

Correspondence on 'Glucosamine and O-GlcNAcylation: a novel immunometabolic therapeutic target for OA and chronic, low-grade systemic inflammation?'

The editorial by Herrero-Beaumont and Largo in the October issue¹ highlighted the benefits of glucosamine (GlcN) in the treatment of rheumatic conditions but also the potential gain in treating conditions such as coronary vascular disease, cancer and type 2 diabetes. GlcN has been shown to induce an increase in O-GlcNAcylation which displays a key regulatory role in inflammation and immune activation and as discussed by Jensen *et al*² may be the mechanism by which functional recovery improves following episodes of cardiac ischaemia. By contrast, chronic decreases of O-GlcNAcylation have been negatively implicated with various degenerative diseases such as Alzheimer's disease and osteoarthritis (OA).³

In our experience, patients with OA are frequently prescribed GlcN, with variable outcomes. It has been proposed that this agent accumulates in joint cartilage, and promotes the synthesis of proteoglycans.⁴ We have radiolabelled GlcN with ^{99m}Tc and administered it intravenously to patients with varied rheumatic conditions including rheumatoid arthritis, ankylosing spondylitis and OA.⁵ GlcN consumption was ceased

3–5 days prior to administration of this agent, to reduce any competitive inhibition of uptake.

Whole-body nuclear medicine scans were acquired over the ensuing 24 hours. In patients with OA, a similar pattern of uptake between individuals was observed that consisted of enhanced tracer uptake along the articular surface of the involved joints. More severe cases of OA also demonstrated mild diffuse uptake in the synovium, and this correlated with the clinical severity. Furthermore, the synovial uptake in severe cases of OA was typically less intense than that seen with patients with mild active rheumatoid arthritis. No uptake was demonstrable in the unaffected joints (figure 1).

Interestingly, tracer accumulation in the synovial fluid was not present. Synovial fluid (10–20 mL) removed from patients with severe OA or rheumatoid arthritis, surprisingly contained no radioactivity. This suggests that GlcN is confined to the tissues of the joint. Elsewhere, there was avid accumulation of ^{99m}Tc-GlcN in the kidneys and in the urinary bladder (figure 1), where this agent is excreted. Mild uptake in the liver and to a lesser degree in the other normal tissues was apparent. Uptake in skeletal muscle was increased in patients with myositis.⁶

Radioactivity in the region of the heart was equivalent to blood pool activity. There was no localisation to the heart muscle. However, our studies were not designed to evaluate patients with ischaemic heart disease. There were no documented heart disease patients in our cohort. Since glucose becomes the preferred substrate during ischaemia, further evaluation of this agent in patients with ischaemic heart disease to elucidate the mechanism of action and diagnostic/prognostic risk is warranted.

The exact mechanism(s) by which GlcN exerts its anti-inflammatory properties remain controversial. GlcN has a similar structure to glucose. A hydroxyl side chain of glucose is substituted with hydrogen to form deoxyglucose, and with an amine to form GlcN. Deoxyglucose is a competitive inhibitor of glycolysis. It is known to be taken up by cells and metabolised via the hexokinase biosynthetic pathway, leading to the formation of deoxyglucose-6-phosphate, which in turn cannot be metabolised further. As tumours upregulate glucose consumption, deoxyglucose has been employed as a tumoricidal agent, suppressing glucose metabolism, and thus 'poisoning' the tumour cells. Limited success was observed.⁷ In much the same way, GlcN may achieve its beneficial effects by suppressing glucose metabolism, and thus quelling inflammation and the subsequent cascade of related events. In the case of cardiovascular events, such metabolic changes induced by GlcN in the coronary vessels may help influence clinical outcomes.

Socrates Angelides ,¹ Nicholas Manolios²

¹Nuclear Medicine, The University of Sydney Faculty of Medicine and Health, Sydney, New South Wales, Australia

²Rheumatology, The University of Sydney Faculty of Medicine and Health, Sydney, New South Wales, Australia

Correspondence to Dr Socrates Angelides, Nuclear Medicine, The University of Sydney Faculty of Medicine and Health, Sydney, New South Wales, Australia; Socrates.Angelides@health.nsw.gov.au

Correction notice This article has been corrected since it published Online First. The provenance and peer review statement has been included.

Contributors NM and SA reviewed the relevant literature pertaining to the editorial, as well as preparing and proofreading the submitted letter. They were also responsible for designing the referenced study using ^{99m}Tc-glucosamine in patients with rheumatic conditions. Further they were involved in the recruitment of the patients. Finally, they prepared the corresponding submitted manuscript and collated the related references.

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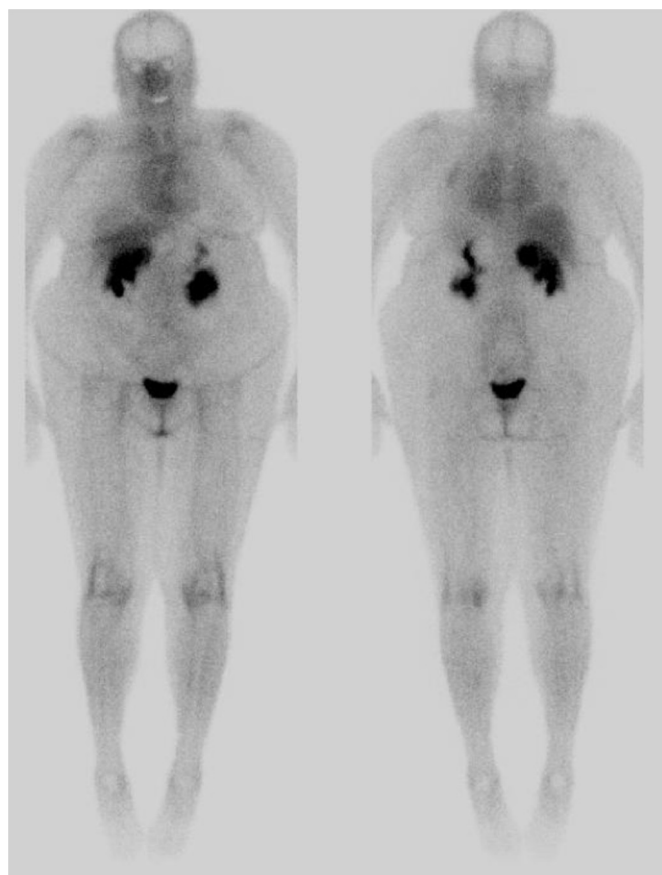


Figure 1 A patient in her seventies with documented moderate osteoarthritis of the knees and, to a lesser extent, of the shoulders given intravenous ^{99m}Tc-labelled glucosamine. There is increased uptake involving the articular surface of the knees and shoulders, with mild uptake in the knee synovium. The irregular shape of the kidneys is due to underlying polycystic kidney disease.

Competing interests None declared.

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ORCID iD

Socrates Angelides <http://orcid.org/0000-0002-9181-5760>

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