnel angles. The reference line for all sagittal measurements was a line connecting the most proximal anterior and posterior aspects of the tibial plateau on the sagittal MRI slice containing the view with the widest part of the tibial tunnel aperture (Fig. 1).

Using a digital, metric scale, the total anterior–posterior (AP) size of the tibia, the anterior-most position of the tibial ACL tunnel (ATT), and the posterior-most position of the tibial tunnel (PTT) were measured from the posterior tibial cortex. Measurement accuracy was made to the nearest 1 mm. These distance measurements, as well as the tunnel center position, were expressed as percentages of the total tibial AP depth from the posterior tibial cortex as measured on the sagittal MRI slice containing the view with the most posterior tibial tunnel intra-articular aperture. In addition, tibial tunnel sagittal width (TW) at the aperture was calculated based on the difference between the anterior-most and posterior-most positions. As the ACL tunnel is typically positioned near 66% of the AP depth of the tibia from the posterior tibial cortex, patients were categorized as having a preoperative "posteriorized" tibial tunnel if the posterior-most aspect of the tibial tunnel was less than 55% of the AP depth of the tibia from the posterior tibial cortex. Patients were categorized as having a preoperative "wide" tibial tunnel if the tibial tunnel sagittal width at the aperture was greater than 12 mm, and the original operative report described a less than or equal 10 mm tunnel diameter. Sagittal graft angle was defined as the angle measurement between the previously described reference line and a line directly through the center of the tibial tunnel (Fig. 1a).

Surgical Technique

After induction of general anesthesia in the supine position, a diagnostic arthroscopy was performed and the remnant of the torn ACL graft was resected using a motorized shaver. Other intra-articular pathologies such as meniscus tears or cartilage lesions were addressed as indicated. A revision notchplasty was performed if necessary for femoral tunnel placement, along with removal of previously placed hardware as indicated.

On the back table, a fresh-frozen femoral head and neck non-irradiated allograft was fashioned into a cylindrical dowel bone graft with a slightly larger diameter than the reamer size used to ream the revised tunnel. The length of the bone graft was kept as long as possible, as it could be trimmed later in the procedure. The leading edge of the cylindrical

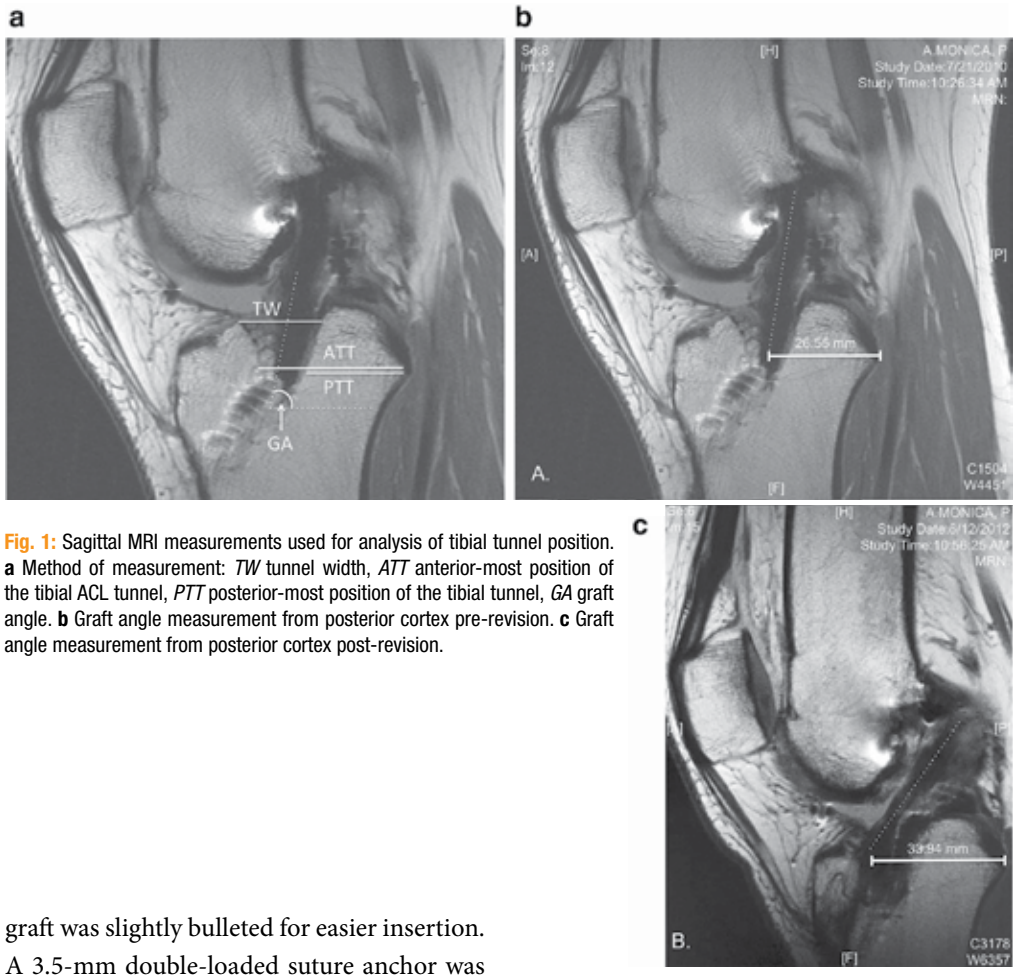

Fig. 1: Sagittal MRI measurements used for analysis of tibial tunnel position. **a** Method of measurement: *TW* tunnel width, *ATT* anterior-most position of the tibial ACL tunnel, *PTT* posterior-most position of the tibial tunnel, *GA* graft angle. **b** Graft angle measurement from posterior cortex pre-revision. **c** Graft angle measurement from posterior cortex post-revision.

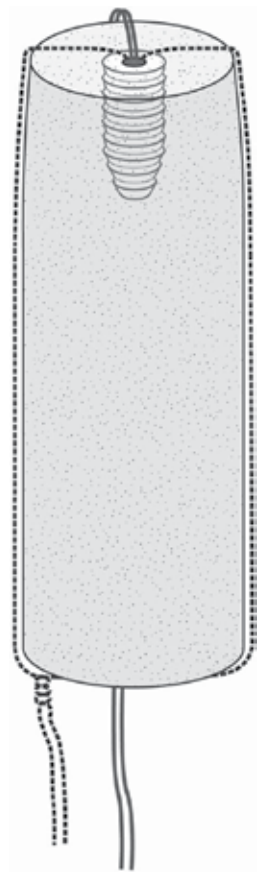

Fig. 2: This animated figure demonstrates the preparation of the graft with suture anchor in proximal end and sutures pulled posteriorly.

graft was slightly bulleted for easier insertion. A 3.5-mm double-loaded suture anchor was then drilled and attached in the center of the cephalad end of the graft that will enter the joint. The sutures are then pulled down posteriorly, medially, and laterally, but not anteriorly, along the graft (Fig. 2).

The same incision for the primary ACL was used and lengthened as necessary for the revision procedure. Under arthroscopic visualization, an ACL tibial tunnel guide was used to drill a guide pin through the center of the previous tibial tunnel (**see video online**). The selected fully fluted tibial reamer, chosen to match the original tunnel diameter on MRI, was then used to ream the original tunnel to a consistent diameter and to remove residual graft tissue (Fig. 3a).

The graft was then gently impacted into the tibial tunnel while the suture limbs were held posteriorly to avoid being later cut with the reamer. Proper graft positioning was confirmed under direct arthroscopic visualization. The graft was then trimmed flush with the cortical surface of the anterior tibial cortex as needed and the suture limbs were then fixed into the anterior tibia to prevent displacement using a suture anchor just distal to the bone grafted tunnel (Fig. 3b).

Upon completion of the bone-grafting portion of the procedure, a guide pin was positioned at the new desired position of the ACL tibial tunnel using an ACL tibial tunnel

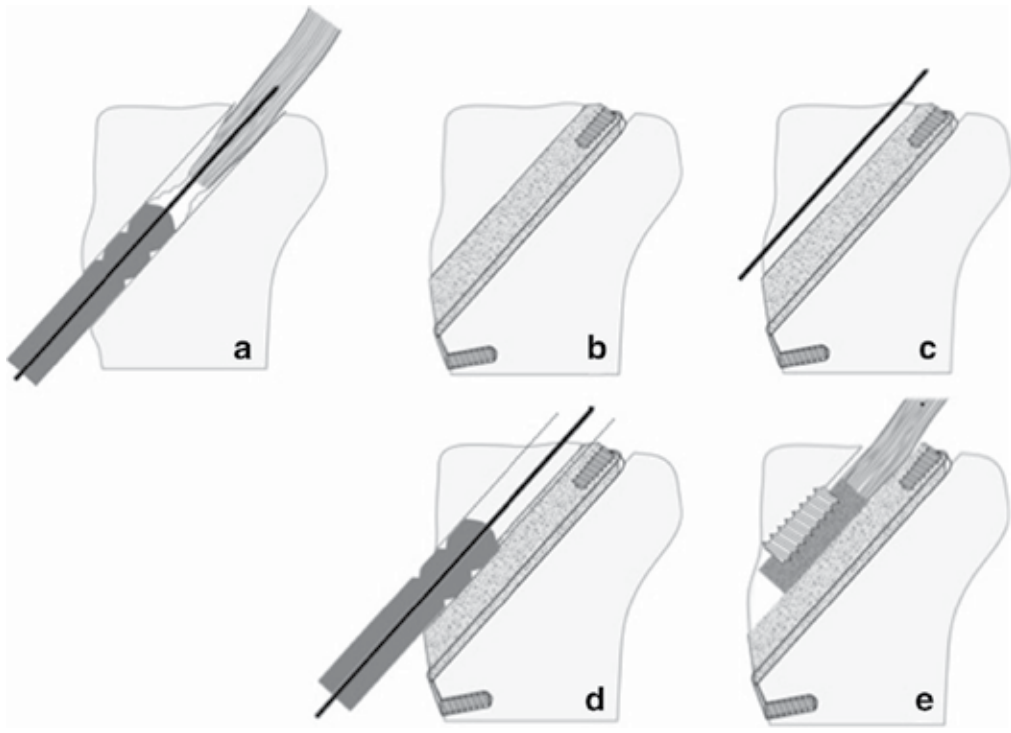

Fig. 3: Surgical technique. **a** Drill guide pin through the center of the previous tibial tunnel and ream original tunnel to a consistent diameter. **b** Graft is gently impacted into tibial tunnel under direct arthroscopic visualization while sutures are held posteriorly. Graft is then trimmed flush with anterior tibia and suture limbs are fixed to tibia with second suture anchor. **c** Position guide wire anterior to bone graft. **d** Gently ream new tunnel and perform revision ACL. **e** Completed revision ACL with anteriorized tibial tunnel.

guide (Fig. 3c). The guide pin was visualized within the joint just anterior to the grafted tunnel in the tibial plateau. An appropriately sized cannulated fluted reamer was then carefully used to create the revised tunnel. While it was common for a small portion of the bone graft to be removed by the reamer, as long as the sutures remained posterior to the reamer and fixed in place, the bone graft remained stable (Fig. 3d).

The new graft was then positioned just along the anterior edge of the bone graft in the tibia and fixed with the surgeon's method of choice (Fig. 3e). A Lachman test was performed to ensure stability at the conclusion of the procedure.

Institutional review board approval was obtained prior to initiation of the study.

Statistical Analysis

Exploratory statistics were presented for all baseline preoperative measurements. For continuous variables, interval change at final follow-up was computed in a paired fashion rather than group-wise, and significance was tested with a paired t test. For all parameters, interval change was computed as last value—baseline value. This is because higher values indicate improvement for most physical exam, functional or MRI parameters. All statements of significance imply statistical significance with $p < 0.05$ after conservative, Bonferroni-type multi-test correction. Due to the limited sample size, no covariate analysis was performed, either to assess correlations among outcome measures, or to control for potential confounders. Functional outcomes were compared between patients with and without tunnel widening preoperatively for the purposes of exploratory statistics. The power of paired t tests is 82.1% for $N = 15$ samples with a large effect size (Cohen's $d = 0.8$).

Results

Eighteen patients (eight female, ten male) with an average age of 26.7 years (range 16–48 years) underwent single-stage ACL revision reconstruction with the described technique. Mean follow-up was performed at 35.1 months (range 24–68 months). There were no patients lost to follow-up. Table 1 presents demographics and baseline surgical characteristics. Concomitant procedures performed at the time of revision included meniscectomy ($n = 4$), meniscal repair ($n = 11$), synovectomy ($n = 3$) and removal of hardware ($n = 5$). The onset of symptoms was acute in 12 patients and insidious in 6 patients. Surgical time was increased by an average of 28 min compared with the senior author's standard primary ACL reconstruction procedure. There were no perioperative complications requiring revision surgery.

> *Tunnel malposition is reported to be the most common mechanism for anterior cruciate ligament graft failure and recurrent instability.*

Physical Examination

Tables 2 and 3 present physical examination findings at baseline and at final follow-up, respectively. No patients had an effusion. Seventeen of 18 patients (94.4%) had a negative Lachman test and negative pivot shift test at final follow-up. One patient had a grade 2A Lachman test and a grade 1 pivot shift test but experienced no subjective instability. In this one patient, postoperative MRI at 12 months demonstrated increased signal with intact ACL fibers suggestive of a high-grade partial tear. The patient experienced no limitations in his desired activities. Average postoperative knee flexion, extension and ROM were similar to preoperative values with no statistically significant difference.

Functional Outcomes and Sports

Table 4 presents functional measures preoperatively, and Table 5 presents changes in functional outcomes at final follow-up. At baseline, the Tegner score had a median of 3, interquartile range of 2, and range of 1–7. At final follow-up, the Tegner score showed a statistically significant increase ($p < 0.001$) with a median of 2, an interquartile range of 2.25, and a range of −1 to 6. All subscales of the KOOS (Fig. 4) and the Lysholm scale showed statistically significant improvements ($p < 0.001$). The VR-12 physical component score was significantly improved, though the mental component score only showed a trend towards improvement. Preoperatively, four patients were collegiate athletes: two gymnasts, one basketball player, and one softball player. Two of the four patients (50%) who were collegiate athletes returned to their previous sport at or above the preoperative level of competition. Of the two patients who did not return, one played softball and the other was a gymnast. The softball player graduated from college and pursued a career outside of athletics. The gymnast elected to stop competing as a result of her knee injuries, although she denied any knee pain or subjective instability at final follow-up.

Table 1: Pre-revision demographic and surgical characteristics ($N = 18$).

