

## OSTEOARTHRITIS

## Identification of a metabolomic biomarker for knee OA

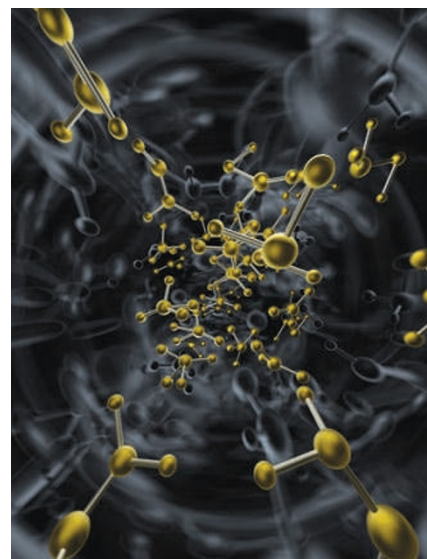
The development of disease-modifying drugs for patients with osteoarthritis (OA) has been hampered somewhat by difficulties associated with the accurate assessment of therapy responses in clinical trials using radiographic techniques. For this reason, there is an urgent need for reliable, readily measurable biomarkers that can be used to characterize disease status, prognosis and treatment responses in these patients. In a study published in the June issue of *Annals of the Rheumatic Diseases*, Zhai and colleagues at Kings College London used a metabolomics approach to identify metabolite ratios associated with the presence and disease severity of knee OA.

The first stage of the study involved a sample of unrelated white women enrolled in the TwinsUK cohort (123 with knee OA and 299 control individuals). Serum samples were collected after an overnight fast, and were analyzed with the AbsoluteIDQ kit (Biocrates Life Sciences, Innsbruck, Austria), a mass-spectrometry-based metabolomics kit that measures the concentration of 163 metabolites, including amino acids, acylcarnitines, sphingolipids and glycerophospholipids. Ratios of paired metabolite concentrations

were used as proxies for enzymatic reaction rates, and were tested for their association with knee OA.

14 ratios were identified as being significantly associated with knee OA ( $P < 1.9 \times 10^{-6}$ ). These associations were then tested in an independent replication sample of 76 patients with knee OA and 100 controls from the Chingford Study (a prospective, population-based, longitudinal study of OA and osteoporosis). Two ratios—valine to histidine and 'xleucine' (combined leucine and isoleucine) to histidine—were found to be associated with knee OA. In addition, both ratios were associated with disease severity as assessed by radiographic Kellgren–Lawrence (KL) score (increase of 0.09 per KL grade;  $P \leq 0.001$ ).

The investigators note that both ratios involve the three branched-chain amino acids (BCAAs) valine, leucine and isoleucine. Indeed, serum concentrations of these BCAAs were considerably elevated in patients with OA compared to controls in both study populations. The increased serum levels of BCAAs could be a sign of joint collagen degradation. Furthermore, increased levels of free



BCAAs have been shown to increase the production of cytokines, which might itself lead to increased collagen breakdown. The authors conclude that the BCAA-to-histidine ratio represents the first serum metabolomic marker of knee OA, and has potential utility in clinical practice.

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**Original article** Zhai, G. *et al.* Serum branched-chain amino acid to histidine ratio: a novel metabolomic biomarker of knee osteoarthritis. *Ann. Rheum. Dis.* **69**, 1227–1231 (2010)