Obesity Comorbidity

Osteoarthritis, obesity and weight loss: evidence, hypotheses and horizons – a scoping review

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Summary

Obesity is widely acknowledged as a risk factor for both the incidence and progression of osteoarthritis, and has a negative influence on outcomes. Loss of at least 10% of body weight, coupled with exercise, is recognized as a cornerstone in the management of obese patients with osteoarthritis, and can lead to significant improvement in symptoms, pain relief, physical function and health-related quality of life. However, questions still remain surrounding optimal management. Given the significant health, social and economic burden of osteoarthritis, especially in obese patients, it is imperative to advance our knowledge of osteoarthritis and obesity, and apply this to improving care and outcomes. This paper overviews what is already known about osteoarthritis and obesity, discusses current key challenges and ongoing hypotheses arising from research in these areas, and finally, postulates what the future may hold in terms of new horizons for obese patients with osteoarthritis.

Keywords: Obesity, osteoarthritis, treatment, weight loss.

Abbreviations: BMI, body mass index; CAROT, Influence of Weight Loss or Exercise on Cartilage in Obese Knee OA Patients; IL, interleukin; MMP, matrix metalloproteinase; NIH, National Institutes of Health; OA, osteoarthritis; WOMAC, Western Ontario and McMaster Universities.

Introduction

The association between osteoarthritis (OA) and obesity is well established; widely acknowledged as a risk factor for both the incidence and progression of OA (1), obesity also has a negative influence on disease outcomes such as the need for surgery (2). Hence, weight loss, coupled with exercise, is recognized as an important approach in the management of obese patients with OA (3).

Despite the high volume of publications on the subject, there are still gaps in our understanding of the pathogenesis of OA in the obese patient. Increasing prevalence of these two interlinked conditions (4,5), and the associated health, social and economic consequences, make it imperative to advance our knowledge of OA and obesity, and apply this to improving care and outcomes for patients.

This paper overviews what is already known about OA and obesity, discusses current key challenges and ongoing hypotheses arising from research in these areas and, finally, postulates what the future may hold in terms of new horizons for obese patients with OA.

Evidence

Osteoarthritis imposes a serious and growing health burden

The global prevalence of OA continues to escalate, both as a result of an ageing population (6) and as a result of the

current obesity epidemic, with obesity in the elderly becoming an increasing problem (7).

In 2000, 600 million people worldwide were aged ≥60 years, representing a threefold increase compared with 1950 (6), and the number is expected to triple again to reach 2 billion by 2050 (6). This trend is a cause for concern given that, as evidenced by data from the United States, the prevalence of OA rises steeply in older people, with approximately 34% of those aged ≥65 years estimated to have OA, compared with 14% of adults aged ≥25 years (8).

Similarly, the global prevalence of obesity has nearly doubled since 1980 (9), with 475 million adults now estimated to be obese (body mass index [BMI] ≥ 30 kg m^{-2}), and a further 1 billion considered to be overweight (BMI 25–29.9 kg m^{-2}) (4). When the Asian-specific definition for obesity (BMI > 28 kg m^{-2}) is taken into account, the number of adults worldwide considered to be obese rises to in excess of 600 million (4). Obesity in the elderly is a particular concern, with a prevalence of 20–30% in Europe, rising to > 35% in the United States (7). Furthermore, the prevalence of obesity is continuing to increase, even among older age groups (7). Again, this is cause for concern given the well-established association between obesity and OA (1,10).

OA is a leading cause of disability and has a significant impact on health-related quality of life (1,8). Approximately, 80% of affected individuals have some degree of movement limitation, while 25% are unable to perform major activities of daily living (8). Knee OA is of particular importance, as the knee is a key factor in ambulation and therefore social involvement (10). In a survey looking at the changing profile of joint disorders with age, knee and back problems were most frequently reported (approximately 10%), with knee problems having the greatest increase in prevalence with age compared with other joints (11). Knee pain is present in a large proportion of the elderly, with 25% of people aged > 55 years experiencing a persistent episode of knee pain and around 10% experiencing painful disabling knee OA (12). OA is also costly, accounting for a > $10 billion per year health care spend in the United States (13), much of this attributable to loss of working days and the cost of knee and hip replacements (14).

