

# Cartilage quality, overweight and osteoarthritis: a case for new behaviour?

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Joint cartilage is indeed a metabolically active tissue. In this issue of *Annals of the Rheumatic Diseases*, the results of the study by Anandacoomarasamy *et al*<sup>1</sup> highlight two important issues of joint cartilage and osteoarthritis (OA): cartilage repair and OA progression. Unfortunately, many people equate cartilage repair with procedures that fill cartilage defects rather than replacing degraded molecules with newly synthesised molecules and consider that joint cartilage deterioration in OA is inevitable. In an elegantly designed study in obese subjects, the authors use MRI and delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) to show that weight loss is associated with improvement in medial knee cartilage quality and quantity. In the light of OA mainly developing medially and considering that cartilage quality and OA risk are probably related, their results have significant preventive implications.

In the cartilage matrix, aggrecan is a highly negatively charged proteoglycan that is entrapped in a collagen fibrillar network through carboxylated or sulphated glycosaminoglycans (GAGs). GAGs can bind up to 50 times their weight in water resulting in a swelling pressure that is normally constrained by the tensile strength of the collagen network.<sup>1</sup> This interaction is the key mechanism behind the viscoelastic properties of the articular cartilage, which provides joints with the necessary resistance to mechanical loading.<sup>2,3</sup>

The molecules in the cartilage matrix are continuously and balanced turned over. In joint disease, however, increased degradation versus biosynthesis finally results in the hallmark of OA, namely gradual cartilage loss and overt radiographic changes. The degradation and loss of GAGs is usually considered an early feature in developing OA. However, it is

unclear to what extent GAG loss is relative or absolute: less GAG due to dilution by oedema or decreased biosynthesis versus degradation ratio. This may have implications in OA development since OA risk is probably related to the *in vivo* functional properties of the cartilage.<sup>4</sup> An attractive hypothesis is that a cartilage of low quality, meaning relative depletion of aggrecan and other matrix molecules, impedes the load distribution across the joint with more stress on the collagen fibre network and results in subsequent fibre damage by fatigue, further cartilage swelling and disease progression. However, convincing longitudinal human studies in support of these observations are still lacking.

To develop cause-related treatment strategies for OA, it is fundamental to understand early molecular events in the pathogenesis. This will enable OA interventions to be carried out in the preradiographic course of OA before irreversible collagen network changes and subsequent cartilage loss occur. From this perspective, it is remarkable that so many OA studies still include subjects with radiographic changes. This is, however, not the case in the Anandacoomarasamy *et al* study.<sup>1</sup> dGEMRIC is therefore a promising method to identify subjects who later develop radiographic OA changes.<sup>5,6</sup>

In dGEMRIC, a negatively charged contrast agent is injected intravenously. Given time to distribute, it is accumulated more in the subject's cartilage that is poor in GAG (negative charge) as opposed to subjects having a cartilage matrix with more GAG, meaning that lower GAG concentration leads to higher contrast agent distribution and reduced T1 relaxation time, which can be quantified using MRI. As a cartilage assessment method, it is preferably used in a manner similar to that done by Anandacoomarasamy *et al*,<sup>1</sup> before cartilage loss occurs and particularly in cohorts at risk of developing knee OA such as obese or meniscectomised subjects. To support a link between early matrix GAG alterations and subsequent OA, cohorts need to be followed until

radiographic OA develops. Important additional studies are those that show that an intervention improves cartilage quality in subjects at OA risk. Where the former studies take 10–15 years, the latter studies lack convincing evidence that intervention prevents OA.

1. In the Anandacoomarasamy *et al* study of an obese cohort,<sup>1</sup> where only one-third had clinical OA, subjects were scheduled for gastric banding or exercise and diet programmes. Results show weight loss to be associated with improved dGEMRIC index and cartilage quantity medially in the knee. As the authors conclude, this has important public health implications regarding the OA subject's quality of life and need for total joint replacement operations. Related to this, two issues need to be considered: 1. the reliability of assessing cartilage quality and GAGs with dGEMRIC and the preventive significance of improved cartilage quality with respect to OA;
2. obesity as a risk factor for knee OA and the feasibility of weight loss as a preventive strategy in obese subjects.

## dGEMRIC

Without doubt, this *in vivo* method to assess cartilage quality related to GAGs of human joints has increased our knowledge of cartilage biology during the last 10–15 years. The validation of dGEMRIC is not complete but the principle behind the method, the *in vivo* relationship between T1 relaxation time in the presence of GD-DTPA<sup>2-</sup> (T1Gd or the 'dGEMRIC index') and GAG content, has been evaluated *in vitro* against biochemical and histological reference techniques<sup>7–9</sup> and between contrast medium concentration and mechanical properties of cartilage.<sup>10</sup> Still, other factors and matrix molecules may also affect matrix diffusivity and subsequent T1Gd.

