Review

Our biology working against us in obesity: A narrative review on implications for management of osteoarthritis

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ARTICLE INFO

ABSTRACT

Obesity is the major modifiable risk factor for osteoarthritis (OA). A major focus of management in OA is weight loss. Although we live in an obesogenic environment, obesity has a predominantly genetic and epigenetic basis. This explains a person's weight set point which is defended by biological mechanisms making weight loss difficult to achieve and maintain long term, regardless of the methods used. Significant weight regain occurs after weight loss, with weight tending to return to pre-treatment levels after cessation of interventions including the glucagon-like peptide-1 (GLP-1) agonists. An area that has received little attention is the slow, insidious weight creep of 0.5–1 kg/year over adulthood that sees individuals relentlessly increase weight. There is evidence that low intensity, personalised lifestyle interventions can prevent this weight creep, providing patients with achievable goals. In this narrative review, we examine the evidence for weight loss in OA, the biological mechanisms that make weight loss difficult to achieve and maintain and the potential negative impacts on patients. We review the evidence for preventing weight gain, the improvement in patient outcomes and the potential for significant healthcare savings through reduced knee replacements. We propose a combined approach of weight loss when indicated, together with targeting weight creep across adult years and the potential role of metformin. Implementing these combined approaches is likely to be more effective in improving patient related outcomes, reducing joint damage and healthcare costs, than our current focus on achieving weight loss in OA.

1. Introduction

Obesity is the major modifiable risk for osteoarthritis (OA) [1,2]. Much of the focus in the management of OA is on weight loss which is difficult to achieve and even more difficult to maintain. In this review we examine the biological mechanisms that explain these challenges, the effect of our current approaches, the potential of the new weight loss drugs and the missed opportunity to prevent weight creep.

2. The role of genetics in obesity

Although the current environment is obesogenic, there is strong evidence that obesity has a predominantly genetic [3–5] and epigenetic [6–8] basis that explains a person's weight set point. This weight set point is believed that the body seeks to maintain the body weight at a stable range by moderating energy intake and metabolism [9,10]. Evidence for the genetic predisposition of obesity has come from identical twin and adoption studies [3–5]. Differences among individuals have been shown in forced overfeeding studies where, despite a group of individuals being overfed by the same amount, a range of weight gain has been observed [11]. In those who did not gain weight, there was an increase in energy expenditure by around 2000 kJ [11]. This increase in energy expenditure was caused by an increase in spontaneous movement, not as an increase in metabolic rate. There is also evidence that leptin level is proportional to the fat content of the body [12]. A genetically thin person put in an obesogenic environment will produce leptin which suppresses hunger so that although they will gain weight, they may not develop obesity. It has also been shown that our bones weigh us. Studies in rodents have shown that osteocytes send an as yet unknown signal, to the brain to suppress hunger as they detect a higher weight [13].

Genetic and epigenetic factors combined with the current obesogenic environment have seen obesity rates continue to increase. For example, the US obesity prevalence increased from 30.5% to 42.4% from 1999 to 2000 through 2017 to 2018 [14]. During the same time, the prevalence of severe obesity increased from 4.7% to 9.2% [14]. Similarly, overweight and obesity in adults have reached epidemic proportions in the

World Health Organisation (WHO) European Region with estimates that 59% of adults are living with overweight or obesity [15].

3. Our current approach to tacking obesity in OA: weight loss

Our current approaches to dealing with obesity in OA focus on weight loss in those who are already overweight or obese. There is ample evidence that weight loss is possible, but hard to achieve. Many approaches have been shown to be effective for weight loss. Although there are many different variations to this theme, they all include reducing calorie intake and increasing energy expenditure. Approaches include limiting the time during which food is eaten, as with the 5/2 diet, or manipulating the dietary intake as with ketogenic diets where the build-up of ketones reduces the sensation of hunger. Ketones reduce hunger in two ways, they act directly on the brain to suppress hunger and also prevent most of the changes in hormones that lead to increased hunger after weight loss [16]. These are also combined with exercise programs to increase calorie expenditure. The effectiveness of any approach is largely determined by individual preference and compliance.

A key feature of weight loss is that a small reduction in calories is not sufficient to lose weight as the relation between calorie intake and weight loss is not linear [17]. As soon as weight is lost, energy expenditure from spontaneous activity reduces so that for a given reduction in calories less weight is lost [18]. This is a common complaint among those trying to lose weight: the first weight loss is easy, then weight loss stops. Initial weight loss plateaus by approximately 5% weight loss as many hormonal changes leading to weight regain are then in place [19]. For this reason, most weight loss approaches include a low energy intake in order to achieve the required weight loss [19]. This is a common feature of successful diets in the OA area which combine very low energy intake together with physical activity programs to increase energy expenditure [20,21].