In the efforts to reduce the health, social and economic burden of OA, obesity seems an obvious target, given its role as a key and modifiable risk factor for OA. Early diagnosis of OA is also imperative; and, as obese patients have a greater risk of developing OA, they should be monitored for signs of the disease.

Obesity is a risk factor for incidence and progression of osteoarthritis, and negatively influences disease outcomes

Obesity is widely acknowledged as a risk factor for OA, with every 5 kg of weight gain conferring a 36% increase in the risk of knee OA (1). There is evidence that the risk accumulates with increased exposure to high BMI throughout adulthood, with an association between BMI and later knee OA starting as early as 20 years in men and 11 years in women (15). In addition, body weight influences the severity of OA; obese individuals have significantly more severe joint degeneration in the knees compared with normal weight or underweight individuals (16). Data from a case–control study have also indicated a strong association between increasing BMI and surgical replacement of hip and knee joints (2).

Of note, obesity and OA collectively reduce mobility. This can initiate a vicious cycle of events: reduced activity, further weight gain and decreased muscle strength, leading to increased joint problems and disease progression (10). Hence, weight loss is a primary goal in obese individuals with OA.

Weight loss can prevent onset of osteoarthritis, relieve symptoms, improve function and increase quality of life

Results from the Framingham study have demonstrated that weight loss reduces the risk for OA in women. In this study, a 5.1-kg reduction in weight over a 10-year period decreased the likelihood of women developing symptomatic knee OA by 50% (17). In a subgroup analysis, weight loss was associated with a significant reduction in OA risk in individuals with high baseline BMI (25 ≥ kg m^{-2}), but not in those with BMI < 25 kg m^{-2} (17).

One major reason for this is that weight loss reduces joint loads. For example, a study of overweight and obese older adults with knee OA estimated that every pound of weight lost resulted in a fourfold reduction in the load exerted on the knee per step during daily activities, which appears to be clinically meaningful (18). Similar findings have been reported in other studies (19,20).

Weight loss can also relieve symptoms in obese patients with OA including, importantly, pain. Of note, decreasing body fat and increasing physical activity are particularly important in producing symptomatic relief of knee OA (21). Recent data from a cohort study of 1,410 individuals with symptomatic knee OA suggest that a significant dose–response relationship exists between changes in body weight and corresponding changes in self-reported Western Ontario and McMaster Universities' (WOMAC) pain, as well as physical function scores (Fig. 1) (22). While loss of approximately 5% of body weight has been shown to provide some relief in obese patients with OA (23), several studies have indicated that the ultimate goal should be an initial decrease in body weight of at least 10%, in order to provide significant reductions in pain (22,24). This is supported by clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults
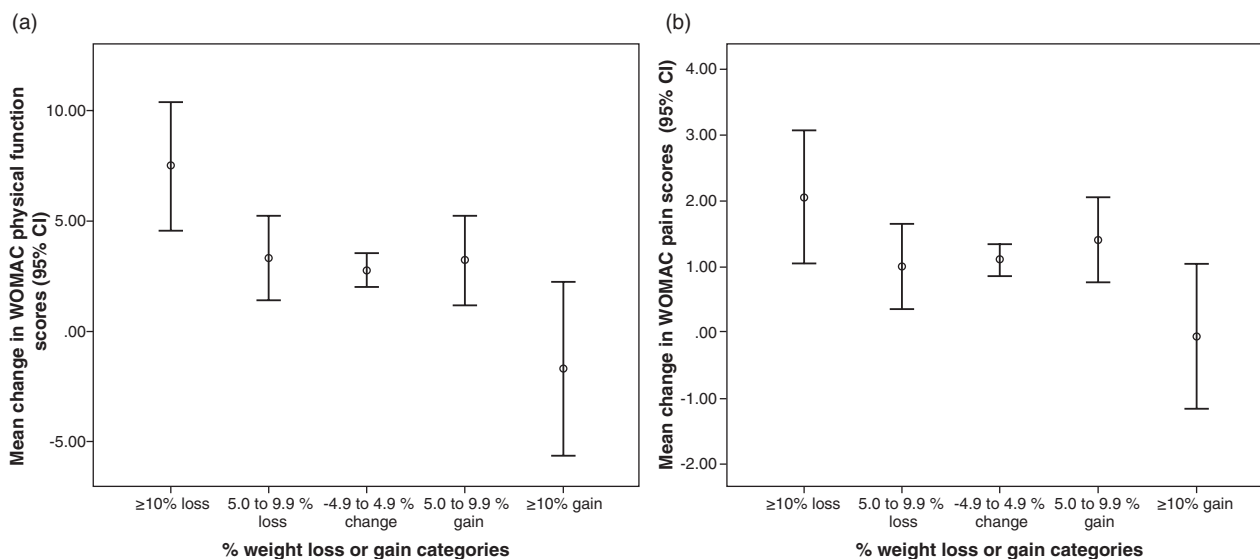
Figure 1 Dose–response relationship for the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function (a) and pain (b) scales. Point estimates and 95% confidence interval (95% CI) bars were derived from unadjusted estimates. Reproduced with permission from Riddle DL, Stratford PW. *Arthritis Care Res (Hoboken)* 2013; **65**: 15–22 (22)

