The chicken or the egg? Hyperuricaemia, insulin resistance, and hypertension.

Running Title – Hyperuricaemia and insulin resistance

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Apparently the egg came first. I recall considerable time spent discussing this causality dilemma during school days. These discussions were of little practical importance but here we are many years later considering a similar quandary, which might influence treatment of cardio-metabolic diseases. What comes first, hyperuricaemia or the diseases themselves? They are linked but we don't know whether the relationship is causal. We must solve this puzzle. Hyperuricaemia is common, it is increasing in prevalence [1] and we have widely available cheap drugs to address it.

Uric acid is a breakdown product of purine metabolism, regulated by the enzyme xanthine oxidase. Humans have higher levels of uric acid than most mammals due to a loss of function mutation in the gene encoding the uricase enzyme. We rely on renal and intestinal secretion of uric acid to maintain homeostasis. Hyperuricaemia can arise due to reduced renal or extra-renal excretion or over production of uric acid. Genes account for approximately 7% of its variance. Diuretics and beta-blockers, high intake of meat, seafood, fructose, alcohol, and sodium also raise uric acid levels [2]. The relationship with fructose intake is particularly interesting [3]. Fructose metabolism by fructokinase causes a fall in intracellular ATP concentrations and generates intracellular uric acid [4]. This intracellular uric acid causes a mitochondrial oxidative stress, leads to more generation of fructose via stimulation of aldose reductase, and up-regulates fructokinase activity. Experimental studies have shown this increase in intracellular uric acid to increase hepatocyte sensitivity to triglyceride accumulation [5]. Fat accumulation in the liver is a common finding in people with insulin resistance and cardio-metabolic

disease. Reducing (serum and intracellular) uric acid concentrations has been shown to allay features of metabolic syndrome in experimental models. Febuxostat, a xanthine oxidase inhibitor, was associated with reduced insulin resistance in people with gout in a recent observational study [6].

Pre-clinical studies suggest hyperuricaemia induces hypertension and that uric acid reduction lowers blood pressure. In rodent models, inhibition of uricase and hyperuricaemia, leads to a rise in blood pressure [7]. This can be prevented by use of drugs that lower serum uric acid through reduced formation (a xanthine oxidase inhibitor, allopurinol) or increased renal excretion (a uricosuric agent, benziodarone). Although caution is needed before assuming these findings will translate to humans who lack functioning uricase, clinical trials are suggestive. Randomised trials show that 4 weeks treatment with allopurinol 400 mg or probenecid reduces blood pressure in hyperuricaemic adolescents with early hypertension by approximately 10 mmHg (systolic) [8]. This supports a causative role for hyperuricaemia in the early stages of hypertension. The fact that both a uricosuric drug and allopurinol were effective is important. Allopurinol has additional uric acid independent effects, which may be more important in older adults [9]. The importance of hyperuricaemia in later stages of hypertension is less clear. Mendelian Randomisation studies do not convincingly show a relationship between instrumental variables for serum uric acid and blood pressure levels in adulthood and pre-clinical studies suggest hyperuricaemia induced hypertension may ultimately become uric acid independent. Several randomised trials have failed to demonstrate a consistent effect on blood pressure in older adults [10]. These are important notes of caution, there

are mechanisms through which hyperuricaemia could cause hypertension including reduced nitric oxygen levels in the endothelium, oxidative stress, and activation of the renin-angiotensin system [11]. A neutral Mendelian Randomsation study does not mean that uric acid lowering drugs will not be effective - many targets of drugs known to reduce blood pressure and cardiovascular risk (such as the renin angiotensin system) were not prominent in large genome wide association studies.

So uric acid may be a causative factor in development of insulin resistance and hypertension but novel analyses and rigorous clinical trials are needed to provide further clarity. Han and colleagues [12] present such a novel analysis where they attempt to establish the temporal relationship between hyperuricaemia, insulin resistance and hypertension. They used a cross-lagged path analysis. This technique studies the directional relationship between variables at different time points. A non-significant difference between the cross-lagged path coefficients implies a bidirectional relationship. Thus, if there is no difference between the coefficient of variable x at time 1 to variable y at time 2 and that of variable y at time 1 to variable x at time 2 then one variable does not obviously precede the other. In the case of a causal unidirectional relationship, the coefficient of the causal variable at time 1 to the other at time 2 should be significantly greater than that of the other scenario.

Their analysis was performed in 8,533 people aged between 20 and 74 years old, from the large Chinese city of Harbin. People with type 1 diabetes mellitus were excluded and average follow-up was 5.3 years. Hepatic insulin resistance, using the homeostasis

assessment model for insulin resistance (HOMA-IR), and peripheral insulin resistance, indicated by the Gutt index, were measured. The authors adjusted for potential cofounders including age, gender, BMI, alcohol consumption, smoking, regular exercising, caloric intake, renal function and follow-up duration. The cross-lagged path coefficient between baseline UA and follow-up HOMA-IR was significantly greater than the coefficient from baseline HOMA-IR to follow-up UA. Similar was found for the Gutt index suggesting the relationship between uric acid and insulin resistance is unidirectional, with hyperuricaemia coming first. This relationship was strongest in people with hypertension. Insulin resistance, and in particular peripheral insulin resistance, partially mediated the effect of uric acid on development of hypertension.

The authors surmise that hyperuricaemia contributes to insulin resistance and that this contributes to hypertension. This may be true but there is much to be done before these results are of practical significance. Even if they are correct, and the relationship is truly unidirectional, it remains association nonetheless. Causality is no more implied. These results do not tell us whether there is a window during which treatment of hyperuricaemia will be effective. There are marked differences in diet, including in fructose ingestion, in Chinese populations compared with other countries. These findings may not be generalizable. The estimate for the path coefficients was attenuated by adjustment for renal function and such a change raises the possibility of residual confounding. One possible sources of confounding include measurement error in assessment of covariates, inclusion of patients with type 2 diabetes mellitus, and use of other drugs that can influence insulin resistance over time.

Clever people and good science solved the chicken and egg dilemma and we hope this will also solve the uric acid puzzle. Cracking this could impact how we treat the millions of people with cardio-metabolic disease, and not just occupy the minds of children in junior school.

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