	Mean	SD	Min.	Max.
Age (years)	26.7	7.6	16	48
Follow-up (months)	35.1	12.2	24	68
Onset (months)	2.4	0.8	1	3
Interval (months)	69.8	54.4	7	204
	Value	**Frequency**	**%**	
Sex	F	8	44.4	
	M	10	55.6	
Side	L	12	66.7	
	R	6	33.3	
Prior surgeries	1	16	88.9	
	2	2	11.1	
Prior graft type	Allograft	6	33.3	
	Autograft	12	66.7	
Prior graft site	Achilles	1	5.6	
	BTB	15	83.3	
	HS	2	11.1	

Table 2: Pre-revision physical examination (*N*=18).

	Mean	SD	Min.	Max.
Flexion (°)	132.8	5.5	120	145
Extension (°)	–2.1	3.7	–10	0
ROM (°)	134.9	7.1	120	145
	Value	**Frequency**		**%**
Pivot	1	3		16.7
	2	15		83.3
Effusion	0	14		77.8
	1	3		16.7
	2	1		5.6
Instability	1	5		27.8
	2	13		72.2
Lachman	2A	1		5.6
	2B	13		72.2
	3B	4		22.2

Table 3: Changes in physical examination at minimum 24-month final follow-up (*N*=18).

	Mean	SD	95% High	95% Low	*p* value
Flexion (°)	0.278	6.524	3.522	–2.967	n.s.
Extension (°)	0.500	2.662	1.824	–0.824	n.s.
ROM (°)	–0.222	7.780	3.647	–4.091	n.s.
	Value	**Frequency**		**%**	
Pivot	0	1		5.6	
	1	17		94.4	
Effusion	0	18		100.0	
Instability	0	18		100.0	
Lachman	Normal	17		94.4	
	2B	1		5.6	

Table 4: Preoperative functional scores.

	Mean	SD	Min.	Max.
Lysholm	65.6	12.8	35.0	88.0
KOOS symptoms	70.1	15.4	36.0	92.9
KOOS pain	75.5	16.7	39.0	97.2
KOOS activity	83.9	18.6	50.0	100.0
KOOS sports	48.9	27.2	0.0	100.0
KOOS QoL	35.1	25.3	0.0	87.5
VR-12 PCS	44.3	8.4	21.8	56.8
VR-12 MCS	49.8	10.5	25.7	64.0

Table 5: Changes in functional outcomes at minimum 24-month final follow-up (*N*=18).

	Mean	SD	95% High	95% Low	*p* value
Δ Lysholm	20.0	15.0	27.4	12.6	0.000
Δ KOOS symptoms	12.9	11.8	18.8	7.0	0.000
Δ KOOS pain	15.4	18.7	24.7	6.1	0.003
Δ KOOS ADL	13.5	19.0	23.0	4.0	0.008
Δ KOOS sports	32.8	26.4	45.9	19.7	0.000
Δ KOOS QoL	37.2	28.5	51.4	23.1	0.001
Δ VR-12 PCS	10.3	9.7	15.1	5.5	0.000
Δ VR-12 MCS	2.2	9.5	6.9	–2.5	n.s.

Imaging

For MRI assessment, three of 18 patients were not willing to obtain MRI at 12-month follow-up, though all participated in final clinical evaluation. Table 6 presents MRI measures of tunnel geometry and orientation at baseline preoperatively. All patients met the criterion for a posteriorized tibial tunnel, with the posterior aspect of the tibial tunnel less than 55% from the posterior cortex. Nine patients (50%) met the criterion for a wide tibial tunnel, with the tibial tunnel sagittal width at the aperture greater than 12 mm. Between patients with and without wide tunnels preoperatively, there were no significant differences in the postoperative improvement of KOOS symptoms KOOS pain, KOOS activity, KOOS sports, KOOS QoL, Tegner, Lysholm, VR12-PCS, or VR12-MCS. Table 7 presents the interval changes in MRI parameters at final follow-up. There are statistically significant changes in all parameters except for coronal plane angulation. The average postoperative posterior tunnel position was significantly anteriorized by 13.5% compared to preoperatively. There was a significant decrease in tunnel width in the nine patients with preoperative tunnel widening and a 1.7-mm decrease on average for all patients. There was a significant decrease in sagittal graft angle of 11.6° on average.

Discussion

The most important findings of this case series were that a single-stage ACL revision for posterior or widened tibial tunnels was an effective procedure at restoring knee stability and improving clinical outcome scores. There are clear advantages to a one-stage approach, assuming adequate placement and fixation of the graft can be achieved [18]. The two-stage approach necessitates multiple anesthetics as well as additional periods of activity modification. In addition, a period of several months is required between procedures that allow for adequate bone graft incorporation. During this time patients may experience periods of continued knee instability, which may result in further cartilage and meniscus damage. As a result, several authors have described techniques that reproducibly achieve secure graft fixation when bone grafts or other material is used to change tunnel position in a single-stage revision procedure [2, 4, 15, 19].

Comparing one-stage and two-stage techniques of revision ACL reconstruction, similar results have been reported by other authors. Wright *et al.* performed a systematic review of studies evaluating the outcome of revision ACL reconstruction with a minimum of 2-year follow-up and noted objective graft failure in 13.7% [20]. Mean Lysholm score was 82.1, and mean Tegner activity level was 6 [1]. Similar results were observed in this study with clinical evidence of graft compromise in one patient (7%), a mean postoperative Lysholm score of 90, and a mean postoperative Tegner activity level of 5.8. The authors of the systematic review did not describe the incidence of tunnel bone grafting or the results of one-stage versus two-stage procedures. The current study demonstrated that 50% of the patients who were competitive athletes were able to return to their previous sport at or above their preoperative level of competition. The current literature has reported similar figures, with approximately 60% of patients being able to return to sports after single-bundle revision ACL reconstruction, although this figure is not specific to collegiate or professional athletes or if bone grafting was required [6, 8].

The results of this new single-stage revision ACL reconstruction technique are also similar to reported outcomes following traditional two-stage methods for specifically managing malpositioned tunnels. At a minimum follow-up of 3 years, Thomas *et al.* reported on 49 patients treated with two-stage revision ACL reconstruction and demonstrated that 6% of patients had a side-to-side difference of less than 5 mm, suggesting a failed reconstruction [18]. The current study showed clinical laxity in only one patient (7%) at final follow-up, but ligament arthrometry was not carried out so true comparison of laxity with other studies cannot be made.

The present study did not detect a difference in post-operative outcomes between patients with and without preoperative tunnel widening greater and lesser than 12 mm; however, this finding must be considered exploratory only as the study was not powered to test this hypothesis specifically. The correlation between tunnel widening and clinical outcome remains unclear. Multiple studies have demonstrated no significant correlation between tunnel widening and patient function or knee laxity [5, 7, 11], however, the 12 mm cut off for tunnel widening has also been shown to result in increased laxity between 5 and 15 year follow-up [22]. However, tunnel widening is thought to interfere with graft fixation and healing, and, when associated with large bone defects, can be a significant challenge in revision ACL reconstruction. As a result, a variety of surgical strategies exist for management of tunnel widening to allow for initial secure graft fixation in the revision setting [1, 12]. The single-stage tibial tunnel grafting technique described in this study resulted in improved clinical function in patients with preoperative tunnel width greater than 12 mm, with no significant difference in clinical outcome or knee stability compared with patients without preoperative tunnel widening at final follow-up.

Several recent publications have described techniques to address malpositioned femoral

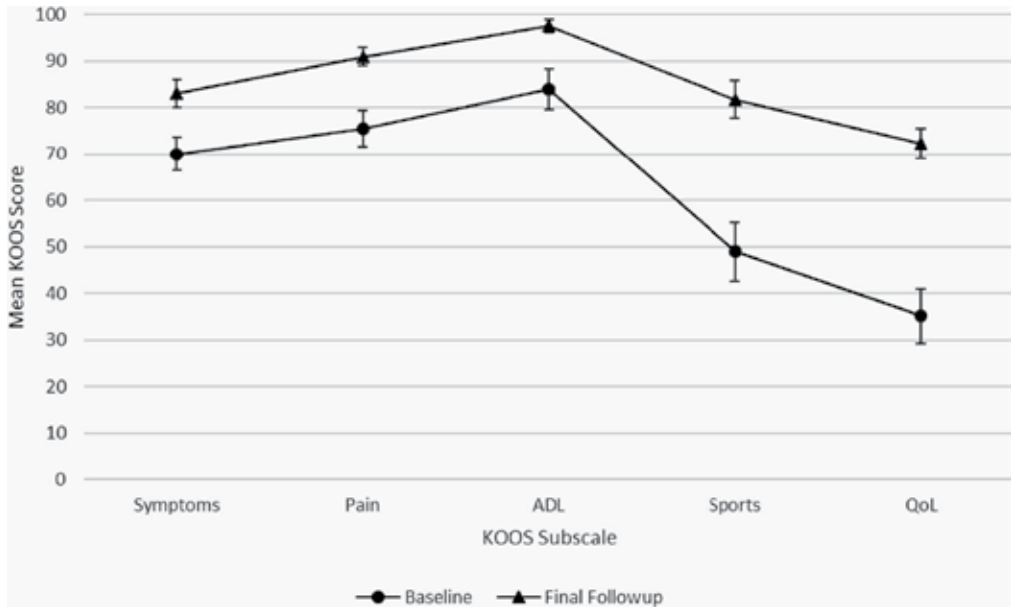

Fig. 4: Graphical representation of the mean KOOS subscale scores for *N* = 18 patients preoperatively and postoperatively. Error bars represent standard error of the mean.

Table 6: Preoperative MRI measurements (*N* = 15).

	Mean	SD	Min.	Max.
Posterior tunnel (mm)	24.8	4.6	13.4	31.5
Posterior tunnel (%)	47.2	6.8	30.4	54.9
Anterior tunnel (mm)	37.2	6.3	22.5	45.9
Anterior tunnel (%)	70.8	9.2	51.0	83.2
Tunnel center (mm)	31.0	5.4	18.0	38.7
Tunnel center (%)	59.0	7.8	40.8	69.1
Tunnel width (mm)	12.3	2.3	9.1	15.6
Sagittal angle (°)	71.8	8.4	56.5	85.4
Coronal angle (°)	77.3	6.8	66.8	88.4
Tibia AP (mm)	52.4	4.6	44.1	60.4

Table 7: Change in MRI measurements at 12 months follow-up (*N* = 15).

	Mean	SD	95% High	95% Low	*p* value
Δ Posterior tunnel (mm)	6.9	4.1	9.2	4.6	0.000
Δ Posterior tunnel (%)	13.5	8.4	18.1	8.9	0.000
Δ Anterior tunnel (mm)	5.2	5.0	8.0	2.5	0.001
Δ Anterior tunnel (%)	10.3	9.8	15.7	4.8	0.001
Δ Tunnel center (mm)	6.1	4.4	8.5	3.6	0.000
Δ Tunnel center (%)	11.9	8.9	16.9	7.0	0.000
Δ Tunnel width (mm)	−1.7	2.0	−0.6	−2.8	0.005
Δ Graft angle (°)	−11.6	8.6	−6.9	−16.4	0.000
Δ Coronal graft Angle (°)	−3.4	6.9	0.4	−7.3	n.s.

tunnels and residual bone voids in a single stage [2, 4, 15, 19]. Battaglia *et al.* described a technique using freeze-dried allograft bone dowels to fill cylindrical bone defects measuring up to 16 mm in diameter resulting from malpositioned and/or widened femoral tunnels [1]. Barrett *et al.* described a technique for treating femoral bone voids in revision ACL reconstruction with the use of a biocomposite synthetic dowel graft for isolated cylindrical defects of less than 11 mm [2]. Vaughn *et al.* performed a biomechanical cadaver study using bioactive moldable calcium phosphate cement for femoral bone defects [19]. They demonstrated excellent initial fixation strength and suggested that this technique may be a treatment option for contained femoral bone defects in a single-stage revision ACL reconstruction procedure.

The findings presented in this study have clinical significance when revision ACL reconstruction in the setting of posterior or widened tibial tunnels is encountered. The ability to improve knee stability and outcome scores in a single revision surgery is a tremendous advantage that avoids the additional costs and risks of a second surgery while expediting the patient's return to activities. Although there have been several described techniques for femoral-sided bone defects in revision ACL reconstruction, no previous investigations have been described for treatment of a malpositioned tibial tunnel in a single-stage revision ACL reconstruction. The anteriorization technique described in this study allows for creation of a customizable graft for both width and length to accommodate any sized potential tibial defect, even those wider than 16 mm. This technique also allows for specific fixation of the graft through the length of the tibial tunnel and provides initial secure graft fixation to prevent migration or dislodging of the implanted graft while preparing a new tunnel and implanting the ACL revision graft.

This study has several limitations. First, there were a relatively small number of patients in the study cohort even though no patients were lost to follow-up. This smaller cohort is likely a result of relatively few patients meeting inclusion criteria requirements, especially compared to primary ACL reconstruction. Second, there was significant variation amongst the study group in the time between primary and revision surgeries, ACL grafts used, preoperative and postoperative activity level and arthroscopic treatment of meniscal tears. Third, the mean average follow-up of 35 months may not be adequate to provide perspective on longer-term clinical outcomes. Only longer follow-up can give us information on the durability of this single-stage technique. Last, this study lacks a control group and there are multiple potential confounding patient and operative variables. An attempt was made to minimize these variables by prospectively evaluating patients with strict inclusion and exclusion criteria.

Conclusion

Revision ACL reconstruction utilizing a single-staged tibial tunnel grafting technique resulted in improved knee pain, function, and stability at a minimum of 24-month follow-up.

Funding: No funding was necessary for the completion of this study.

Compliance with Ethical Standards

Conflict of interest: The authors report no conflicts of interest related to this article.

Ethical approval and informed consent: IRB approval and informed consent was obtained for this investigation.

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Efficacy of High-Intensity Laser Therapy in Comparison with Conventional Physiotherapy and Exercise Therapy on Pain and Function of Patients with Knee Osteoarthritis: A Randomized Controlled Trial with 12-Week Follow Up

Knee osteoarthritis (KOA) is one of the most common musculoskeletal disorders causing pain and functional impairment. The purpose of the study is to compare the effects of high-intensity laser therapy (HILT), conventional physical therapy (CPT), and exercise therapy (ET) on pain and function in patients with KOA. The study was designed as an assessor-blind randomized controlled trial. Ninety-three patients (aged between 50 and 75 years) with proved KOA were included and randomly allocated into three groups, and received 12 sessions of HILT, CPT, or ET. The outcomes were pain intensity measured by visual analog scale (VAS), knee flexion range of motion (FROM), timed up and go test (TUG), 6-min walk test (6MWT), and functionality of knee measured by the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) questionnaire. Statistical analyses were done to compare the amounts at the baseline, immediately after treatment and after 12 weeks. HILT was significantly more effective than the other groups in decreasing the VAS, increasing FROM and improving the scores of WOMAC (total and function subscale) both after treatment and after 12 weeks. The effect of HILT and CPT on the TUG, 6MWT, and WOMAC pain subscale was not significantly different after treatment, and both were better than ET. HILT was significantly better than the others after follow-up, particularly more effective on the stiffness subscale of WOMAC. HILT combined with exercise therapy, as a useful therapeutic approach, could have positive influences on KOA.