from the Obesity Education Initiative of the National Institutes of Health (NIH), which recommend an initial goal for weight loss of 10% from baseline in obese individuals (25). If successful, further weight loss may be attempted if required. Importantly, concomitant with OA pain reduction comes increased mobility and physical function (3,22,24). Quality of life is also improved following weight loss in patients with OA, as evidenced by improvements in the composite physical health score of the Short Form-36 Health Survey, as well as improvements in satisfaction with body function and appearance (26).

Further insight comes from the Influence of Weight Loss or Exercise on Cartilage in Obese Knee OA Patients (CAROT) study, which evaluated the effects of an intensive weight-loss programme over 16 weeks in obese patients with knee OA. This low-energy, formula-diet, weight-loss programme was shown to reduce OA symptoms (27), although no changes were demonstrated in bone marrow lesions in response to weight loss (28). The impact of increased knee joint loading because of improved ambulatory function and walking speed following weight loss was also investigated; no acceleration of symptomatic and structural disease progression was observed in patients with increased joint loads relative to those with reduced joint loads (29).

Weight loss and exercise is the optimal approach to managing obese patients with osteoarthritis

Guidelines from the American College of Rheumatology (30) and European League Against Rheumatism (31) recommend the need for weight loss as well as exercise in the

management of overweight or obese patients with OA. Several studies support the combination of exercise and weight loss, together with appropriate analgesia, as a cornerstone for these patients (3,32). These studies have highlighted important benefits of combined exercise and diet therapy compared with either exercise or diet alone, including greater improvements in gait, knee pain and physical function (32). Although long-term weight loss can be achieved through calorie restriction alone, the addition of exercise is also required in order to significantly improve mobility (an important determinant of disability), self-reported function and pain (3). In addition, the CAROT study indicated a decrease in lower extremity muscle mass and muscle strength following weight loss in obese patients with knee OA, suggesting that significant weight loss should be followed by an exercise regimen to restore or increase muscle mass in this patient population (33).

In contrast to weight loss among the general population, where rapid initial weight loss can indicate a poorer long-term prognosis in terms of regaining weight (25), greater initial weight loss in obese people with OA is associated with better long-term prognoses, and can be associated with better compliance with treatment (34). However, this is in contrast with clinical opinion recommending a slower rate of weight loss (34).