*In vivo* the day-to-day reproducibility is good<sup>11</sup> and intra- and interobserver variability is low using standardised regions of interest.<sup>12</sup> Cross-sectional studies in a variety of clinical cohorts suggest that human cartilage is adaptive<sup>13</sup> and that patients at OA risk have a lower dGEMRIC index,<sup>14–17</sup> whereas subjects with stronger quadriceps show better cartilage quality.<sup>14</sup> Furthermore, it has been suggested that one likely cause for the considerable variation in synovial fluid biomarker concentration in seemingly homogenous patient materials is the relationship between synovial fluid marker concentration and the marker content in the cartilage, which

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may indeed be individually variable without pathology.<sup>18</sup>

In longitudinal studies, dGEMRIC shows that exercise improves knee cartilage quality in healthy subjects and in middle-age preradiographic OA patients.<sup>19</sup> Thus, a predictive value of dGEMRIC regarding joint failure has been suggested.<sup>5-6</sup> However, meniscectomy may impair cartilage quality.<sup>21</sup>

Recently, cartilage-specific factors that are to be considered when using dGEMRIC have been communicated. A dGEMRIC analysis, which confirms an inhomogeneous cartilage GAG profile, shows that a true equilibrium never occurs in vivo due to concomitant wash-in and wash-out processes.<sup>22</sup> Accordingly, the selection of the time window for imaging is important. Fortunately, the enhancement of cartilage is relatively stable when using a delay of 90 min for the knee<sup>23</sup> and 60 min for the hip.<sup>15</sup> The Hawezi *et al* study concludes that cartilage thickness measurements together with depth-wise analysis of contrast concentration, including a T1 analysis without contrast, will facilitate dGEMRIC interpretation at least in cross-sectional studies.<sup>22</sup>

There is a potential risk of a dosing bias in overweight/obese subjects.<sup>24</sup> GdDTPA<sup>2-</sup> is distributed solely in the extracellular water. Weight loss that generally involves fat tissue may pose a problem when deciding the dose per weight in the first versus second dGEMRIC examination. Fortunately, a recent body composition analysis in obese subjects after bariatric surgery demonstrated that extracellular water does not change with weight loss.<sup>25</sup> This, together with the fact that quality changes only occurred in the medial compartment in the Anandacoomarasamy *et al* study,<sup>1</sup> suggests that cartilage thickness and dosing are not significant causes of their results and conclusions.

**OBESITY**

The reason for the increased incidence of knee OA and likely progression of OA in obese subjects is not entirely clear.<sup>26-28</sup> Obviously, obesity increases the load across the joint. However, one should bear in mind that obesity is only a proxy for joint load, suggesting that functional quadriceps exercises to decrease the concentration of the load across the joint may provide joints with similar protection against overload as weight loss.<sup>29</sup> A study that specifically monitored the dynamic load on the medial compartment of the knee by measuring the adduction moment showed that the risk of knee OA progression increased more than

six times with a 1% increase in adduction moment.<sup>30</sup>

Recently, a study suggested a relationship between obesity and adductor moment after weight loss. Aaboe *et al* showed an average weight loss of 14% of the baseline body weight and a 12% decrease in knee abductor moment in 157 obese knee OA patients after a 16-week dietary programme.<sup>31</sup> Bliddal *et al* in another recent study report a weight loss of 11% as well as symptom improvement at 1-year after an intensive low-energy diet in obese patients with knee OA.<sup>32</sup> In the Anandacoomarasamy *et al* study, gastric banding subjects lost 18% of their weight.<sup>1</sup> Although it is doubtful that gastric banding will be used to prevent OA, these studies are encouraging in the perspective of the Felson and Zhang study,<sup>27</sup> which calculated that one-third of knee OA cases could be avoided if people maintained a body mass index of 25 kg/m<sup>2</sup> or less.

In summary, weight loss in combination with quadriceps functional exercises preferably implemented in a patient education programme may have a considerable impact on OA prevention (www.boaregistret.se). Regardless of the need for further validation, dGEMRIC is a clinically relevant measure of cartilage quality that has shown to be predictive of future OA. The Anandacoomarasamy *et al* study supports its use in further OA intervention studies.<sup>1</sup>

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