Source: Nazari, A., Moezy, A., Nejati, P. *et al. Lasers Med Sci* (2019) 34: 505. https://doi.org/10.1007/s10103-018-2624-4. © Springer-Verlag London Ltd., part of Springer Nature 2018.

Streptococcus is well associated with a myriad of inflammatory diseases. Among others, this bacterium is linked to the triggering of psoriasis and to post-streptococcal reactive arthritis (PSRA), an arthritis which is typically confined to peripheral joints. Three patients who developed acute psoriatic spondyloarthritis (SpA) following a recent streptococcal infection are described in this article.

ACUTE ONSET OF PSORIATIC SPONDYLOARTHRITIS AS A NEW MANIFESTATION OF POST-STREPTOCOCCAL REACTIVE ARTHRITIS: A CASE SERIES

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Key Points

- Our case series describes three cases of acute psoriatic spondyloarthritis that occurred within 7–10 days of a confirmed streptococcal infection and progressed to full blown chronic disease.
- Acute psoriatic spondyloarthritis as a manifestation of post streptococcal reactive arthritis should be considered in the differential diagnosis of new onset inflammatory back pain followed by psoriasis in young adults who had a recent throat infection.

Group A streptococcus (GAS), e.g., *Streptococcus pyogenes*, is an aerobic Gram-positive bacterium that is associated with a diverse spectrum of syndromes that usually occur 1–3 weeks after a throat or skin infection [1]. Among the post-streptococcal rheumatic diseases, acute rheumatic fever (ARF) and post-streptococcal reactive arthritis (PSRA) are considered the most common clinical entities, each with a distinct pattern of clinical manifestations [2–10]. ARF is mainly characterized by migratory, non-erosive, self-limited polyarthritis with predominant involvement of the large joints and also by carditis, chorea, erythema marginatum, and subcutaneous nodules (major Jones criteria) [2]. In contrast, PSRA is usually manifested by acute non-migratory peripheral arthritis that may affect any joint, and has a protracted course and low responsiveness to NSAIDs [4]. In a subset of patients with PSRA, arthritis of the lower extremities and/or the involvement of the axial spine (rarely) resemble the articular disease in patients with classic reactive arthritis [6]. However, unlike PSRA, reactive arthritis is usually triggered by enteric and genitourinary pathogens (e.g., *Salmonella*, *Shigella*, *Chlamydia*, and *Yersinia*) and may be characterized by a wide spectrum of extra-articular symptoms, including ocular,

cardiac, gastrointestinal, or genitourinary, as well as mucocutaneous lesions [11]. A triad of symptoms (conjunctivitis, arthritis, and urethritis) is found in only one-third of reactive arthritis patients. Among the dermatological manifestations of reactive arthritis is keratoderma blennorrhagicum, a hyperkeratotic erythematous dermatitis that is clinically and histologically comparable with pustular psoriasis [12]. Similarly, streptococcal infection may induce guttate psoriasis, presented by a sudden onset of diffuse red and scaling papules, that commonly resolves after several months or may progress to plaque psoriasis [13, 14].

Additionally, it has been reported that streptococcal throat infection led to a worsening of chronic plaque psoriasis [15]. To the best of our knowledge, acute psoriatic spondyloarthritis (SpA) as a manifestation of PSRA has yet to be reported, despite the known relationship between streptococcal infection and inflammatory arthropathy and the known relationship between such an infection and psoriasis.

In the current case series, we present three patients who developed psoriatic SpA following a recent streptococcal infection. Two of them experienced new-onset pustular and guttate psoriasis, and in the remaining patient, pustular palmoplantar psoriasis exacerbated after 15 years of full remission.

We searched for cases of axial spondyloarthritis as a manifestation of PSRA in the published literature. Additionally, the association between streptococcal infection and psoriasis or psoriatic arthritis (PsA) was reviewed.

Case 1

A 37-year-old woman presented to the emergency department with a severe inflammatory low back pain for the past seven days followed by a pustular rash located on her shins, groins, and lower abdomen. Two weeks prior to the admission, the patient was diagnosed with tonsillopharyngitis that was supported by a positive throat culture for GAS, and treated accordingly with oral penicillin V. She had no previous history of arthritis, back pain, enthesopathy, uveitis, psoriasis, or other extra-articular symptoms of axial spondyloarthritis. She denied a recent urinary, gastrointestinal, or ocular infection, or the presence of a sexually transmitted disease (STD). Family medical history was unremarkable.

The examination revealed chest wall and thoracic spine tenderness, bilateral positive FABER (Patrick) test, positive sacroiliac distraction test, and a pustular psoriasis on her lower limbs sparing the palms of her feet.

Blood analysis revealed elevated C-reactive protein (CRP) of 94 mg/L (normal < 5 mg/L). Anti-nuclear antibodies (ANA), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), human leucocyte antigen-B27 (HLA-B27), and viral hepatitis serologies were negative. A radionuclide bone scan demonstrated increased uptake in several joints including the right sternoclavicular joint, left costovertebral joint, and both sacroiliac joints.

Magnetic resonance imaging (MRI) of the lumbar spine and sacroiliac joints showed acute bilateral sacroiliitis, along with active corner inflammatory lesions at L2–L4 (Fig. 1). The patient was diagnosed as having PSRA with axial involvement followed by pustular psoriasis and was started on intravenous (IV) methylprednisolone therapy for 3 days. She was discharged on naproxen 500 mg twice daily which was later changed to etoricoxib 90 mg/day with partial improvement. One month later, in light of a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of 6.9 and severe pustular psoriasis, biological treatment with adalimumab (40 mg every two weeks subcutaneously) was initiated. Following this treatment, the psoriasis resolved completely within one year and BASDAI decreased to < 3. One year later, while being treated with adalimumab, the patient had another episode of tonsillitis with a new episode of inflammatory back pain. The back pain improved with the continuation of adalimumab and etoricoxib.

> ***Among the post-streptococcal rheumatic diseases, acute rheumatic fever (ARF) and post-streptococcal reactive arthritis (PSRA) are considered the most common clinical entities, each with a distinct pattern of clinical manifestations.***

Case 2

A 35-year-old woman was referred to a rheumatologist due to inflammatory back pain and pain in the buttocks for two months that was concomitant with diffuse non-pruritic red and scaling papules. During the last year, she had several episodes of tonsillitis and high fever that required treatment with antibiotics. The last episode occurred 10 days prior to the onset of back pain and rash, and

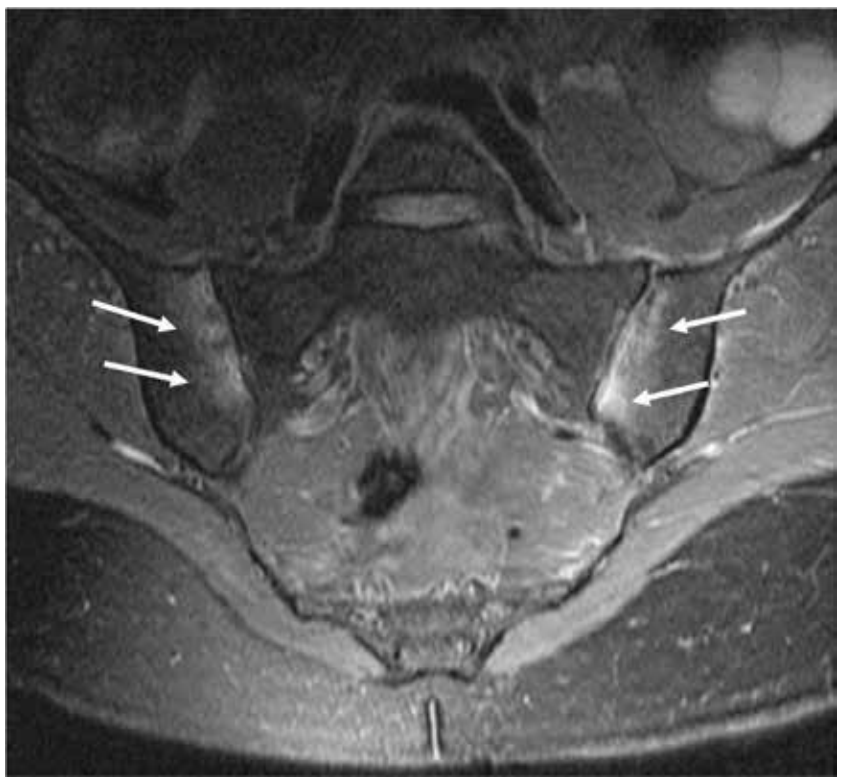

Fig. 1: Case 1. Pelvic magnetic resonance imaging of the sacroiliac joints with gadolinium enhancement and fat suppression performed 10 days after admission. High signal intensity is seen bilaterally at the subcortical bone marrow as well as inside the sacroiliac joint (*arrows*). Compatible with sacroiliitis.

she was treated with amoxicillin/clavulanate for 10 days.

She had no previous history of articular or extra-articular manifestations of axial spondyloarthritis, but had a family history of psoriasis in a second-degree relative.

Physical examination revealed arthritis of the left sternoclavicular joint, tenderness of the left tibialis posterior tendon, and a positive bilateral FABER (Patrick) test. Skin examination revealed teardrop-shaped rash on both legs and on the right forearm that were consistent with guttate psoriasis.

Blood analysis showed increased CRP level (40 mg/L), while HLA-B27, RF, ANA, and viral hepatitis serologies were negative. The serum anti-streptolysin O (ASO) titer was high (510 IU, normal < 200 IU) and confirmed the preceding streptococcal infection.

Magnetic resonance imaging of the lumbar spine and sacroiliac joints showed acute bilateral sacroiliitis. MRI of the spine revealed active corner inflammatory lesions on the anterior vertebral edge of L1, L2, L3, C5, and D1.

She was diagnosed with PSRA with axial involvement followed by guttate psoriasis and treated with NSAIDs including etoricoxib (90 mg/day for ten days) followed by etodolac (800 mg/day), with only a partial improvement. Afterwards, she was treated for four months with oral corticosteroids (prednisone at a dosage of 40 mg/day with gradual tapering) in combination with oral sulfasalazine (1.5 g/day), with a resolution of the rash and peripheral arthritis but without alleviation of inflammatory back pain. After 4 months of treatment, she had a BASDAI score of 5 and started treatment with infliximab (5 mg/kg every eight weeks). One year after the commencement of infliximab, her BASDAI reduced to 2.5, she had no rash, and her CRP level was within normal limits.

> *Post-streptococcal reactive arthritis appears to be a rare heterogeneous clinical entity that may present as axial spondyloarthritis in a subset of patients.*

Case 3

A 36-year-old woman was admitted to the Department of Internal Medicine due to severe inflammatory low back pain that lasted for a week. Additionally, she had pustular rash that covered the forearms, right hip, left ankle, and the palms of both hands. Two weeks before the hospitalization, she was diagnosed with follicular tonsillitis. At that time, since the patient had allergy to penicillin, treatment with first-generation cephalosporins was initiated for one week with a full resolution of symptoms. Her previous medical history included pustular psoriasis that was successfully treated with phototherapy and topical corticosteroids without recurrence of psoriasis for 15 years. She had no previous history of articular or extra-articular manifestations of axial spondyloarthritis. Prior to the hospitalization, she was treated with ibuprofen (1200 mg/day) and with injections of diclofenac sodium (75 mg) intramuscularly for 5 days.

Physical examination revealed pustular psoriasis on the arms and palms, as well as bilateral tenderness of the sacroiliac joints with a positive FABER test. No peripheral arthritis, enthesitis, tendinitis, or limitation of spinal movement was observed.

Blood analysis revealed elevated C-reactive protein (CRP) of 9 mg/L (normal < 5 mg/L), while HLA-B27, RF, ANA, EBV, CMV, HIV, and viral hepatitis serologies were negative. The first ASO test that was performed at the same day of hospitalization was invalid due to technical issues, but a repeated test that was done 5 weeks after the acute infection was positive (250 IU). MRI revealed acute bilateral sacroiliitis.

She was diagnosed with PSRA with axial involvement (bilateral sacroiliitis) followed by pustular palmoplantar psoriasis. Parenteral corticosteroids, particularly methylprednisolone at a dosage of 250 mg/day, were given for 4 days. Afterwards, she was treated for two weeks with oral corticosteroids at a dosage of 20 mg/day with a rapid tapering. In addition, etoricoxib (90 mg/day) was administered for three months with clinical improvement. The patient continued to receive topical treatment for psoriasis and remains in follow-up in our outpatient clinic.

The demographic and clinical characteristics of all three patients with psoriatic SpA are summarized in Table 1.

Table 1: Characteristics of patients affected by psoriatic SpA.

Feature	Patient 1	Patient 2	Patient 3
Gender (M/F)	F	F	F
Age at diagnosis (years)	37	35	36
Evidence of GAS infection	Positive throat culture	ASO—510 IU	ASO—250 IU
Onset of arthritis after infection (days)	7	10	7
Axial involvement	Bilateral SI/lumbar spine	Bilateral SI/lumbar spine	Bilateral SI
Peripheral involvement	Arthritis—right SCJ	Arthritis—left SCJ, tendinitis—TP	No
Type of psoriasis	Pustular	Guttate	Pustular palmoplantar
Family history of psoriasis	No	Yes	No
Previous psoriasis	No	No	Yes, pustular
CRP (mg/L) (normal < 5 mg/L)	94	40	9
HLA-B27	Negative	Negative	Negative
Response to NSAIDs	Low	Low	Moderate
Treatment with TNF-α blockers	Adalimumab	Infliximab	No
Duration of follow-up (months)	12	12	3

ASO serum anti-streptolysin O, *CRP* C-reactive protein, *GAS* group A streptococcus, *IU* International units, *NSAIDs* nonsteroidal anti-inflammatory drug, *PSRA* post-streptococcal reactive arthritis, *psoriatic SpA* psoriatic spondyloarthritis, *SCJ* sternoclavicular joint, *SI* sacroiliitis, *TNF-α* tumor necrosis factor alpha, *TP* tibialis posterior

Discussion

Post-streptococcal reactive arthritis appears to be a rare heterogeneous clinical entity that may present as axial spondyloarthritis in a subset of patients [6]. In our experience, while psoriatic SpA is relatively common, its presentation as a part of PSRA has not been described previously. We report three cases of HLA-B27-negative patients who developed psoriatic SpA following a recent episode of tonsillopharyngitis that occurred, on average, 8 days beforehand. A streptococcal infection was confirmed by a positive throat culture or ASO test. The main presenting syndrome was inflammatory back pain with evidence of acute bilateral sacroiliitis

and inflammatory spinal lesions on MRI. One patient had a family history of psoriasis and developed guttate psoriasis. In the remaining two patients, the GAS infection was followed by the occurrence of pustular psoriasis or its exacerbation after prolonged remission. At presentation, all patients had clinical characteristics of PSRA and fulfilled the classification criteria for psoriatic arthritis (CASPAR). All our patients had clinical features of psoriatic SpA that progressed to full-blown chronic disease with low-moderate response to NSAIDs and corticosteroids. Two patients required initiation of tumor necrosis factor alpha (TNF-α) blockers.