The NIH guidelines recommend that, in order to achieve 10% weight loss over 6 months, overweight patients (BMI 27–35 kg m^{-2}) should aim for a decrease of 300–500 kcal day^{-1} (1,300–2,100 kJ day^{-1}), resulting in weight loss of about 250–500 g week^{-1}. For more severely obese patients (BMI > 35 kg m^{-2}), deficits of up to 500–1,000 kcal day^{-1} (2,100–4,200 kJ day^{-1}) are required for

weight loss of about 500–1,000 g week^{-1} (25). For obese people with established OA, who may have relatively low activity levels and inactivity-induced lean mass atrophy (35), weight loss tends to be less than expected (36) and the energy deficit of an effective diet has to be greater to compensate for this (AR Leeds, personal communication).

Opinions on the optimal method for weight loss are varied. While evidence supports a calorie-restricted diet, the evidence to support differences in diet composition is limited and inconclusive. Although it is critical – especially in elderly OA patients – to introduce a low-calorie diet that still provides all the essential nutrients, maintenance of recommended daily calcium intake is particularly important for women who may be at risk of osteoporosis (25). For some obese patients, compliance with long-term lifestyle changes is low and other approaches, such as bariatric surgery (e.g. laparoscopic adjustable gastric banding or sleeve gastrectomy) (37,38) or pharmacotherapy, may be the best way to achieve weight loss.

While exercise can aid weight loss, there is also evidence of other benefits that exercise can have in patients with OA, even in those with severe OA (39,40). For example, exercise has been shown to strengthen muscles that support the joints, reduce pain and improve physical function (32,40,41). Both aerobic walking and quadriceps' strengthening exercises have been shown to reduce pain and disability in subjects with knee OA, but in a systematic review of 13 randomized clinical trials, it was not possible to identify the superiority of one approach over the other (40). Although the optimal exercise regimen for OA patients is not currently known, it is important – especially in elderly OA patients – to tailor the exercise programme according to patient mobility, comorbidities and patient preferences (42).

Hypotheses

In addition to what is already known, there exists a number of intriguing questions surrounding the treatment of obese individuals with OA, which are worthy of further exploration.

Should exercise be postponed until weight loss has been achieved?

It has been postulated that exercise may cause further joint damage in obese patients with OA because of the increased strain and load on the joints. This leads to the hypothesis that weight loss should be achieved prior to commencing exercise. This theory is supported by evidence from an 8-week study assessing the effect of rapid diet-induced weight loss on physical function in 80 obese, knee OA patients (24). In this study, implementation of a low-energy diet (3.4 MJ day^{-1}) led to a weight loss of 11.1%, compared with 4.3% in individuals on a control diet

(5 MJ day^{-1}). In the group on the low-energy diet, physical function – as assessed by WOMAC function score – was significantly improved versus baseline; there was no significant change in the control group (24). This finding suggests that rapid weight loss enabled obese OA patients to subsequently obtain a higher degree of physical activity compared with the control group.

However, initial findings indicate that patients who exercise following dietary weight loss actually gain weight (H Bliddal, personal communication), but this requires further investigation.

Can weight loss be maintained?

Weight loss is clearly important in managing obese OA patients, but once it has been achieved, how difficult is it to maintain this weight loss? In a prospective study assessing the effects of physical activity on weight maintenance in 32 women who had recently (within 3 months) achieved their target for weight loss, the amount of physical activity required to minimize weight gain for 1 year after weight loss was determined (43). It was apparent that active women maintained their weight loss better than inactive women, although the relationship was found to be non-linear. Instead, a threshold-like relationship was observed between physical activity and weight control, with the threshold corresponding to a physical activity level of 80 min of moderate exercise or 35 min of vigorous exercise per day in order to prevent weight regain following weight loss (43).