4. Why is keeping weight off so difficult? Our biology working against us: the set point theory

After the hard work of losing weight, maintaining the lost weight is very difficult, perhaps even more than the original weight loss. There is evidence that our body mechanism strongly defends a person's body weight set point, such that any lost weight is offset by changes in energy expenditure and hormonal changes to defend the lost weight [18,19]. Clinicians treating obesity have repeatedly observed that it is a hard battle for people to maintain weight loss, with high failure rates despite most of those who lose weight being motivated. Rates of weight regain

are high in the first year [22], with most people regaining their lost weight by 5 years [23,24]. A recent systematic review and meta-analysis found faster regain in weight after weight loss was associated with greater initial weight loss, that the continued availability of the programme to participants outside of the study predicted a slower weight regain, but that provision of financial incentives predicted faster regain in weight [25].

There is a common myth that people regain weight because they return to their old habits. However, the body weight set point could play a role in impeding weight loss maintenance. After weight loss, the levels of hunger controlling hormones such as leptin, cholecystokinin and GLP-1 change in a direction to make the individual more hungry [26–28], as shown in Table 1 and there is a reduction in energy expenditure [29], changes that are long lasting, still present at 6 years [30,31] to account for weight regain.

5. Can biology reset the weight set point after weight loss?

A key question is if the weight set point can reset, especially in response to weight loss. Most of the evidence suggests that the weight set point does not reset at a lower weight, but rather, as weight increases, the body defends the higher weight. There is no evidence that the body weight set point can reset at lower levels. The set point is determined by which gene is not functioning correctly. For example, if the melanocortin 4 receptor is mutated or deleted and cannot send its signal it appears like the set point is set high [32]. Until we can change gene sequence or expression the set point cannot be altered.

Evidence for this comes from several studies. In a long-term follow up of 272 patients [mean age 42 years; 82% female; mean body mass index (BMI) 48.1 kg/m^2] undergoing roux-en Y gastric bypass for severe obesity, it was found that all patients dropped to their nadir weight (BMI 28.6; 88.6% excess weight loss) at 2.2 $\pm$ 1.9 years post operatively. Nevertheless, all patients experienced significant weight regain from lowest to 5 and 10 years after surgery, with a drop in excess weight loss to 76% at 5 year follow-up and further down to 67.6% at a mean of 11.4 year follow-up [33]. Also, it was observed that those with super obesity (BMI$\geq$50) lose more rapidly from preoperative BMI to the lowest BMI, compared to those with morbid obesity (BMI<50), but regained weight more rapidly than those with morbid obesity thereafter, suggesting that the weight set point was not altered after their initial successful weight loss.

Similarly, a systematic review included >13,000 patients who had bariatric surgery and were followed up for 62.4 $\pm$ 25.8 months, showed that at least 1 in 6 [17.6%, 95% confidence interval (CI) 16.9–18.3]

Table 1
Weight loss related hormonal changes.

	Origin	Role	Settings			
			In obesity (compared to normal weight)	Dietary weight loss (initial)	Surgical weight loss	Weight loss (1 year)
Leptin [26, 35]	Adipose tissue	*Anorexigenic hormone:* Reduces food intake & increase energy expenditure	↑	↓↓	↓	↓
CCK [28,36]	Gut	Inhibits food intake, suppresses satiety	↑	↓↓	↔	↓↓
Ghrelin [35,27,69]	Stomach	*Orexigenic hormone:* Increases food intake	↑	↑↑	↓↓ (post gastric bypass) ↑ (post DJBL)	↑
Peptide YY [69]	Ileum	Inhibits food intake	↓	↓	↑ (post DJBL) ↑ (RYGB)	↓↓
GLP-1 [35, 69]	Distal intestine	Inhibits food intake	↑	↔	↑↑ (post DJBL) ↑↑ (post RYGB)	↓

↓↓: significantly reduced, compared to baseline (prior to weight loss).
↓: reduced, compared to baseline (prior to weight loss).
↔: no changed, compared to baseline (prior to weight loss).
CCK: cholecystokinin.
DJBL: duodenal-jejunal bypass liner (endoscopic device that mimic small bowel mechanisms of Roux-en-Y gastric bypass).
RYGB: Roux-en-Y gastric bypass.