There is limited data regarding axial spondyloarthritis as a part of PSRA [3, 5–10]. A few case reports and case series reported the development of axial involvement in both HLA-B27-positive and HLA-B27-negative patients with PSRA [3, 6]. One of the first reports of PSRA with axial involvement was made in 1982 and presented a HLA-B27-positive woman with peripheral arthritis and sacroiliac pain following a streptococcal throat infection [16]. More recently, an interesting study including 25 PSRA patients reported that 6 of them had axial disease and 3 of them were positive for HLA-B27. It has been suggested that HLA-B27-positive patients have a higher susceptibility to developing sacroiliitis [3]. Additional features of spondyloarthritis such as enthesitis and tenosynovitis have also been reported in the setting of PSRA, either with or without the presence of arthralgias or arthritis [7, 10]. Furthermore, concomitant anterior uveitis in HLA-B27-negative patients with PSRA had been also described, and this complication should be identified early and treated accordingly [17].

Several lines of evidence support the idea that psoriasis may be a sequela of streptococcal infection [13–15]. For example, the reported incidence of streptococcal infections preceding guttate psoriasis ranges between 56 and 97% [13]. Likewise, the potential association of this type of infections and the development of PsA has been also explored [18]. Thus, in one study, the prevalence of anti-DNase-B antibodies was 51% in patients with PsA, in comparison with 10% in healthy controls [19]. An additional study found an association between PsA and the presence of *Streptococcus pyogenes* itself [20]. In particular, higher levels of 16S rRNA of *Streptococcus pyogenes* were observed in the blood of 19 patients with PsA, in comparison with patients with rheumatoid arthritis or patients with other types of arthritis. In contrast, another study has not found increased incidence of a preceding streptococcal infection in patients with PsA [21].

The pathogenic mechanisms underlying the development of PSRA are not fully understood. While various factors are involved in the pathogenesis of classic reactive arthritis, including genetic factors (i.e., HLA-B27), bacterial antigenicity, and the type of host response (i.e., Th1/Th2 imbalance), it is unknown whether these factors are involved in the pathogenesis of PSRA [11]. Regarding the genetic aspect, while HLA-B27 is positive in 50 to 80% of patients with reactive arthritis [11] and in 20–35% of patients with PsA [22], its prevalence in patients with PSRA is similar to the prevalence in the general population [5]. However, additional genetic factors associated with psoriasis and PsA, such as HLA-Cw6, may be possibly involved in the pathogenesis of acute psoriatic SpA triggered by GAS infection [23]. In our case series, all patients were HLA-B27 negative, but one of them had a family history of psoriasis.

> ***One of the clinical features of post-streptococcal reactive arthritis is a prolonged course with low-to-moderate response to nonsteroidal anti-inflammatory drugs.***

Since classic reactive arthritis, PSRA, and psoriasis all represent post-infectious entities, molecular mimicry should be considered to be one of the pathogenetic mechanisms in these disorders. Similarly, this mechanism may be possibly involved in acute psoriatic SpA. It has been postulated that the extensive homology between streptococcal M proteins and human epidermal keratin may play a role in the pathogenesis of psoriasis [24]. Thus, the disease may be initiated by CD8 T cells that recognize the streptococcal M protein in the palatine tonsils and the keratin in the skin. Subsequently, skin-homing CD4 T cells, along with γδ T cells, could play the role of an amplifier of inflammation and contribute to a self-sustaining inflammatory loop in the dermis [25, 26]. In the case of PsA, the pathogenic link between inflammatory T cell responses arising in the skin and the potential development of this disease has been recently investigated. Thus, markedly increased levels of IL17-producing CD8 T cells were found in synovial fluid of patients with PsA, and they were correlated with the disease severity [27].

One of the clinical features of PSRA is a prolonged course with low-to-moderate response to NSAIDs [3]. Similarly, two of our patients were refractory to NSAIDs and corticosteroids, and one of them had no response to sulfasalazine. There are no guidelines regarding further treatment in non-responders, and these patients are usually treated with corticosteroids and non-biological DMARDs, mainly sulfasalazine. Based on the efficacy of TNF-α blockers in both PsA and reactive arthritis, two of our acute psoriatic SpA patients were commenced on TNF-α blockers (adalimumab or infliximab), with a good response. To the best of our knowledge, only one case report described successful treatment of refractory PSRA with a TNF-α blocker (adalimumab) [28].

In our case series, all patients received short-term antibiotics. Currently, there is no consensus about the necessity and the duration of antibiotic prophylaxis for adults with PSRA. In two cases series, no increased risk of carditis was found in patients with PSRA who did not receive antibiotic prophylaxis during long-term follow-up [29, 30]. Similarly, there are no specific recommendations regarding prophylactic antimicrobial therapy or tonsillectomy for the treatment or prevention of flares in patients with psoriasis or PsA.

In conclusion, we present an interesting case series of three HLA-B27-negative patients who presented with acute psoriatic SpA triggered by GAS infection. Our observation suggests that this clinical entity should be considered in the differential diagnosis of new-onset inflammatory back pain followed by psoriasis in young adults who had a recent throat infection.

Compliance with ethical standards

Ethics: We have been officially waived from the IRB committee approval, as this is a case series.

Disclosures: None.

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Spinal fusion for severe neuromuscular scoliosis is a difficult procedure, with a high rate of complications. Among them, pancreatic fracture should be considered when abdominal pain persists in the postoperative period. Conservative management is advocated especially in case of a poor general condition.

PANCREATIC FRACTURE: A RARE COMPLICATION FOLLOWING SCOLIOSIS SURGERY

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A 14-year-old girl was referred to the spine clinic at our institution for severe neuromuscular scoliosis as a consequence of cerebral palsy following a great prematurity (30 weeks of gestation). She had a 120° right thoracolumbar curve on preoperative radiographs and was Risser Stage 1 (Fig. 1).

A gastric tube had been inserted months before to improve enteral intake ahead of the spinal procedure. We performed a posterior instrumentation, correction and fusion from T2 to S1 using hybrid implants with screw hook and sublaminar bands (Fig. 2). Cranial and caudal rods were connected using dominoes to improve the reduction, and achieve spinal balance. The surgical procedure was uneventful as well as the immediate postoperative course. During the first week after the procedure, the patient gradually developed abdominal symptoms including mild abdominal pain, vomiting and abdominal distension despite ceasing any enteral intake. As fever appeared at day 7, biological workup showed an increased lipase blood level (272 U/ml) associated with 27,000/ml white blood cells and C protein-reactive level of 105 mg/l.

Diagnostic Imaging Section

A CT scan then showed a major intra-peritoneal effusion associated with a suspected jejunal perforation and a corporeal fracture of the pancreas (Fig. 3).

Historical Review of the Condition, Epidemiology, Diagnosis, Pathology, Differential Diagnosis

Scoliosis is frequent in cerebral palsy patient with a reported incidence from 4 to 65% [1]. The aims of surgery are to stop the progression and re-balance the spine, therefore, allowing a seated position and facilitated nursing. Surgical correction of neuromuscular

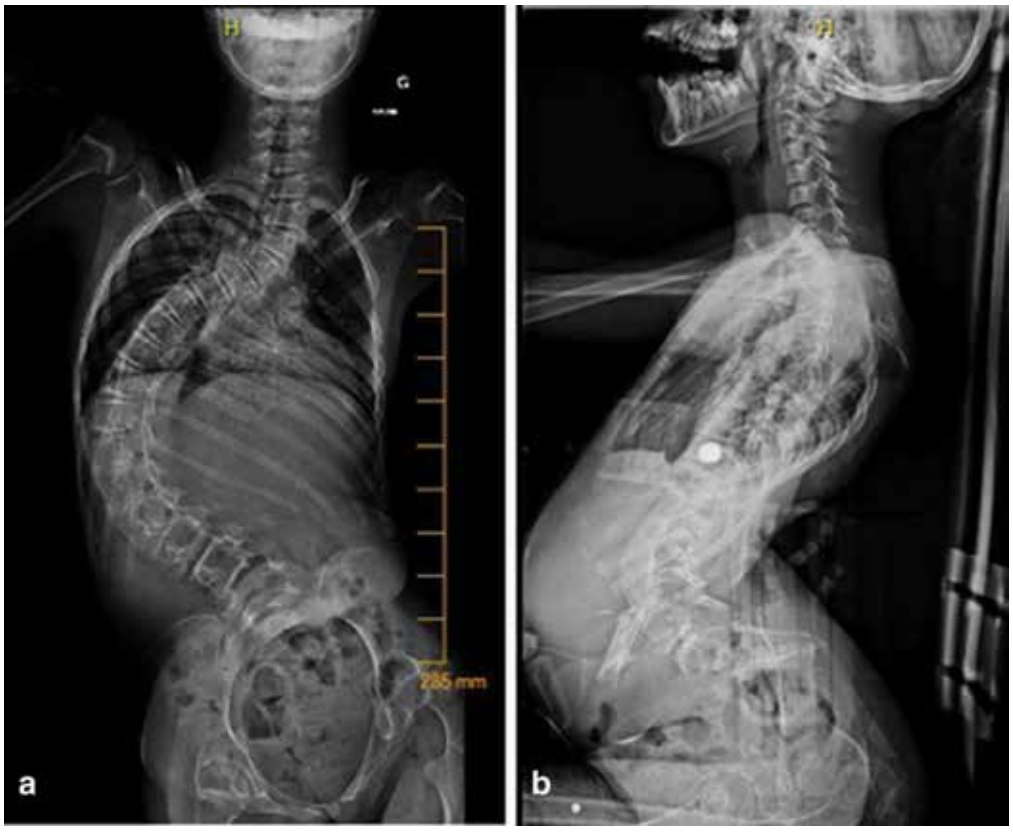

Fig. 1: Preoperative anteroposterior radiograph (**a**) and lateral (**b**) showing a major thoracolumbar scoliosis with pelvic obliquity.

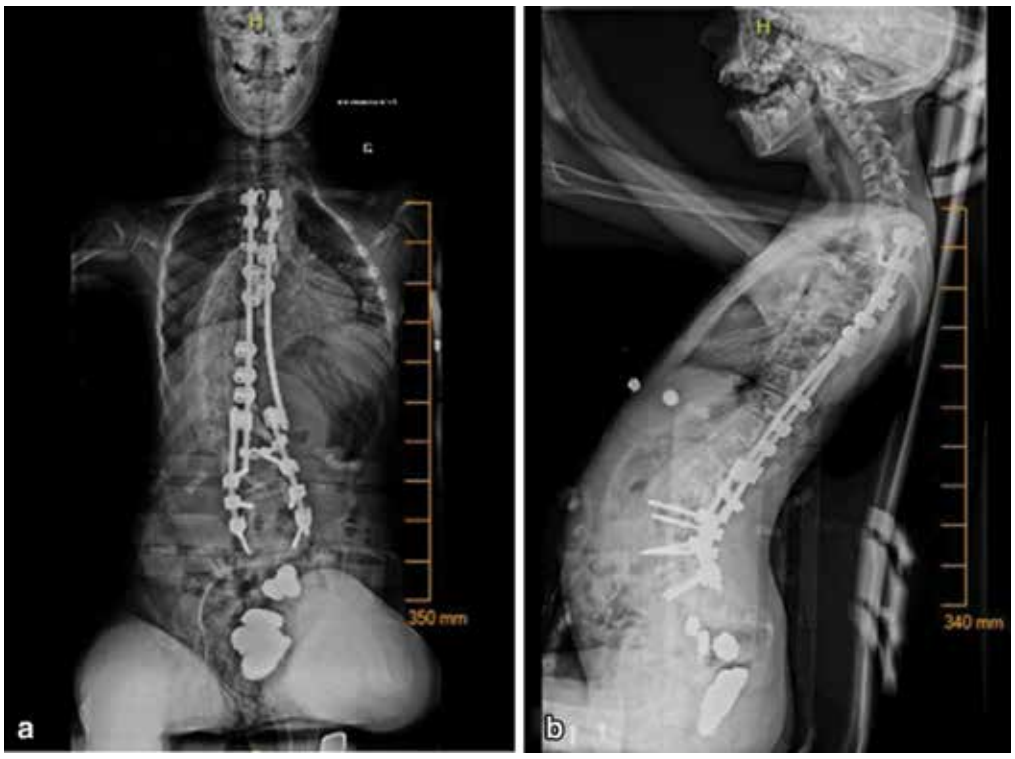

Fig. 2: Postoperative radiograph showing T2–S1 fusion with hybrid instrumentation and a satisfactory curve correction.

scoliosis allows a major benefit from a respiratory and autonomic point of view.

In cerebral palsy, several comorbidities and a major thoracolumbar deformity are often associated, increasing the risk of major complications [2, 3]. In these patients, surgery bears a higher risk of mortality and morbidity, according to data from the scoliosis research society (SRS), with 0.3 and 17.9%, respectively [4].

Not only septic, neurological but also digestive complications are classically described [5]. Among the latter category, some are nonspecific, such as reflex ileus, but others are inherent to the biomechanics of spinal deformity correction (Fig. 3).

The superior mesenteric artery syndrome is the most reported digestive complication of scoliosis surgery, but pancreatic injuries are scarcely described. Studies on acute pancreatitis found prevalence rates ranging between 8.5 and 31% [6, 7]. Pathophysiology remains unclear, but the hypothesis of a pancreatic compression against the spinal block, associated with an induced hypo-perfusion is the most plausible [8]. Clinical picture may include mild specific abdominal pain associated with an increased blood lipase and amylase up to three times the normal levels. Abdomino-pelvic CT scan usually confirms the diagnosis, although it is not systematically ordered [9, 10].

Unlike induced pancreatitis, we report here the case of a pancreatic fracture discovered early postoperative of posterior spinal fusion for thoracolumbar scoliosis with a major Cobb angle of 120° in an adolescent with neonatal cerebral palsy.

Pancreatic trauma is rare, accounting for less than 1% of all abdominal traumas [11]. The deep position of this organ can explain the injury mechanism, with lesions occurring as it is crushed against the fulcrum of the spine during an often indirect trauma. Clinical diagnosis is difficult and often delayed, in an exclusive indirect or direct traumatic context [12, 13].

This diagnosis is confirmed by abdomino-pelvic CT scan, leading to a staging of severity described by Moore *et al.* [14]. Abnormal pancreatic function tests may frequently be absent in an early stage. This confirmation may also be delayed and subtle due to underestimated lesions according to the imaging specificity and sensitivity (around 80%) [15].