Despite evidence of its benefits, weight loss through diet and exercise is notoriously difficult to achieve and sustain in the long term, with patient non-compliance being a key problem. Factors that appear to pose a particular risk for weight regain include a history of weight cycling, disinhibited eating, binge eating, more hunger, eating in response to negative emotions and stress, and more passive reactions to problems (34). In the Look Action for Health in Diabetes trial, which evaluated the cardiovascular effects of intensive lifestyle intervention in patients with type 2 diabetes, initial mean weight loss was 8.6%, declining to an average weight loss of 6.0% after 10 years (44). Although modest weight loss was sustained over the length of the trial, patients were specifically recruited if they were motivated to lose weight through lifestyle intervention and were only included in the study if they could complete a maximal-fitness test at baseline (44). Maintenance of weight loss in non-motivated individuals is likely to be even more difficult over time, with particular difficulties encountered in maintaining standard diet and exercise programmes in previously sedentary, overweight adults with OA and its associated mobility disability (3). Of note, while the general advice is to exercise to maintain weight loss, this may not be possible in obese knee OA patients because

of the potential adverse effects of exercise on the joints during training (10). This highlights the need for strategies to improve patient adherence to diet and exercise programmes (3), as well as additional ways to support patients in achieving sustainable weight loss.

In fact, there are a number of approaches aimed at improving compliance and supporting long-term weight control. A review of factors associated with weight loss maintenance by Elfhag and Rössner proposes that contributors to successful long-term weight loss include achieving initial weight loss, reaching a self-determined goal weight, having a physically active lifestyle, maintaining a regular meal rhythm including breakfast and healthier eating, exerting control of overeating and instigating self-monitoring of behaviours (34). In addition to an internal motivation to lose weight, other important factors include social support, better coping strategies and ability to handle life stress, self-efficacy, autonomy, assuming responsibility in life, and overall more psychological strength and stability (34).

Patient–therapist contact appears to be a key factor in achieving weight loss of approximately 10% over a period of 16–26 weeks (45). Continued contact appears to be effective whether it occurs in person (e.g. by attending weight maintenance classes) or through telephone, post or email-based communications (45).

Does weight loss need to be a key focus both before and after surgery in osteoarthritis patients?

End-stage OA is treated with surgery, in particular, knee and hip replacements. Obese individuals with OA are more likely to require surgery, as shown by a case–control study involving > 7,000 individuals, which demonstrated a strong association between increasing BMI and total hip and knee replacements (2). It has been postulated that outcomes from surgery are negatively influenced by weight and that weight loss should therefore be a key focus both before and after surgery in OA patients.

Given these considerations, a case could be made for bariatric surgery prior to knee or hip replacement in obese patients with OA. A study of 20 total hip and knee arthroplasties performed in patients with morbid obesity who were treated with bariatric surgery before arthroplasty showed a reduction in BMI prior to arthoplasty, improvements in Knee Society/Harris hip scores and a high level of patient satisfaction at follow-up, and minimal complications (46). However, while these findings support the use of bariatric surgery in morbidly obese patients with OA, in whom arthroplasty may otherwise be considered too risky, there are limited data in the literature assessing the effectiveness of bariatric surgery in overweight/obese patients with OA. Indeed, a recent systematic review highlighted the

paucity of data in this area and called for further research (47).

One assumption that may be made is that post-surgery patients lose weight because they are able to be more active. However, data show that almost a third of patients gain ≥5% of their baseline body weight after surgery (48).

Somewhat surprisingly, a significant association was not found between increasing BMI and the risk of knee or hip revisions of previous joint replacement surgeries (2). Further evidence comes from a study assessing the effect of body weight on outcomes after total knee arthroplasty, using the Nottingham Health Profile to assess health status and the Knee Society score to assess clinical outcome at baseline and 12 months after surgery (49). Over this period, the study demonstrated that body weight did not adversely influence the outcome of total knee arthroplasty (49). Further studies are needed to inform optimal pre- and post-surgical management.

Does weight loss have an impact on the progression of osteoarthritis?