patients had ≥10% weight regain post bariatric surgery. Although this weight regained was attributed to a variety surgical-related, psychiatric-related, dietary-related and genetically related factors [34], there was evidence showing that Peptide YY, GLP-1 and ghrelin levels changes in a favourable direction to prevent weight regain post-operatively (Table 1) [35,36]. However, it is unknown whether these initial gut hormonal changes would persist long term. This was also observed with the Fen-Phen combination drug which was found to cause heart valve problems and thus ceased [37]. Among the 21 patients who took Fen-Phen with diet and exercise lifestyle modification for 2 years (mean age 46 years, BMI 36 kg/m^2), they had an average of 14% initial weight loss [37]. However, 17 of 21 patients (81%) reduced Fen-Phen doses on their own initiative and 9 of 21 (43%) patients reported non-adherence, because of fears concerning reports (released in August 1996) of a link between weight loss drugs and primary pulmonary hypertension and negative publicity about Fen-Phen. All patients however had regained 22.7 ± 41.6% of their weight by the end of second year upon cessation of the drug [37].

Taken together, these data provide support that weight set point cannot be altered with weight loss, such that ongoing weight loss is dependent on the need for long term use of weight loss medication or other strategies. To date, there is no evidence that lifestyle interventions, obesity medications or surgery alter the set point. This makes weight loss short-lived and operates to drive weight regain once the intervention is discontinued. The therapeutic consequence of this weight set point is that it is likely that therapy will need to be continued long term, regardless of the methods used.

6. The role of new drugs in weight loss

There is a lot of excitement about recent advances in weight loss drug therapies with the glucagon-like peptide-1 (GLP-1) agonists which have a hunger-suppressing action. These include liraglutide which requires a once daily injection and has been shown to result in 6.4% weight loss in those with obesity or overweight with a co-morbidity [38]. Semaglutide has a similar mode of action but the advantage of a once weekly dosing with reported weight loss of 5.9% at 3 months and 10.9% at 6 months [38]. A newer agent, tirzepatide [a GLP-1 and Gastric inhibitory poly-peptide (GIP) dual agonist], has even higher rates of weight loss of 22.5% [39]. These medications are generally well tolerated although nausea and abdominal discomfort may occur in some patients limiting their use and thus are contraindicated in those with a history of pancreatitis. Table 2 compares the % of weight loss among common weight loss drugs. But, to date, there is no evidence that they change the body weight set point so it is likely that individuals will regain the lost weight after discontinuation so these medications may need to be used long term.

Of these new weight loss drugs, only one study examined the effect of this GLP-1 agonist in OA. The clinical trial of liraglutide showed no difference in knee pain between the liraglutide and placebo groups [40]. However, this needs to be considered in context of the overall study as there was a lead in period where both intervention and control groups had very significant weight loss of about 7% before randomisation to medication.

Table 2
Percentage weight loss with currently available weight loss medications.

Drug	% weight loss (%)	Main side effects
Metformin[70]	2.5	Gastrointestinal
Orlistat[71]	3	Gastrointestinal
Liraglutide 3.0 mg[38]	6.4	Gastrointestinal
Phentermine/Topiramate [70]	7.9	Neurological (paraesthesia, dizziness)
Semaglutide 2.4 mg[38]	15.8	Gastrointestinal
Tirzepatide 15 mg[39]	22.5	Gastrointestinal

7. How effective is weight loss in the treatment of OA?

Despite the focus on weight loss in OA, recent meta-analyses have shown that weight loss of 5–10% of total body weight have modest effects on knee pain [standardised mean difference 0.33 (95% CI 0.17, 0.48) [41], of a magnitude similar to paracetamol (effect size 0.21, 95% CI 0.02, 0.41) [42]. Similarly, evidence from meta-analyses did not show a significant effect on structure in knee pain [43]. Knee pain, function and stiffness only improved by 2% for every 1% weight loss [44]. A 20% improvement from baseline is considered a clinically significant improvement according to Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMER-ACT-OARSI) [45]. This would translate to a 10% weight loss needed for a clinically significant reduction in knee pain. In support of this, a recent randomised clinical trial that achieved 10% weight loss over 12 months using a video-based telehealth exercise and ketogenic very-low-calorie diet in the interventions group only showed a mean reduction of pain by 1.3 points difference on a 10-point numeric rating scale (mean −1.3, 95% CI -2.0, −0.7, p < 0.01) compared to the control group [46].