Thus, in the current case, after an initial diagnosis wandering, linked to the nonspecific picture, repeated imaging demonstrated the pancreatic fracture, with a peri-pancreatic and abdominal effusion strongly evocative of a pancreatic fistula, which finally confirms the rare diagnosis of a pancreatic fracture with pancreatic ductal disruption [16] (Fig. 3).

Hypotheses concerning the underlying mechanism have been difficult to confirm, most likely, a massive pancreatic distension occurred during the reduction of the major thoracolumbar deformity. However, the possibility of a direct iatrogenic injury related to the pedicle screws cannot be ruled out. Indeed, a hematoma of the small intestine wall was diagnosed on the initial radiological workup. Moreover, abdominal exploration confirmed proud pedicle screws, although far away from the injured area.

Nevertheless, the modified anatomical

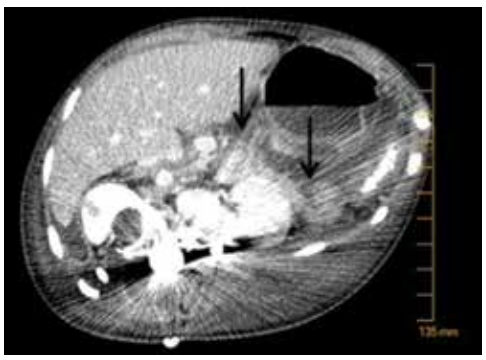

Fig. 3: Abdomino-pelvic CT scan coronal view showing a Grade III pancreatic trauma with Wirsung duct disruption.

reports could explain this late hypothesis. Another similar case has recently been reported by Al-Binali *et al.* [17] with delayed diagnosis of small intestine lesion due to spinal instrumentation (Fig. 4).

Rationale for Treatment and Evidence-based Literature

Pancreatic fractures are severe, with morbidity and mortality rates estimated at 26.5 and 5.3%, respectively. Isolated pancreatic fracture prognosis is directly related to the presence of pancreatic duct disruption. The reported complications are the development of pancreatic pseudocysts, chronic pancreatitis, and rarely diabetes in serious pancreas decay [18].

High severity stages (Moore III–V), high elevation of pancreatic enzymes 15 days later are the most common predisposing factors in pseudocyst occurrence.

Therapeutic management of isolated pancreatic fractures should be exclusively conservative in low-stage lesions (I and II) [19]. The management of high grade fractures (III IV) has long been debated; latest published data tend to underline the value of conservative treatment, even if a pancreatic duct rupture is associated. Reports in favor of early emergency surgery management with ductal rupture argue that this attitude considerably reduces the occurrence of recurrences [20–22] which has been estimated to be around 40%.

Given the high morbidity rate of pancreatic resection (about 60%), the conservative attitude remains preferable in case of isolated pancreatic fracture in hemodynamically stable patients.

When secondary pseudocyst occurs, it seems also advisable to favor a conservative management, which is effective in half of the cases. Expansive pseudocyst, symptomatic or compressive ones, may be managed with either endoscopic or image-guided drainage [23].

Procedure Section

A surgical abdominal exploration confirmed the suspected diagnosis. The jejunal lesion was resected with direct anastomosis. The duodeno-pancreatic region was out of reach due to the local inflammation. Drains were placed in the retrogastric region. During the exploration, the extremities of some lumbar pedicle screws were observed, a few millimeters proud in the lumbar region in the retroperitoneal area but 10 cm away from the pancreatic area. The postoperative course confirmed the pancreatic lesion involving the Wirsung duct as proved by the important leakage with increased lipase level (initially around 500 ml/day). A conservative management was decided with nil per os and initial antibiotics due to the jejunal perforation.

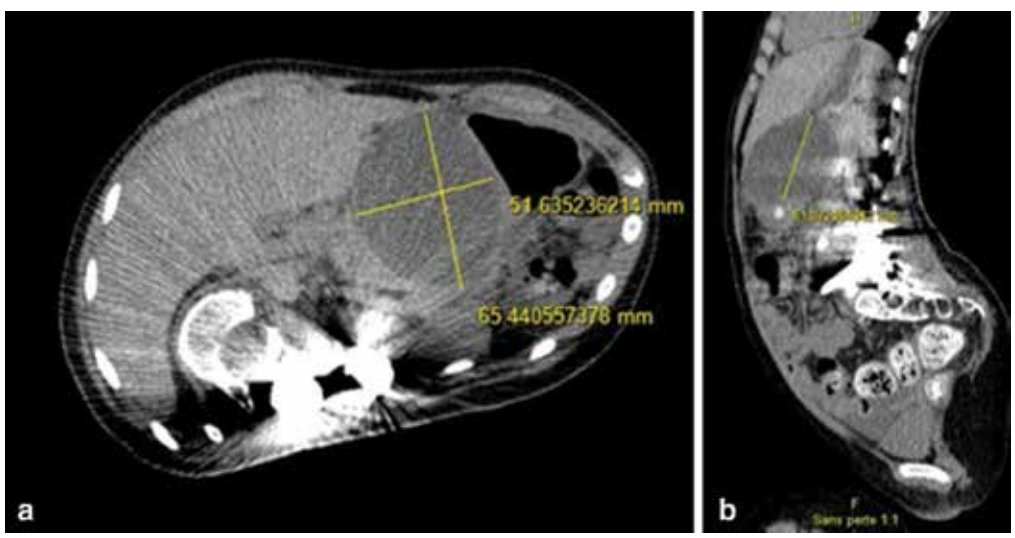

Fig. 4: Abdomino-pelvic CT scan, coronal (**a**) and axial (**b**), showing an expanding pancreatic pseudocyst (about 6 cm in diameter).

In spite of the pancreatic duct rupture, we favored the conservative approach for our patient, given the morbidity and mortality rates of proximal pancreatic surgery in a patient with respiratory and nutritional deficiencies. Furthermore, delayed diagnosis of pancreatic duct rupture also influenced the therapeutic management.

Outcome and Follow-up

During the further weeks, the amount of fluid dropped progressively to disappear whereas a pseudocyst grew from 2 to 6 cm in diameter (Fig. 4). Despite this evolution, it was decided to manage it conservatively because of the absence of induced symptoms. From an orthopedic point of view, the scoliosis correction was satisfactory with a 50% correction and a good spinal balance. Several weeks later, abdominal symptoms reappeared along with the pseudocyst growth and another biological pancreatitis. Endoscopic drainage (gastrocystostomy) allowed improving clinical and biological parameters. After 6 months of follow-up, the patient remained pain-free and lipase level has eventually dropped to normal. Lately an acute digestive peritonitis without evident cause led to the patient death.

Conclusion

Pancreatic fracture in children and adolescents is rare and the diagnosis complex, as its presentation is often nonspecific. To our knowledge, its occurrence in a postoperative context of scoliosis surgery has never been described. If iatrogenic acute pancreatitis is a relatively common entity, pancreatic fracture should also be considered. Conservative management generally allows complete healing after a few weeks. Secondary pancreatic pseudocyst, which is the most frequent complication, can require an endoscopic or image-guided drainage if symptomatic.

Compliance with ethical standards

Conflict of interest: The authors declare no Grant or conflict of interest.

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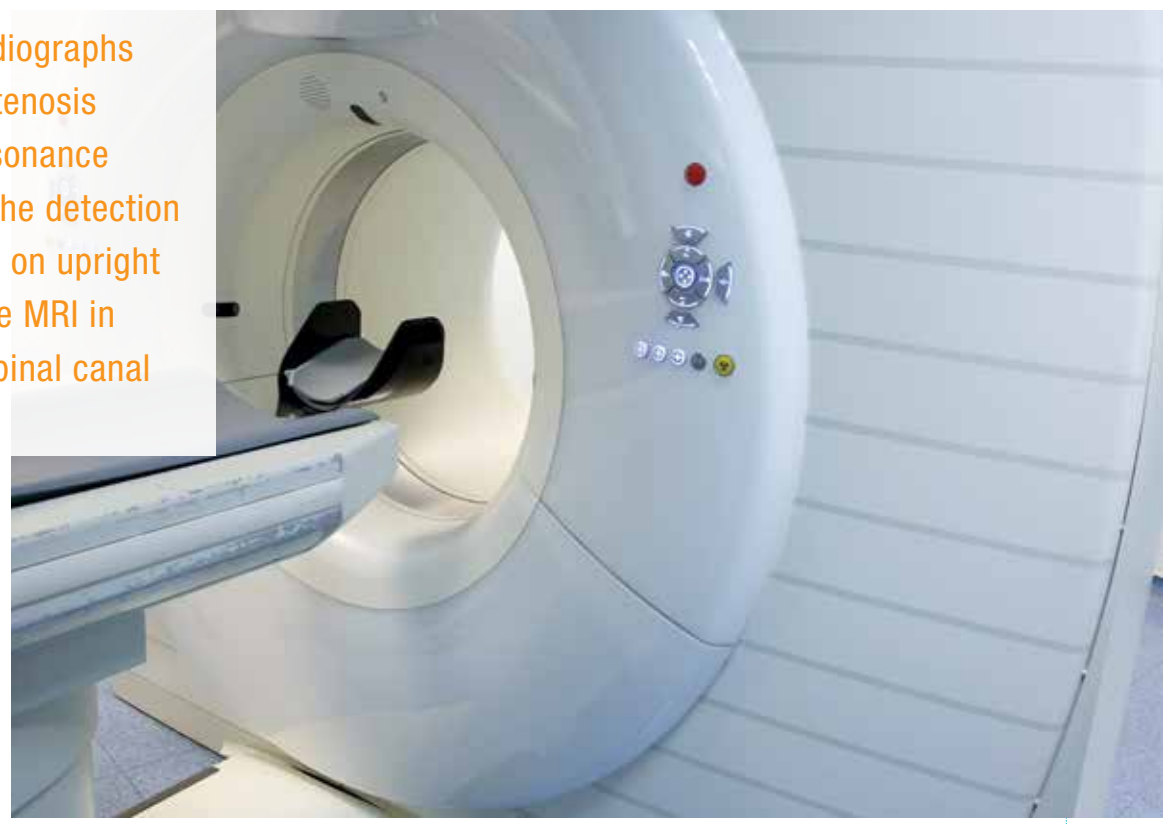
To investigate whether upright radiographs can predict lumbar spinal canal stenosis using supine lumbar magnetic resonance imaging (MRI) and to investigate the detection performance for spondylolisthesis on upright radiographs compared with supine MRI in patients with suspected lumbar spinal canal stenosis (LSS).



CORRELATION OF LISTHESIS ON UPRIGHT RADIOGRAPHS AND CENTRAL LUMBAR SPINAL CANAL STENOSIS ON SUPINE MRI: IS IT POSSIBLE TO PREDICT LUMBAR SPINAL CANAL STENOSIS?

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Spinal canal stenosis is most frequently caused by a gradual narrowing of the spinal canal during aging (degenerative type) and occurs in 75% of cases in the lumbar region. In lumbar spinal stenosis (LSS), compression of the spinal cord and nerves is associated with, for example, lower back pain and abnormal sensations in the lower extremities and buttocks [1]. Degenerative LSS as a result of longstanding intersegmental instability most often occurs at the vertebral segment L4/5 [2] with a prevalence of 4–10% [3, 4] and women above the age of 60 are particularly affected [5].

Imaging for LSS commonly starts with conventional upright radiographs, but often requires additional testing with magnetic resonance imaging (MRI). Several studies have shown a poor morphoclinical correlation between symptoms and imaging findings [6–8] that are mostly based on cross-sectional spinal canal surface measurements only [9–12] in addition to stenosis ratio measurements [13]. To achieve a better morphoclinical correlation, Schizas *et al.* designed a qualitative grading system that takes into account the degree of impingement of neural structures in relation to cerebrospinal fluid (CSF) and is appreciated on axial T2-weighted (T2w)

images of the lumbar spine [14]. According to the authors, a Grade C stenosis (referred to as severe stenosis), unlike in Grade B stenosis (referred to as moderate stenosis), no rootlets or CSF signal are distinguishable, but there is still epidural fat present that is absent in Grade D stenosis (referred to as extreme stenosis; Fig. 1). The study by Schizas *et al.* could not identify a significant relationship between the grade of stenosis and clinical symptoms, as assessed by the Oswestry Disability Index. However, the study indicated that Schizas' stenosis grades C and D may be useful as a predictor of surgical relevant lumbar spinal canal stenosis, because patients with stenosis grades C and D had an increased likelihood of failure of conservative treatment and need for surgery (odds ratio = 29.8). However, a recent study by Weber *et al.* showed that the radiological severity of lumbar spinal stenosis, as assessed by the Schizas grading system, has no clear clinical correlation and should therefore not be overemphasized in clinical decision-making [15].

Listhesis is a well-known cause of LSS and its extent on upright radiographs may point to the grade of stenosis. Therefore, the primary aim of this study is to investigate whether upright radiographs can predict the grade of central lumbar spinal stenosis, as defined by Schizas *et al.* on supine MRI. As a secondary research aim, we pursued investigation of the detection performance of spondylolisthesis using the two techniques, and we strived to identify a cutoff value (in millimeters) for the extent of spondylolisthesis on upright radiographs to detect patients with high-grade spinal canal stenosis.

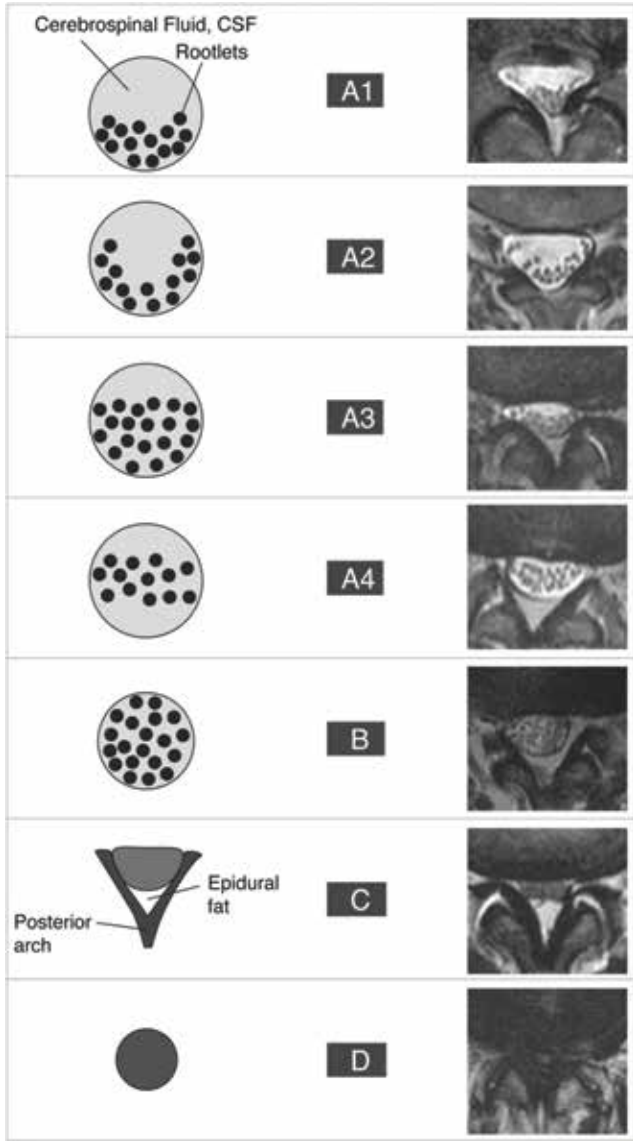

Fig. 1: Original figure from Schizas *et al.* [14]. The qualitative grading system designed by Schizas *et al.* takes into account the degree of impingement of neural structures in relation to cerebrospinal fluid (CSF) and is appreciated on axial T2-weighted (T2w) images of the lumbar spine. In a Grade C stenosis (referred to as severe stenosis), unlike in Grade B stenosis (referred to as moderate stenosis), no rootlets or CSF signal are distinguishable, but there is still epidural fat present that is absent in Grade D stenosis (referred to as extreme stenosis). Image courtesy of Prof Constantin Schizas and reproduced with permission of the publisher LWW.