While the short-term benefits of weight loss in obese patients with OA are undisputed, the effect of weight loss on the progression of OA remains a topic for debate. Some results have suggested a positive effect of weight loss on cartilage in non-OA subjects. For example, in a prospective study of obese adults recruited from gastric banding or diet and exercise programmes, weight loss was found to be associated with improvements in both the quality and quantity of medial articular cartilage (50).

However, other studies have indicated that weight loss does not alter the course of OA, and an association between symptom relief and altered course of structural damage remains to be shown. In the Arthritis, Diet and Activity Promotion Trial, no difference in joint space width (a measure of disease progression) was seen between patients treated with diet, exercise, diet plus exercise or healthy lifestyle (the control group) (3). However, the authors noted that the relatively short duration of the intervention (18 months) coupled with the number of subjects per group (approximately 80) probably prevented the detection of meaningful differences in radiographic disease progression. Hence, more research is required in order to answer this interesting question.

What are the mechanisms linking obesity and osteoarthritis?

Understanding of the mechanisms by which obesity predisposes the onset and progression of OA has evolved over time. Initially, the link between OA and obesity was considered purely biomechanical (18–20). In fact, on closer inspection, the mechanisms linking obesity and OA appear
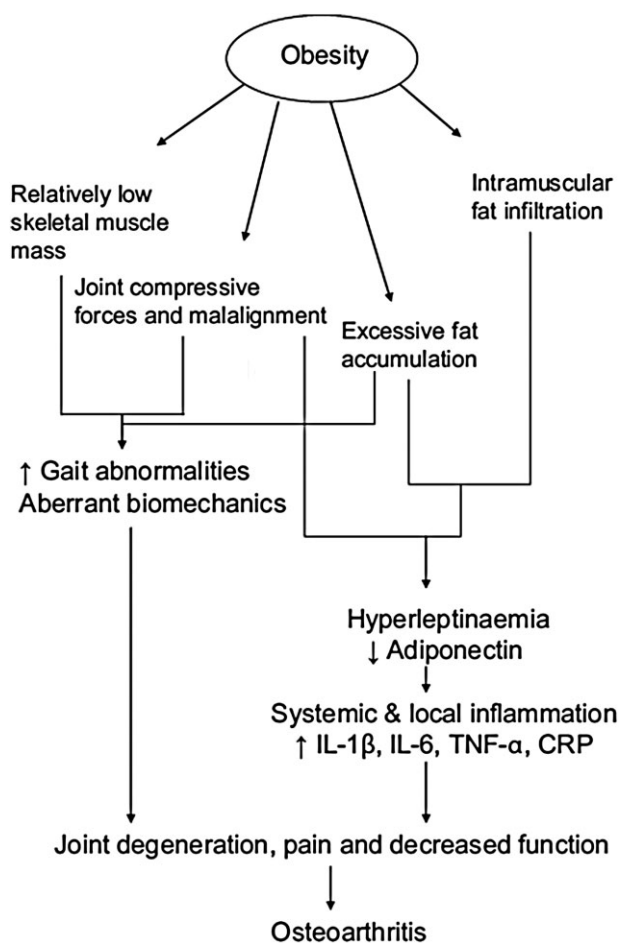
Figure 2 Potential obesity-related pathways that contribute to osteoarthritis.
CRP, C-reactive protein; IL, interleukin; TNF, tumour necrosis factor.
Reproduced with permission from Vincent HK, Heywood K, Connelly J, Hurley RW. *PM R* 2012; **4(5 Suppl)**: S59–67 (37).

to be more complex and multifactorial (Fig. 2) (37). Relative loss of muscle mass and strength over time also contributes to the onset of OA in obese individuals. Although muscle as well as fat mass increases with weight gain, overall, the volume of muscle mass remains relatively low and inadequate to match the loads placed upon it (37).