8. Is promoting weight loss totally harmless?

Despite the modest, at best, effect of weight loss in OA, clinical practice guidelines continue to advocate for weight loss as a key recommendation in the management on knee and hip OA [47], as shown in Table 3. This is largely based on the notion that weight loss is likely to have overall health benefits and no anticipated harms. However, this may be an overly simplistic view. Patients with OA reported being aware that their weight contributes to their OA and that they have tried unsuccessfully to lose weight [48]. They describe dissatisfaction with their weight, and feelings of anxiety and disempowerment about being unable to lose weight. Repeated failures to lose weight have been shown to demoralise patients and to perpetuate negative thoughts and self-blame that makes weight loss even harder to achieve [49,50]. More than 50% of people who are over-weight and obese reported experiencing weight stigma [51], and feel they are being 'blamed' for not getting better. This can have negative effects including maladaptive coping mechanisms such as unhealthy eating behaviours and exercise avoidance. It can also have unintended clinical effects with 50% of women who are overweight and obese reporting that they did not attend a medical appointment where they thought they might be weighed [52]. Thus, it is important to be aware that even though targeting obesity is important, repeated lack of success can have negative impacts on the individual.

9. Approaches to managing obesity

Despite a major focus on weight loss in the management of obesity, the WHO recommend maintaining weight and preventing weight gain in

Table 3
Summary of management of obesity in knee osteoarthritis guidelines.[47]

	Is weight loss recommended?	Is weight maintenance recommended?	Is prevention of weight gain recommended?
AAOS 2021 [72]	✓		
VADoD 2020 [73]	✓		
Zhang 2020 [74]	✓		
ACR 2019 [75]	✓		
OARSI 2019 [76]	✓		
ESCEO 2019 [77]	✓		
ISR 2019 [78]	✓		
RACGP 2018 [79]	✓		
TLAR 2017 [80]	✓		
PANLAR 2016 [81]	✓		
NICE 2014 [82]	✓		
EULAR 2013 [83]	✓	✓*	
MSR 2013 [84]	✓		

* In the context of weight loss.

addition to weight loss in the management of obesity [53]. This may seem self-evident, but if weight was maintained there would not be the need to lose the additional weight that has been slowly gained. In most countries rates of overweight and obesity are increasing despite an ever-increasing prevalence in weight-loss attempts, suggesting that individuals are aware of the importance of addressing obesity. For example, a systematic review concluded that more than 40% of the general population are trying to lose weight [54] and it has been reported that the global market for weight loss products and services was $254.9 billion in 2021 ($66 billion in United States of America) [55]. We may need more personalised approaches to target obesity in OA, such that for those with overweight and obesity, while there is an ongoing need to lose weight, the focus should also be directed to not gaining any further weight; but when targeting obesity for those with normal weight, emphasis should be on weight maintenance and weight gain prevention.

10. Maintaining weight: preventing weight creep

There is a steady weight gain across large parts of the community in many countries that sees an increasing proportion of the population shift from healthy weight to overweight and obesity [56–58]. The weight gain is typically accelerated during early adulthood and in certain transitional stages of life such as pregnancy [59]. On average, weight tends to slowly accumulate at a rate of 0.5–1 kg per year (1–2lbs) from early to middle adulthood [56–58]. Analysis of the recent National Health and Nutrition Examination Survey (NHANES) data found that over a 10-year period, women gained 5.4 kg and men gained 2.6 kg[60] with the greatest weight gains in young and middle-aged adults.

11. Is there evidence that preventing weight creep could be beneficial in OA?

Obesity affects joints such as the knee over the life course with obesity-related structural changes demonstrated early in the course of the disease before any clinical disease is detected [61,62]. This may explain why weight loss has only a modest effect on knee joint health once significant OA is present (evidenced by structural damage) [43,61].

There is evidence that a low intensity, lifestyle community-based program that prevented weight gain significantly reduced knee pain in community-based rural women [63]. In a trajectory analysis of a large community-based cohort followed from early adulthood to their mid 60s, 6 patterns of weight gain were identified. It was estimated that knee replacements could be reduced by 28.4% if individuals from each trajectory followed the trajectory that was one lower [64], requiring an average 8–12 kg less weight gain over that time period regardless of the individual's baseline weight. At a community level, most of the prevention of knee replacements would be expected in those with borderline obesity or class 1 obesity (BMI 30–34.9 kg/m^2) even though greatest risk of knee replacement was in those with Class 2 obesity (BMI 35–39.9 kg/m^2) or higher. This is because in this study, as with many populations, a higher overall proportion of the population had a BMI of <35 kg/m^2 thus targeting this group will improve outcomes for a greater number of individuals. This is a group that have the potential to benefit from preventing the weight creep. Currently, the clinical approach to targeting obesity which may include drugs and surgery are focussed on those with Class 2 obesity or higher [39,40].