Materials and Methods

This study was conducted in compliance with the Declaration of Helsinki and was approved by the local ethical committee of the University Zurich, Switzerland. All patients received written and oral information about the study and gave their written informed consent to participation.

Study Population

Conventional radiographs and MR images of 143 patients (75 female, 68 male, mean age 72 ± 9 years, range 51–90 years) were retrospectively evaluated. All patients were participants of a larger multicenter study (Lumbar Stenosis Outcome Study [LSOS]) and were prospectively and consecutively included between 2014 and 2016 at one of the ten participating centers. The LSOS investigates the effectiveness of various treatment options in patients with symptomatic lumbar spinal canal stenosis based on an inter-disciplinary approach [16]. Inclusion criteria for the LSOS comprise: age over 50 years and a high clinical suspicion of lumbar spinal canal stenosis that is defined by uni- or bilateral neurogenic claudication, with pain in the buttocks and/or lower extremities provoked by walking or extended standing and relieved by rest and/or bending forward. Furthermore, patients with evidence for stenosis caused by tumor, fracture, infection or significant deformity (> 15° lumbar scoliosis) and those with preceding operations of the lumbar spine were not included. Additional selection criteria specifically for this present study were the availability of conventional X-ray images of the lumbar spine in lateral and anteroposterior projection in the standing position. The interval between X-ray and MRI had to be within 2 weeks. Degenerative listhesis types in the anteroposterior direction only were included and no listhesis due to spondylolysis or listhesis in the medial–lateral direction. Additionally, patients with a congenital narrowed spinal canal, as assessed by MRI at level L4/5 were excluded [9].

Imaging

Magnetic Resonance Imaging

All scans of the lumbar spine were performed with the routinely used MRI protocols in supine position for patients with known or suspected lumbar spinal canal stenosis

(Siemens Magnetom Avanto 1.5 T, Espree 1.5 T, or Verio 3 T; acquisition of, for example, sagittal T2w images [TR/TE 3,740 ms/118 ms, field of view 300 mm, slice thickness 4 mm, matrix 512×256 pixels], sagittal T1w [TR/TE 500 ms/11 ms, field of view 300 mm, slice thickness 4 mm, matrix 512×256 pixels] and transverse T2w [TR/TE3,700 ms/115 ms, field of view 220 mm, slice thickness 4 mm, matrix 512×256 pixels] images, protocol for the 1.5 T Avanto MR scanner).

Radiographs

The lumbar spine was examined using standard digital X-ray equipment in lateral and anteroposterior projection in an upright position.

Image Analysis

Image analysis was performed by a board-certified radiologist with 8 years of experience in spinal imaging (S.W.). To evaluate the intra-reader agreement regarding the listhesis measurements, all measurements were repeated after a time interval of 4 weeks to prevent recall bias. To evaluate the inter-reader agreement, a second board-certified reader (T.F.) with 6 years of experience in spinal imaging repeated all listhesis measurements. Both readers were blinded to patient's names, gender, age, and to the data of the second imaging modality in addition to the results of the other reader.

First, the upright lateral radiographs were evaluated. Image analysis included the evaluation of the presence or absence of listhesis and measuring the extent (in millimeters) of the listhesis (Fig. 2a), as proposed by Dupuis *et al.* [17]. Anterior spondylolisthesis was defined as an anterior slipping of vertebra L4 on L5 of ≥3 mm [18]. If a spondylolisthesis ≥3 mm was detected, grading was additionally performed according to the Meyerding classification system [19]. Second, the same patients were evaluated on supine midsagittal T2w MR images (Fig. 2b) by measuring the distance between two parallel lines, as previously described by Niggemann *et al.* [20]: the first line connects the upper and lower dorsal edges of the cranially located vertebra, whereas the second line originates from the upper dorsal edge of the caudal vertebra. The LSS grading according to Schizas *et al.* [14] at vertebral level L4/5 (Fig. 2c) has already been performed within the framework of the LSOS database [16]. The Schizas classification is explained extensively in the Introduction section.

> *In lumbar spinal stenosis (LSS), compression of the spinal cord and nerves is associated with, for example, lower back pain and abnormal sensations in the lower extremities and buttocks.*

Statistical Analysis

Statistical analysis was performed using commercially available software (IBM SPSS Statistics, Version 21.0.; IBM, Armonk, NY, USA). Categorical variables were expressed as frequencies and percentages; continuous variables were expressed as median ± interquartile range including their corresponding 95% confidence intervals (CIs). Testing for normality was performed using the Shapiro–Wilk test.

Intra-reader and inter-reader agreement regarding listhesis measurements was determined by using intraclass correlation coefficient (ICC) statistics (two-way mixed, consistency, single measures) with their corresponding 95% CI. The ICC was defined as follows: poor (ICC, ≤0.69), fair (ICC, 0.70–0.79), good (ICC, 0.80–0.89), or high (ICC, ≥0.90) [21]. Presence or absence of anterolisthesis was compared among radiographs and MRI using the Chi-square test. Student's paired *t* test was used for comparing anterolisthesis measurements (in millimeters) from radiographs with measurements on MRI with corresponding mean differences. The Wilcoxon signed-rank test was used to assess differences among the listhesis grading (Meyerding classification) among radiographs and MRI. Spearman's rho correlation test was used to assess for correlations between the extent of anterolisthesis on radiographs and MRI and the grade of central spinal canal stenosis according to the Schizas classification. Sensitivity and specificity in addition to positive predictive value (PPV) and negative predictive value (NPV), with their corresponding 95% CI for the determination of the grade of spinal canal stenosis by the grade of anterolisthesis on radiographs, were calculated using Chi-squared tests. A p value of < 0.05 was used to denote statistical significance.

Results

The Shapiro–Wilk test demonstrated non-normally distributed data for listhesis measurement on radiographs and MRI ($p < 0.05$, each).

Intra-and Inter-reader Analysis

Measurements of the anterolisthesis on radiographs and MRI demonstrated a high intra-reader agreement regarding the degree of anterolisthesis in millimeters (ICC = 0.945 [95% CI, 0.907–0.968] and ICC = 0.918 [95% CI, 0.831–0.961] respectively, each $p < 0.001$).

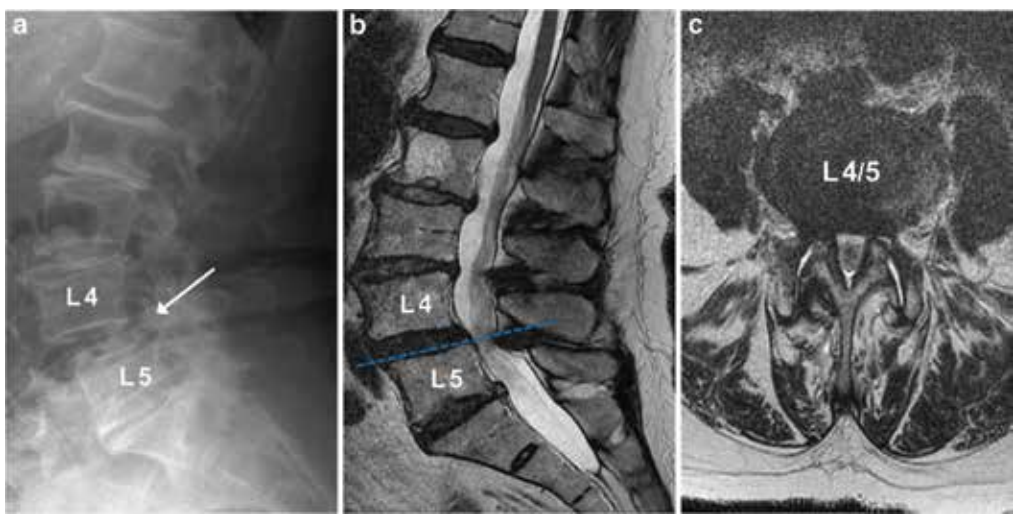

Fig. 2: Example of a 58-year-old male patient with lower back pain and abnormal sensations in both lower extremities and buttocks, suggestive of lumbar spinal stenosis. The anterolisthesis visible at L4/5 on **a** the upright radiograph is markedly greater (*arrow*) compared with **b** the supine acquired sagittal T2w MR image. The extent of anterolisthesis measured on the radiograph (**a**) correlates with the grade of stenosis according to Schizas *et al.* [14] as assessed on **c** the axial T2w MR image. In **c**, no rootlets or cerebrospinal fluid signal are distinguishable within the dural sac at level L4/5, but there is still epidural fat present, which is equivalent to a severe grade C stenosis. *Blue dashed line* in **b** indicates the axial level shown in **c**.

Similarly, the inter-reader analysis demonstrated a high agreement regarding the degree of anterolisthesis on radiographs and MRI in millimeters (ICC = 0.907 [95% CI, 0.845–0.945] and ICC = 0.9 [95% CI, 0.795–0.952] respectively, each $p < 0.001$).

Listhesis and Spinal Canal Stenosis

Anterolisthesis was detected in 54 patients on radiographs (38%) and in 28 patients on MRI (20%, $p < 0.001$, Fig. 3). This results in 18% more detected patients with anterolisthesis ≥3 mm by means of standing radiographs compared with MRI. With the exception of one case, all cases of anterolisthesis that were detected by MRI were also visible on the corresponding radiographs. Retrospectively, in this single case, an anterolisthesis of 3 mm was measured on the MR scan, whereas only a small step of 2 mm was visible on the radiograph. Therefore, in a total of 55 patients, an anterolisthesis was detected on radiographs and/or MRI. In cases with detected listhesis on both imaging modalities ($n = 27$), the extent of listhesis was significantly ($p < 0.001$) larger on upright radiographs (9 ± 5 mm, 95% CI, 7–10) compared with supine MRI (5 ± 3 mm, 95% CI, 4–7), mean difference 2.9 ± 1.9 mm (Fig. 4). The Meyerding listhesis classification demonstrated a statistically significantly higher grade of listhesis on radiographs (median Meyerding: grade 1 = 76%, grade 2 = 25%, grade 3 = 0%) compared with MRI (median Meyerding: grade 1 = 96%, grade 2 = 4%, grade 3 = 0%; $p < 0.001$).

> *Our study showed that in 18% of patients, anterolisthesis of the lumbar segment L4/5 would have been missed if only supine MRI and no upright radiographs were taken into account.*

According to the LSOS database [16], the following Schizas grades have been assigned to the 55 patients of our study who showed an anterolisthesis on radiographs and/or MRI: Schizas Grade A: $n = 14$ (25.5%); Grade B: $n = 7$ (13%), Grade C: $n = 20$ (36%); Grade D: $n = 14$ (25.5%). A positive correlation was found regarding the extent of listhesis on radiographs (in millimeters) and the grade of Schizas spinal canal stenosis on MRI ($r = 0.563$, $p < 0.001$). No significant correlation was found regarding the extent of listhesis (in millimeters) on MRI and the Schizas grade of stenosis ($r = 0.134$, $p = 0.497$). In addition, a positive correlation was found regarding the Meyerding grade of anterolisthesis on radiographs and the Schizas grade of stenosis ($r = 0.346$, $p < 0.05$), whereas no significant correlation was found when comparing the Meyerding grading on MRI with the Schizas classification ($r = 0.233$, $p = 0.234$). Anterolisthesis measurements of ≥5 mm on radiographs were seen in 36 of the 143 cases (25%). Applying this cutoff value (≥ 5 mm) results in a specificity of 90% (95% CI, 0.808–0.955), PPV of 78% (95% CI, 0.619–0.882), sensitivity of 43% (95% CI, 0.308–0.559), and an NPV of 65% (95% CI, 0.560–0.738) for detection of patients with a grade C or D stenosis according to the Schizas classification. The prevalence of patients with Schizas' grade C and D stenosis in our patient population with symptoms of lumbar spinal canal stenosis ($n = 55$) was 34 out of 55 (62%). This prevalence is very similar to 61.8% described in the original study published by Schizas *et al.* [14].

Discussion

Our study showed that in 18% of patients, anterolisthesis of the lumbar segment L4/5 would have been missed if only supine MRI and no upright radiographs were taken into account. Furthermore, the extent of anterolisthesis was significantly underestimated on MRI alone. Both conclusions are likely due to the weight-bearing conditions prevailing during upright radiograph acquisition [22, 23]. In the standing position, the spine is loaded, the intervertebral space decreases in cases with preexisting osteochondrosis, which leads not only to a decrease in the craniocaudal neuroforamina diameter [24], but also to an increase in the pressure on

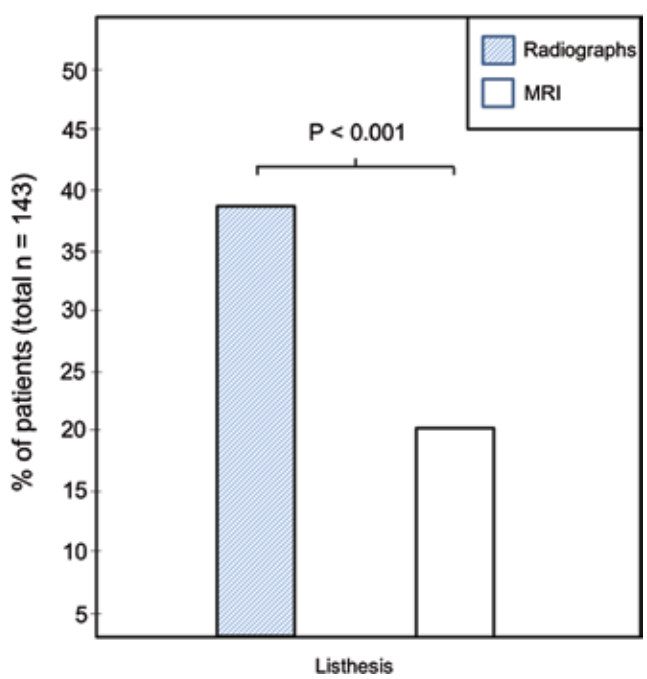

Fig. 3: Anterolisthesis was detected in significantly more patients on radiographs ($n = 54$, 38%; *hatched bar*) compared with MRI ($n = 28$, 20%; *plain bar*), $p < 0.001$. Total patients $N = 143$.