There is also evidence that mechanical stress may lead to the release of a range of pro-inflammatory mediators from joint tissues, including interleukin (IL)-1beta, cyclooxygenase-2, prostaglandin E_2, matrix metalloproteinase (MMP)-2, MMP-3, IL-6, MMP-9, MMP-13, receptor activator of nuclear factor-kappaB ligand, fibroblast growth factor-2 and IL-8 (51–55). Of note, pro-inflammatory cytokines such as IL-6 and C-reactive protein have been shown to predict both the incidence (56) and progression (57,58) of arthritis. Furthermore, recent evidence from the Intensive Diet and Exercise for Arthritis study suggests that weight loss may have anti-inflammatory, as well as biomechanical, benefits in obese subjects with concomitant knee OA, as evidenced by reduced levels of IL-6 (59).

Intriguingly, although a definite association exists between obesity and OA in weight-bearing joints such as the knee and hip, obesity is also associated with the development of OA in non–weight-bearing joints, such as those in the hand (60). This suggests that non-mechanical risk factors must also play a part. In particular, there is interest in the potential role of adipokines (cytokines secreted by adipose tissue). For example, leptin has long been implicated in the pathogenesis of OA, independent of the mechanical effect of obesity (61). However, recent evidence indicates that serum leptin concentration does not correlate with hand OA (62). Adiponectin has been implicated as a predictor of disease progression in early rheumatoid arthritis (63), although its precise role in OA is less clear. There is also interest in the potential role of chemerin in the development and progression of OA, with recent data indicating that chemerin levels may predict the severity of OA (64). Other adipokines with a potential role in the pathogenesis of OA include visfatin, resistin, lipocalin–2, serum amyloid 3, vaspin and omentin (61). Of note, the infrapatellar fat pad, an adipose tissue depot located in the knee joint, may contribute to the pathophysiological changes that occur in the OA joint via local production of cytokines and adipokines (65). Studies are now exploring the potential for adipokines as biomarkers for diagnosing OA at an early stage, which remains a key challenge (66–68).

Also worthy of note is the association of obesity and OA with metabolic abnormalities, such as hyperinsulinaemia and other cardiometabolic defects. OA of the knee is associated with hyperinsulinaemia, which may play a role in OA in overweight patients, possibly via changes in insulin-like growth factor-1 (69). Furthermore, an increased risk of OA has been observed in obese women with cardiometabolic clustering versus those without (70). Notably, obesity was only found to be significantly associated with pain measures or many of the physical functioning performance measures when it was accompanied by cardiometabolic clustering (70). This observation may have significance in terms of optimizing treatment for knee OA.

Horizons

OA imposes a serious and growing health burden and commands increased attention in terms of pathophysiological understanding in order to optimize management of affected patients.

A key question that arises in terms of what the future may hold for obese patients with OA is whether a better understanding of obesity and OA can lead to more effective therapeutic approaches. The ideal treatment would be an intervention that tackles both obesity and OA, providing

584 Osteoarthritis, obesity and weight loss   *H. Bliddal* et al.

obesity reviews

weight loss, but also addressing the underlying mechanisms that link the two conditions. It would need to be acceptable to this patient population for long-term use, as the typical subject with concomitant obesity and OA has lifelong problems with overweight.

Conclusion

It is imperative to diagnose OA as early as possible; as obese patients have a greater risk of developing OA, they should be monitored for signs of the disease. In the future, earlier diagnosis of OA may be aided by the identification of effective biomarkers.

For all obese patients with OA, weight loss should be advocated as a first-line management approach, with a goal of rapid initial weight loss of approximately 10% of body weight. The challenge of how to maintain weight loss, and the question of whether or not weight loss can alter progression of OA, remain key areas of ongoing research.

Another area for focus is advancing our knowledge of the pathophysiology that underpins both OA and obesity. This, in turn, may facilitate the identification of alternative therapeutic approaches. In particular, any approach that tackles both OA and obesity would be a major step forward in stemming the global epidemic of these two interlinked conditions.

Conflict of interest statement

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586 Osteoarthritis, obesity and weight loss *H. Bliddal* et al.

obesity reviews

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