12. Is preventing weight creep a missed opportunity to target a potentially achievable goal in obesity?

In the previous sections we considered the magnitude of the obesity epidemic and the challenges of weight loss and especially maintaining weight loss in context of the biological mechanisms that are strongly geared to defending the individual's weight set point. We also considered the evidence that a significant proportion of the population continues to slowly gain weight. In addition to advocating for weight loss, should we also be more active in advising patients to prevent the weight creep? The two are not mutually exclusive and are likely to have complementary health benefits.

A recent meta-analysis showed that low intensity weight related behaviour interventions that included diet and physical activity and resulted in small energy deficits are effective at preventing weight gain [65]. These were effective across non-obese and obese populations [65]. Slowing the weight creep requires minor lifestyle changes targeting the estimated small cumulative energy imbalance of around 30kj per day (about 4% total energy expenditure). This can be considered more pragmatic, achievable and sustainable across daily life in order to prevent the insidious development of obesity over time. It may be that those carrying extra weight, should be advised to lose weight, if possible, but also be educated to be aware that if they don't take action, they may experience the insidious weight creep, meaning they will have more weight to lose in 5–10 years, perpetuating a vicious weight cycle. This approach is much more achievable than the significant weight loss that is required once an individual has become obese.

13. Could metformin have a role in preventing weight creep?

There is evidence that metformin, a safe, inexpensive medication used for type 2 diabetes results a significant reduction in BMI in obese/overweight individuals [66]. A recent meta-analysis showed in >3000 participants who took metformin, they were able to reduce 3.7 kg weight gain when compared to those who took sulphonyureas (mean difference 3.77 kg, 95% CI 3.07, 4.47) [67]. In those women with overweight or obesity with concurrent polycystic ovary syndrome, metformin was able to reduce weight by 1.36 kg (95% CI -1.56, −1.16) when compared to placebo [67]. The mechanism for weight loss related to metformin is unclear. There is evidence that metformin may reduce appetite and food intake through central nervous system actions [68]. In addition, there may be systemic effects on adipose tissue, the gastrointestinal tract and the liver mediated by the activity of adenosine monophosphate kinase that increase the fat oxidation and decrease lipogenesis through the reduction of circulating lipids, hepatic lipid storage and hepatic steatosis [66].

Metformin could be considered for use at certain "high risk" times for weight gain, to slow the weight creep. The recent NHANES data showed that the mean (±SE) 10-year weight gain in American adults was 4.2 ± 0.2 kg or 6.6 ± 0.2%. After adjusting for age and race, 10-year weight gain (kg) was significantly greater in women (5.4 ± 0.3) than in men (2.6 ± 0.2) and in non-Hispanic Blacks who gained more weight and non-Hispanic Asians. This weight gain is highest between 30 and 59 years [60], a time where pain due to OA in joints such as the knee is common [63]. It may be that metformin could be considered to help with slowing weight gain, especially where there is evidence that this is not being achieved with lifestyle approaches alone. The levels of weight loss associated with metformin suggest that it could have a useful role in slowing the weight creep.

14. Conclusion

Strategies to tackle obesity in OA are likely to have greater benefit if they include personalised approaches to prevent or slow the weight creep as well as weight loss when needed. Preventing weight creep provides patients/consumers with a potentially achievable goal as this requires a modest 4% reduction in energy balance to slow weight gain by 0.5–1 kg/year. This can be achieved by low intensity, personalised lifestyle changes that include small reductions in energy intake or increase in energy expenditure plus the addition of metformin. This could complement our current approaches which focus on weight loss. Weight loss will remain important in the management of obesity in OA. However, weight loss is difficult to achieve and maintain long term due to the biological mechanisms that defend the weight set point. As such, most therapies, including new weight loss drug therapies such as the GLP-1 agonists, will need to be used long term. A combined approach of preventing the

weight creep across adult years, thus reducing early, irreversible joints damage, is likely to improve overall patient and societal outcomes in OA even when weight loss is indicated.

Author contributions

FMC: conception and design; analysis and interpretation of the data; drafting of the article; critical revision of the article for important intellectual content; final approval of the article.

JP: critical revision of the article for important intellectual content; final approval of the article.

YZL: conception and design; analysis and interpretation of the data; critical revision of the article for important intellectual content; final approval of the article.

Role of the funding source

Declaration of competing interest

JP receives payments from Novo Nordisk and I Nova for educational program and medical advisory board. All other authors declare no conflicts of interest. The funders of the study had no role in the study design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Acknowledgements

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