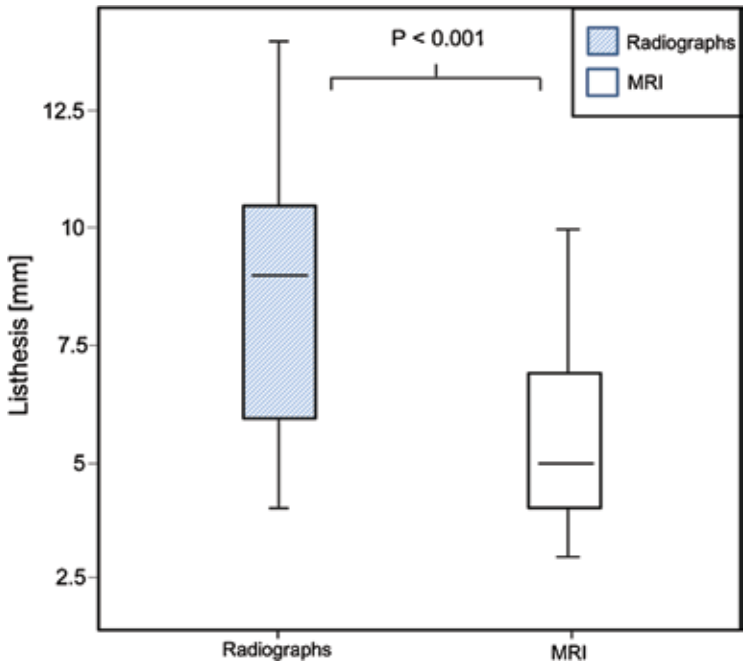

Fig. 4: Larger extents of anterolisthesis were found on radiographs (9 ± 5 mm; *hatched boxplot*) compared with MRI (mean 5 ± 3 mm; *plain boxplot*), $p < 0.001$.

the facet joints, which in turn leads to anterior slipping of the superior vertebra in the further stages of spondylarthrosis [25–28]. These secondary findings of our study concur with those of other studies that showed that upright imaging modalities detect more anterolisthesis than supine imaging [24, 29]. In particular, the study by Segebarth *et al.* showed that 28% of patients with degenerative LSS would be missed on supine MRI alone [30]. The clinical benefit from the detection of anterolisthesis in addition to its severity using upright lumbar radiographs is that the treating physician can estimate to what extent the MRI findings worsen under load-bearing conditions, and that within the scope of surgery planning, a considerable anterolisthesis may require additional dorsal instrumentation [31].

Degenerative spondylolisthesis is a well-known cause of LSS and its extent on upright radiographs may point to the grade of stenosis, the primary hypothesis examined in this current study. To the best of our knowledge, there has been no previous work that assessed the relationship between spondylolisthesis on upright radiographs and central spinal canal stenosis, as defined by Schizas *et al.*, a MRI classification system that considers impingement of neural tissue to yield a better morphoclinical correlation. In our study, we found a positive correlation regarding the grade of listhesis measured on radiographs and the grade of stenosis on MRI ($r = 0.563$). Applying a cutoff value for anterolisthesis ≥5 mm on radiographs results in a specificity of 90% (= high certainty that in the case of anterolisthesis ≥5 mm on radiographs, a Schizas' Grade C/D stenosis is present) and a PPV of 78% for the detection of patients with Schizas' grade C/D stenosis. We have set the cutoff value to 5 mm for anterolisthesis because = that is above the currently accepted threshold of 4 mm for diagnosing lumbar segmental instability [32] and to increase the test specificity. The low NPV and sensitivity suggest that the threshold of ≥5 mm anterolisthesis on radiographs is not suitable for ruling out high-grade spinal canal stenosis.

The clinical benefit resulting from our primary study goal is as follows. In reality, most patients with back pain are treated beyond the setting of University Hospitals and highly specialized spine centers. Most frequently, upright radiographs only are performed in patients seeking help for lumbar back pain as MRI is not affordable in many cases. Our study provides evidence that an anterolisthesis of ≥5 mm on upright radiographs in patients with symptoms of lumbar spinal canal stenosis is indicative of lumbar spinal canal stenosis. Consecutively, in these cases, lumbar MRI is warranted. Therefore, we suggest using upright radiographs as a "gatekeeper" test for patients with symptoms of lumbar spinal canal stenosis.

> ***"The clinical benefit from the detection of anterolisthesis in addition to its severity using upright lumbar radiographs is that the treating physician can estimate to what extent the MRI findings worsen under load-bearing conditions, and that within the scope of surgery planning, a considerable anterolisthesis may require additional dorsal instrumentation.***

Our study has limitations. First, we did not perform a dedicated correlation with clinical findings as this is beyond the scope of our study involving patients with suspected lumbar spinal canal stenosis, which is often accompanied by multisegmental degenerative changes and hence highly diverse symptoms. Second, we included L4/5 level only in the analysis. On the one hand, that may be justified by the fact that the L4/5 level is by far the most affected level of degenerative listhesis [2]; on the other hand, other factors such as the lordotic and lumbosacral angle in addition to the sacral inclination angle are more likely to have a greater influence on listhesis at other lumbar levels. Third, on some radiographs, the delineation of the posterior edge of the vertebra for the listhesis measurement was difficult. Nevertheless, the ICC statistics suggested comparable measurements. Fourth, X-ray geometric magnification may have influenced the anterolisthesis measurements on the lateral radiographs. Finally, despite the inclusion of 143 patients, only 55 patients had anterolisthesis on radiographs and/or MRI; therefore, the study population was relatively small. However, the 95% CI of the listhesis measurements on radiographs and MRI are relatively narrow, which suggests an adequate sample size.

In conclusion, upright radiographs demonstrated more and larger extents of anterolisthesis compared with supine. In addition, in patients with suspected LSS, the extent of anterolisthesis on radiographs (particularly ≥5 mm) is indicative of lumbar spinal canal stenosis and warrants lumbar spine MRI.

Compliance with ethical standards

Conflicts of interest: This study was supported by the Helmut Horten Foundation, Baugarten Foundation, Pfizer-Foundation for geriatrics and research into geriatrics, Symphasis Charitable Foundation and OPO-Foundation. We disclose any financial support or author involvement with organization(s) with a financial interest in the subject matter.

IRB statement: This study was approved by the local ethical committee of the University of Zurich, Switzerland. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent: All patients received written and oral information about the study and gave their written informed consent for participation. The project was registered at http://www.research-projects.uzh.ch/p16804.htm

References available on request
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Source: Finkenstaedt, T., Del Grande, F., Bolog, N. *et al.* *Skeletal Radiol* (2018) 47: 1269. https://doi.org/10.1007/s00256-018-2935-3. © ISS 2018.

TRAPEZIOMETACARPAL JOINT OSTEOARTHRITIS: PHYSICAL AND RADIOLOGICAL EVALUATION

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Physical Evaluation

The trapeziometacarpal (TM) joint represents one of the most common sites of osteoarthritis, mostly in the postmenopausal female population [1].

Patients suffering from TM osteoarthritis develop a radial-sided wrist and hand pain. This pain usually is described as a constant ache that increases during normal daily living activities such as gripping, twisting and pinching.

Furthermore patients could complain about a change of appearance of the thumb with a progressive deformity characterized by metacarpal adduction and hyperextension of the metacarpophalangeal joint, as it happens above all in the advanced stages.

Since several causes different from TM osteoarthritis could lead to a radial-sided pain (Table 1), a complete and careful clinical evaluation must be performed in order to achieve the correct diagnosis and to assess a correct treatment.

At the inspection, while in the advanced stages, there is the typical deformation above-mentioned, in the early stages the joint appears normal and also the range of motion.

In advanced stages a prominence at the base of the thumb could be present, and it may be due to a synovitis or to a subluxation of the base of the metacarpal to the trapezium or to an osteophyte resulting from the degenerative process.

Usually patients localize the pain palmarly at the base of the thenar eminence of the thumb, and it could be elicited by a manual pressure of this point.

In the early stages, the typical instability of the TM joint could be detected by stabilizing the trapezium and translating the metacarpal in dorso-volar and in a radioulnar way, and this manoeuvre results in an abnormal movement of this joint.

Furthermore, applying an axial force during an ulno-radial translation of the TM joint (grind test) could be considered as a provocative manoeuvre since it could elicit pain or discomfort since this manoeuvre increases shear stress at the joint.

An objective and complete evaluation of the thumb must be performed comparing its movement and key pinch force with the contralateral side. In fact, the range of motion usually is diminished; correlating with the degree of degeneration of the joint and key pinch force is not only diminished but also elicits pain.

In very advanced stage of the disease, the physical features change. In fact it is no more possible to assess the laxity of the TM joint because the degenerative process leads to the formation of osteophytes making it stiff. At the inspection, also the normal shape of the thumb changes since the base of the first metacarpal is placed in dorsal subluxation, and it is fixed in adduction. This fact leads to a loss of range of motion in abduction and adduction and to a compensatory metacarpal-phalangeal hyperextension and a flexion of the interphalangeal joint (due to the effect of the flexor pollicis longus) that produces a Z-shaped deformity.

Radiographic Evaluation

The radiographic evaluation of the TM joint is usually performed by standard anteroposterior (AP), lateral and oblique X-rays. Dynamic stress view is not usually routinely performed, but it may be used to confirm the diagnosis.

Table 1: Main possible differential diagnosis in radial-sided wrist pain.

Diagnosis	Clinical examination
De Quervain's tenosynovitis	Pain over the first extensor compartment; Finkelstein test positive
Scaphoid injuries	Pain over the anatomical snuffbox that increases during movement of flexion and extension of the wrist
Scapho-trapezium-trapezoidal osteoarthritis	Pain distal to the scaphoid

The AP view, also called Robert's view [2], must be obtained by fully pronating the forearm and the shoulder internally rotated and placing the dorsal surface of the thumb next to the X-ray plate (Fig. 1).

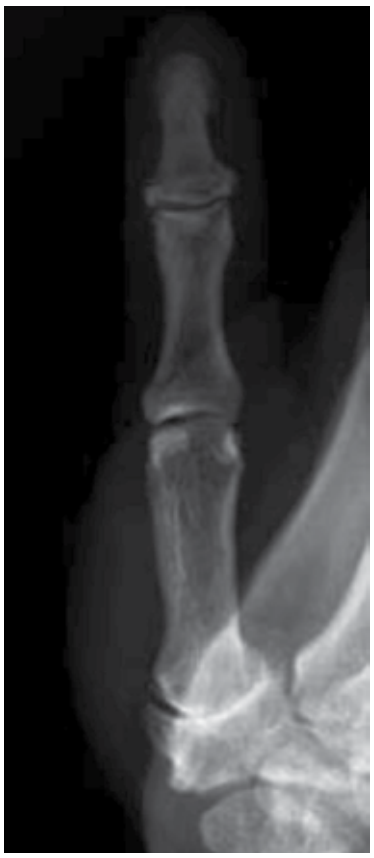


Fig. 1: The AP view, also called Robert's view, obtained by fully pronating the forearm and the shoulder internally rotated and placing the dorsal surface of the thumb next to the X-ray plate.

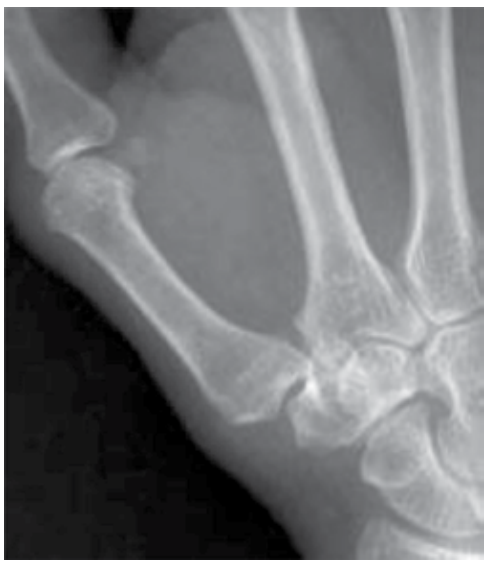


Fig. 2: The lateral view, also called Gedda's or Bett's view, gives a full view of the trapezium and of the trapeziometacarpal space.

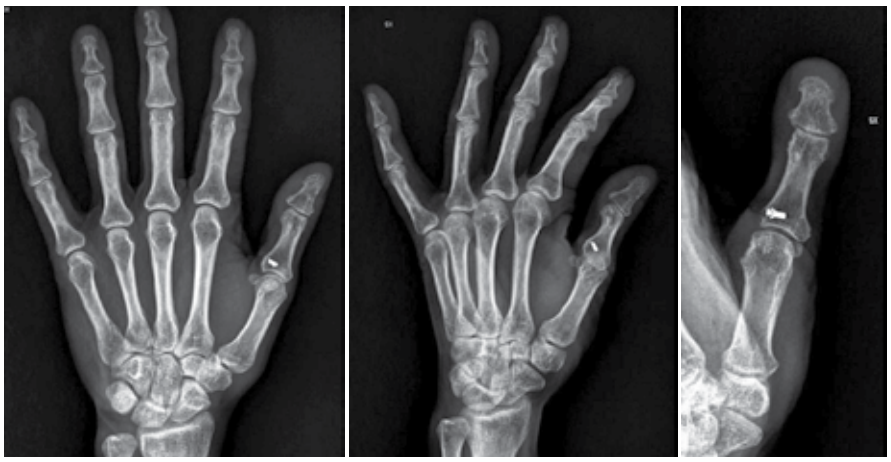


Fig. 3: Stage I: normal or slightly widened TM joint, TM subluxation up to one-third of the articular surface, normal articular contours.

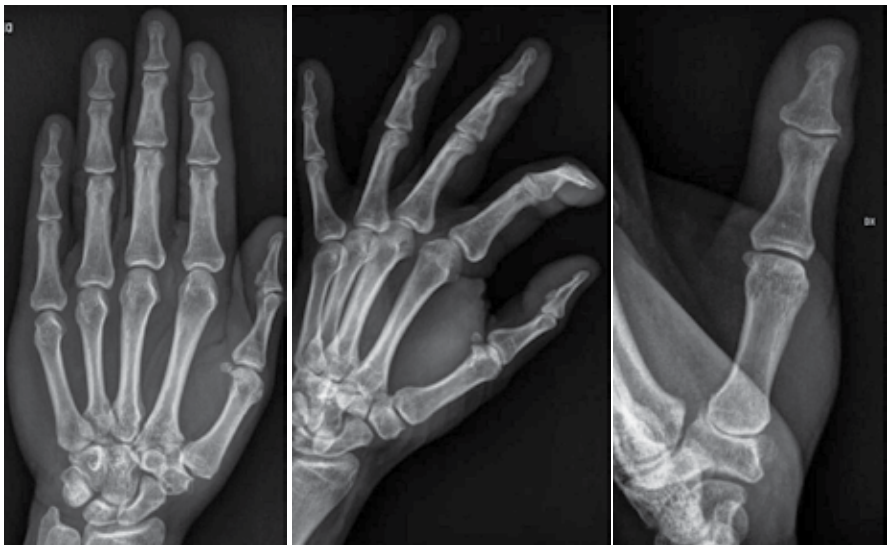


Fig. 4: Decreased joint space and osteophyte < 2 mm.

