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Editorial

The relationship of weight loss to structure modification in knee OA

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The global obesity epidemic continues apace and thus far efforts to reverse this are failing. The osteoarthritis (OA) community should be concerned as this is the leading modifiable risk factor for disease. Greater body mass index and obesity are associated with a heightened risk of hip and knee OA[1] with the obesity attributable risk for OA-indicated knee joint replacement an astounding 31%[2].

This has important implications both from a prevention and disease management perspective. From a prevention perspective thus far there is only one *post hoc* analysis of a clinical trial, demonstrating that a 5% weight loss resulted in a threefold reduction in incident clinical knee OA after 6 years (21% vs 7%), and a 2.5-fold reduction in radiographic knee OA development (16% vs 6%)[3]. An important research priority over the next few years is to establish the prevention benefits of weight loss in persons at high risk for OA.

In those with extant disease there is clear evidence that weight loss (preferably through a combination of diet and exercise) has salient benefits for pain, function, knee loads and other mechanistic outcomes[4]. There appears to be a clear dose–response relationship; the more weight you lose the better and to obtain clinically meaningful effects from weight loss ideally a person should lose over 7.5% of their bodyweight[5]. The challenge in this research arena is implementing these clinical trial findings in pragmatic community settings and sustaining benefits over a long time with the huge challenges related to adherence. This is a currently active area of research with regard to both weight loss and physical activity and innovative evidence-based strategies to improve this field.

Obesity leads to an increase in the biomechanical loading of weight-bearing joints and contributes to metabolic-like inflammation. The pathophysiological mechanisms are generally summarized as obesity distributes biomechanical loading across the knee to affect cartilage volume and bone marrow lesions; also, obesity increases adipose tissue to augment serum and tissue levels of pro-inflammatory cytokines and adipokines, which further accelerate OA development and progression and increase the risk of joint pain and synovitis due to meta-inflammation[6].

While the beneficial effects of weight loss on joint pain and physical function have been demonstrated in knee OA[4], it was not until recently that a series of studies have aimed to shed light on the question of whether weight loss has structural modifying effects. Conflicting results have been reported which may be related to several methodological differences between these studies such as duration of follow up, method of weight loss (diet, exercise, surgery), study design and outcomes examined. In addition, distinct populations were studied such as obese individuals without clinical evidence of knee OA and those with established disease. Among those analyses specifically including OA individuals, no differences were seen in MRI-detected cartilage thickness loss and progression of bone marrow lesions and synovitis between individuals who lost around 10% of their initial body weight through diet, with or without exercise, and those who did not[7,8]. In contrast, 10% weight loss was associated with a slower progression of cartilage thickness loss and an increase in dGEMRIC in the medial compartment (representing an increase in glycosaminoglycan content) in participants with or at risk of knee OA[9]. In those without a history of OA, weight loss has been associated with slower progression of medial cartilage volume loss in knees with a meniscal tear (but not in those with intact meniscus)[10] and smaller increases in cartilage T2 values[11], although no differences were seen in semi-quantitative MRI markers[12].

Gersing *et al.* (ref) have demonstrated that greater than 5% weight loss has a slower increase in cartilage T2 over 96 months compared to a stable weight group in individuals at risk of knee OA or with mild to moderate disease. This is consistent with the aforementioned studies that have shown similar effects with dGEMRIC and T2, albeit over shorter intervals. Furthermore, this is an extension of this group's analysis, previously done at the 48 month time point[11]. The magnitude of effect in this study was considered meaningful by the authors, as the mean change in cartilage T2 between the groups (1.92 ms) over 96 months was relatively large compared to the standard deviation in global knee T2 at baseline (around two-thirds of the baseline standand deviation). The effects found appear to be more profound in the deep layer than the superficial and also more prominent in the medial tibiofemoral compartment than the lateral compartment (although effects were found in both and in the patella). There are also suggestive differences favouring weight loss through diet or diet and exercise vs exercise only.

It is important to recognise that this is a retrospective analysis with plenty of potential for bias and residual confounding. As the motivation and details about behavioural changes in diet and exercise were unknown, controlling for baseline dietary factors (total caloric intake and dietary fiber intake - the latter has been shown to reduce risk of knee OA and related pain13) and physical activity

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at baseline may reduce confounding for the observed associations. Exclusion of those that had weight gain and those whose weight cycled between loss and gain may potentially limit the generalisability of their findings. Furthermore, the method of weight loss (e.g., physical activity vs diet vs a combination) was self-reported, potentially leading to some misclassification. It is also of note that despite the effect on cartilage T2, there was a lack of effect on semi-quantitative scoring. This is concerning as you would have thought that if there were a meaningful compositional change this might be reflected in the overall structure of the knee over the 96 months of study.

As the form of physical activity and alignment condition were unknown for this study, it remains to be determined what the effect of an appropriate form of exercise on OA development and progression is, especially when OA prevalence of the hunter-gatherers was much lower than people who live in the modern society[14]. Because both OA and obesity hinder physical activity, which contributes to lower muscle strength and reduced muscle mass, it remains debatable how muscle strength may protect against OA progression and whether the protective effect depends on the setting of neutral alignment or malalignment[15]. As for now, diet alone or in combination with exercise-induced weight loss seems to be quite consistent regarding the protective effect of/association with knee OA[15].

Nonetheless, it would be important to understand if greater weight loss thresholds than those demonstrated in this paper are clinically meaningful. In addition, it is unclear what the prognostic value of this T2 difference means and whether this has any implications for long-term pain, structure, function or joint replacement requirement. Further, as the connection of gut microbiome with obesity and arthritis has just started to unfold[16], investigation of the gut and their changes of flora through diet, exercise and weight loss may further elucidate insightful pathways and intervention targets for OA onset and progression in the future. Like many engaging areas of research, the questions addressed in this research propose many more that remain to be answered.

Authors contribution

All authors contributed substantially to the conception and design of the article. All authors contributed to the initial draft and revised it critically for important intellectual content and approved its final version.

Conflict of interest

LAD declares partial reimbursement of a conference registration cost by Pfizer, outside the submitted work. DJH provides scientific advisory consulting advice for Pfizer, Merck Serono, Tissuegene and TLCbio. ZD declares no conflict of interest.

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L.A. Deveza
Rheumatology Department, Royal North Shore Hospital and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, NSW, Australia

Z. Dai
Charles Perkins Centre, School of Pharmacy, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia

D.J. Hunter*
Rheumatology Department, Royal North Shore Hospital and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, NSW, Australia

* Address correspondence and reprint requests to: D.J. Hunter, Rheumatology Department, Royal North Shore Hospital and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, NSW, Australia.
E-mail address: David.Hunter@sydney.edu.au (D.J. Hunter).