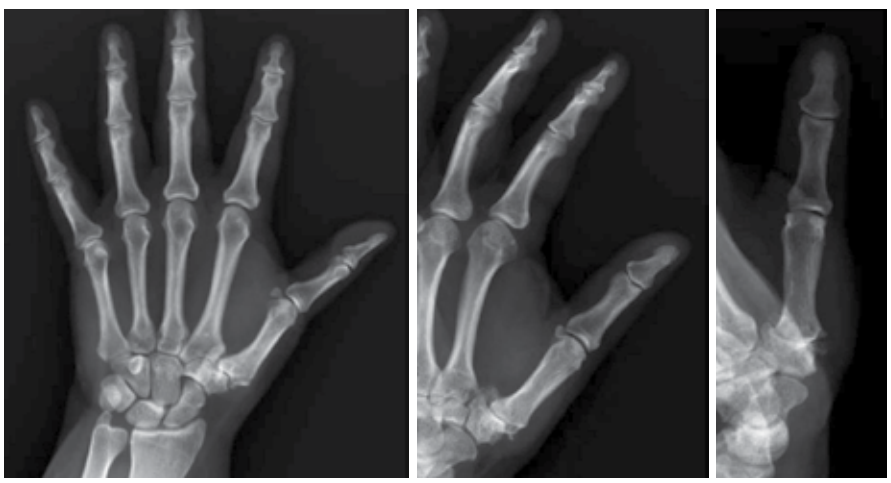


Fig. 5: Stage III: subluxation > than 1/3 of the articular surface, subchondral sclerosis, osteophyte > 2 mm.

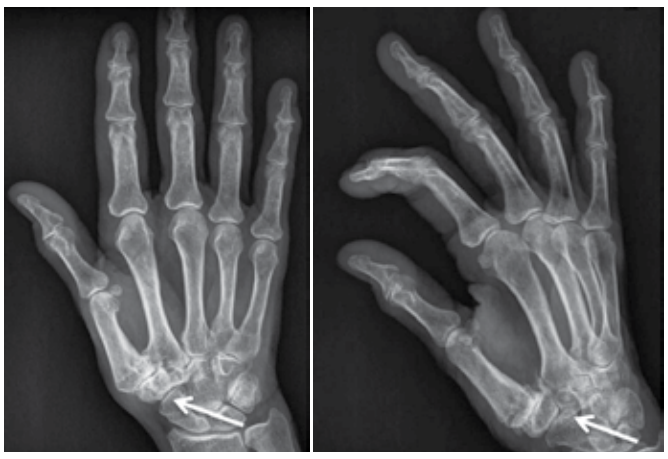


Fig. 6: IV stage: involvement of the scaphotrapezial joint.

This way it is possible to clearly evaluate all the trapezial articular facets and also the trapeziometacarpal osteophytes.

The lateral view, also called Gedda's or Bett's view [3], is obtained with the forearm flat on the table, the hand pronated of 20° with the thumb flat on the X-ray plate and the tube angled 10° from the vertical in distal-to-proximal projection. It gives a full view of the trapezium and of the trapeziometacarpal space (Fig. 2).

The dynamic stress view is an AP view performed with the radial side of the thumb tips pressing together. It is performed only in case of clinically painful TM joint without degenerative signs at the standard views.

The aim of the dynamic view is to demonstrate a hypermobility or an instability at the TM joint through the demonstration of the dorsoradial subluxation of the metacarpal base.

Several classifications for the TM osteoarthritis were presented, but the most used is Eaton-Littler classification, which is a descriptive system of classification.

In 1973, Eaton and Littler [4] first described a classification system based on the evaluation of the lateral view, dividing all cases in four stages:

- Stage I: normal or slightly widened TM joint, TM subluxation up to one-third of the articular surface, normal articular contours (Fig. 3)
- Stage II: decreased TM joint space, TM subluxation up to one-third of the articular surface, osteophyte or loose bodies <2 mm (Fig. 4)
- Stage III: decreased TM joint space, TM subluxation more than one-third of the articular surface, osteophytes or loose bodies >2 mm, presence of subchondral cysts or sclerosis (Fig. 5)
- Stage IV: involvement of the scaphotrapezial joint or, less commonly, of the trapezio-trapezoid joint or of the trapeziometacarpal joint of the second finger (Fig. 6)

This staging system is widely used nowadays, and it is helpful in preoperative planning, but, however, the divisions in the four stages are not always simple, and there is a clinical overlap between the groups.

Furthermore the radiographic stage is not always correlated to clinical symptoms, and as a proof, about 28% of women who have radiographical features of TM osteoarthritis complain about them [5].

Other methods of radiological evaluation, such as CT and MRI, are rarely used, since they do not give further information about TM osteoarthritis and for preoperative planning.

References available on request
Healthcare.India@springer.com

Source: Odella S. (2018) Physical and Radiological Evaluation. In: Trapeziometacarpal Joint Osteoarthritis. Springer, Cham. https://doi.org/10.1007/978-3-319-44336-2_2.

Investigation of the Relationships Between Knee Osteoarthritis and Obesity via Untargeted Metabolomics Analysis

Osteoarthritis (OA), the most encountered arthritis form, results from the degeneration of articular cartilage. Obesity is accepted as a significant risk factor for knee OA (KOA). In this study, it is aimed to determine the variation of metabolites between control and patients with KOA and observe the effect of obesity on KOA via untargeted metabolomics method.

Serum samples of following groups were collected: patient group including 14 obesity (OKOA) and 14 non-obesity (NOKOA) ($n=28$) and control group ($n=15$) from orthopedics and traumatology policlinic. Serum proteins were denatured by acetonitrile and chromatographic separation of metabolites was achieved by LC/Q-TOF/MS/MS method. Data acquisition, classification, and identification were achieved by METLIN database. Cluster analysis was performed with MATLAB2017a-PLS Toolbox 7.2.

Obtained results showed that 244 (patient vs control) and 274 (OKOA vs NOKOA) *m/z* ratios were determined in accordance with LC/Q-TOF/MS/MS analysis. Multivariate data analysis was applied 41 and 36 *m/z* signal ($p \leq 0.01$; fold analysis >1.5) were filtered for patient vs control group and OKOA vs NOKOA, respectively. Twenty-one different metabolites were identified for patient vs control group and 15 metabolites were determined for OKOA vs NOKOA group.

Acid concentration and oxidative stress agents were high in inflammation group and their levels were much higher in obesity. It is claimed that obesity cause oxidative stress and acidosis in arthritis patients. Valine was found to be the only BCAA molecule whose concentration has significantly different in KOA patients. The relation between KOA and obesity was firstly investigated with metabolomics method.

Source: Senol, O., Gundogdu, G., Gundogdu, K. *et al. Clin Rheumatol* (2019) 38: 1351. https://doi.org/10.1007/s10067-019-04428-1.

A Novel Biomarker in Patients with Knee Osteoarthritis: Adropin

Adropin is a newly-discovered peptide hormone. Osteoarthritis (OA) is a kind of joint disease characterized by progressive joint cartilage loss and joint pain. The present study was carried out to investigate adropin and tumor necrosis factor alpha (TNF-α) levels and the relationship between adropin in patients with knee OA classified by Kellgren-Lawrence (KL). A total of 60 knee OA patients and 30 healthy controls were included in this study. KL grading was carried out using the radiographic findings. Demographic characteristics and laboratory parameters were recorded. Adropin and TNF-α levels were determined by using enzyme-linked immunosorbent assay (ELISA). Adropin level was lower in the knee OA patients compared with the healthy controls ($p<0.001$), whereas TNF-α level was higher ($p<0.001$). Adropin level was negatively correlated with TNF-α level, blood white blood cell (WBC) count, and neutrophil-lymphocyte ratio (NLR). However, there was a significant decrease in adropin level and an increase in TNF-α level parallel to the increase in the KL grade. In addition, serum adropin level was found to be significantly lower in KL grade 1 groups compared with healthy controls ($p<0.01$). There was a decrease in adropin level parallel to the increase in the body mass index (BMI), and there was a statistically significant decrease in adropin level in knee OA patients higher than BMI >30 ($p<0.01$). Mean NLR of KL grade 4 was significantly increased compared with other grades ($p<0.05$). The consequence of the present study suggested that serum adropin level could be used as a new biomarker indicating the early grade of knee OA.

Source: Gundogdu, G. & Gundogdu, K. *Clin Rheumatol* (2018) 37: 2179. https://doi.org/10.1007/s10067-018-4052-z.

Causal Association Between Rheumatoid Arthritis and a Decreased Risk of Alzheimer's Disease

This study aimed to examine whether rheumatoid arthritis (RA) is causally associated with Alzheimer's disease (AD).

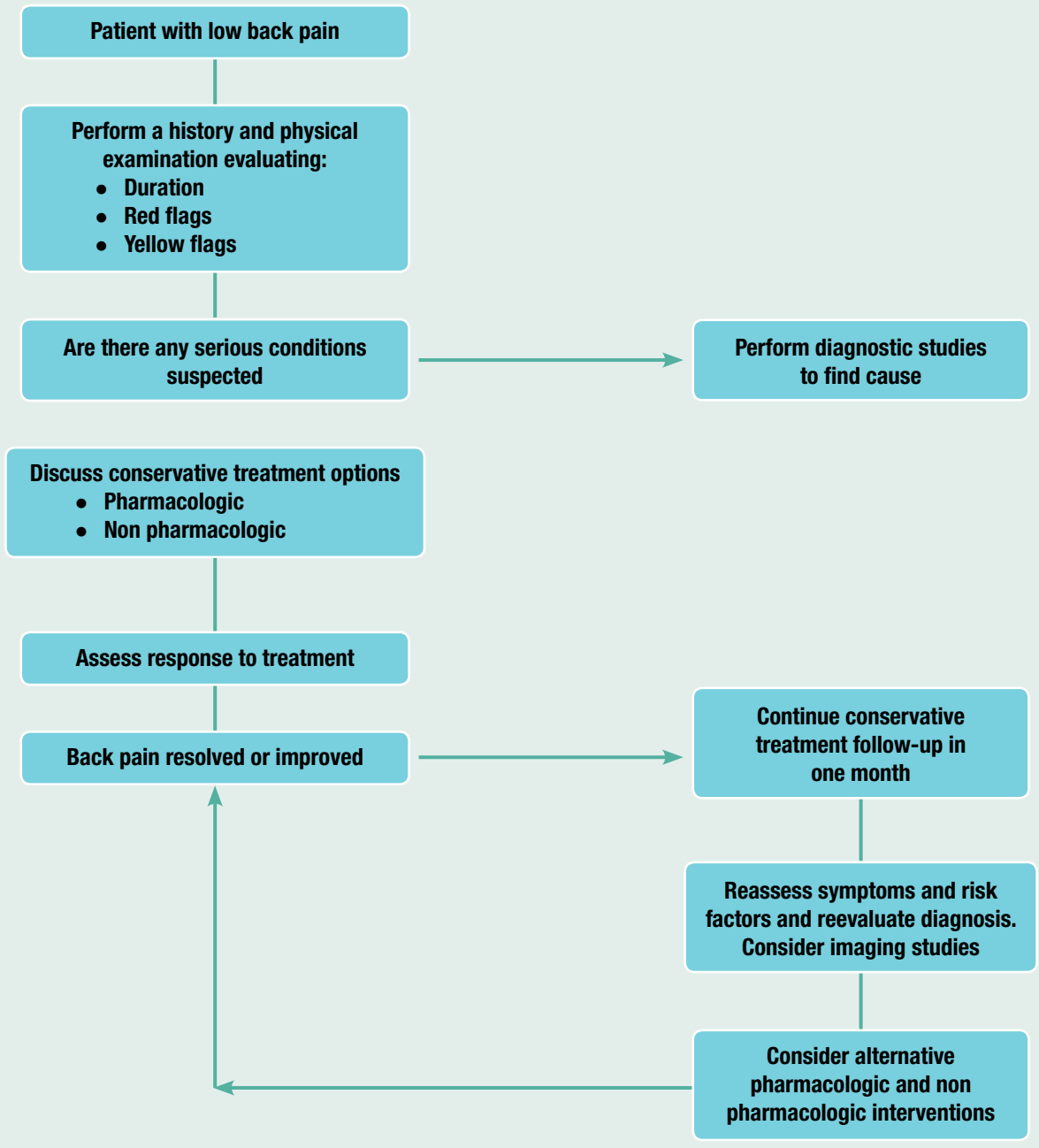
We performed a two-sample Mendelian randomization (MR) analysis using the inverse-variance weighted (IVW), weighted median, and MR-Egger regression methods. We used the publicly available summary statistics datasets from three-stage trans-ethnic genome-wide association studies (GWAS) meta-analyses of 29,880 RA cases and 73,758 controls as exposures and a meta-analysis of 4 GWAS datasets consisting of 17,008 AD cases and 37,154 controls of European descent as outcomes.

We selected 80 single nucleotide polymorphisms (SNPs) from GWAS data on RA as instrumental variables (IVs), 60 of which were associated with RA on a genome-wide significance level. The IVW method showed evidence to support an inverse causal association between RA and AD ($\beta=-0.039$, standard error [SE] $=0.017$, $P=0.021$). MR-Egger regression revealed that directional pleiotropy was unlikely to be a source of bias in the results (intercept $=0.002$; $P=0.649$). The MR-Egger analysis showed no causal association between RA and AD ($\beta=-0.050$, SE $=0.030$, $P=0.096$). However, the weighted median approach showed that RA and AD were causally linked ($\beta=-0.078$, SE $=0.024$, $P=0.001$). The funnel plot did not show heterogeneity between IV estimates based on the individual variants.

The MR analysis supports that RA was causally associated with a reduced risk of AD.

Source: Bae, SC. & Lee, Y.H. *Z Rheumatol* (2019) 78: 359. https://doi.org/10.1007/s00393-018-0504-8.

DIAGNOSTIC AND THERAPEUTIC APPROACH TO LOW BACK PAIN



Source: Urits, I., Burshtein, A., Sharma, M. *et al. Curr Pain Headache Rep* (2019) 23: 23. https://doi.org/10.1007/s11916-019-0757-1. © Springer Science+Business Media, LLC, part of Springer Nature 2019.

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