

Letter

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The coronary artery disease SNP, rs4420638, is associated with diabetic nephropathy rather than end-stage renal disease

Sir,

We recently reported the genetic analysis of coronary artery disease single nucleotide polymorphisms (SNPs) in type 1 diabetic patients with and without diabetic nephropathy [1]. A novel and statistically significant association was observed between a SNP and diabetic nephropathy (rs4420638; \( P_{\text{corrected}} = 0.002 \)). This finding was subsequently replicated in a phenotypically similar case–control collection with type 1 diabetes from the British Isles. In our original report, 27% of the diabetic nephropathy cases had end-stage renal disease (ESRD). We have now sought to clarify if this SNP (rs4420638) was specifically associated with diabetic nephropathy or whether it was associated instead with ESRD, by assessing a further reasonably well-powered case-control collection where all the cases had ESRD. Biological and epidemiological data support genetic susceptibility to ESRD as evidenced by familial clustering of renal failure [2], different prevalence rates in distinct ethnic populations [3] and genetic variants modifying progression [4].

Ethical approval (www.orecni.org.uk) was obtained prior to conducting this study. Patients with ESRD receiving their first renal allograft (\( n = 645 \)) were defined as cases, and their respective deceased kidney donors (\( n = 554 \)) were the control group. All patients were Caucasian. Recipients had a primary cause of renal disease recorded and classified according to the European Dialysis and Transplant Association coding system (www.era-edta.org). The most common causes of ESRD were glomerular disease (21%) and pyelonephritis/interstitial nephritis (20%); fewer than 10% had diabetic nephropathy. Genotyping was performed for rs4420638 using the MassARRAY iPLEX™ assay (Sequenom, San Diego, CA, USA) and statistical analysis conducted as previously described for the case–control collection [1]. Genotyping in the renal transplant population had a success rate of 99.7% with a minor allele frequency of 15%.

In summary, this further research suggests that the coronary artery disease SNP, rs4420638, is associated with diabetic nephropathy rather than ESRD. It will be of interest to try and replicate this finding in a very large type 1 diabetic cohort to try and distinguish between genetic susceptibility to cardiovascular disease versus diabetic nephropathy.

Conflict of interest statement. None declared.

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Letters and Replies

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The role of fructose in inducing metabolic syndrome is speculative

Sir,

The conclusion in the Editorial Review by Cirillo et al. [1] that excessive intake of fructose may have a key role in

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inducing the metabolic syndrome via ATP depletion and uric acid generation is weakened by an over-reliance on unphysiologic protocols that do not reflect real-world human diets.

Much of the experimental evidence cited in support of a significant role for fructose was generated in experimental systems using elevated levels of pure fructose to induce metabolic upsets. The commonly used nutritive (caloric) sweeteners are sucrose, high fructose corn syrup (HFCS), honey and fruit juice concentrates. All are composed of fructose and glucose and deliver approximately equal amounts of each to the bloodstream after absorption. The incidence of individuals consuming only fructose or only glucose in the diet is surely so rare as to be insignificant.

Studies using very high fructose levels may be useful for probing metabolic pathways, but they have very little predictive value for most human diets. Contemporary fructose protocols often compare the effects of pure fructose versus pure glucose in human subjects at levels between 15 and 30% of total energy (see e.g. [2]) and in animals at levels exceeding 60% of calories (see e.g. Cirillo et al. [1], references 23 and 27). Using NHANES 1999–2004 data, Marriott recently estimated mean total fructose intake (added + naturally occurring) at 9.1% of energy for all ages and genders; total fructose intake for even the heaviest consumers—95th percentile 19- to 22-year males and females—was <18% of energy [3].

The practical implications of pure sugar comparisons are seldom discussed, because the dietary consequences are so absurd. Humans get some fructose from natural sources (fruits, vegetables, nuts), but most comes from added nutritive sweeteners, which are half fructose and half glucose. To take in 30% of calories as fructose, 60% of calories in the form of a nutritive sweetener must be consumed. This is clearly a gross distortion of the diet, violates all nutritional guidelines and would occur in only the rarest of circumstances. And since glucose fares so well in comparative metabolic tests, it has been proposed as a replacement for current fructose-containing sweeteners. But glucose lacks the functionality and sweetness of fructose-containing sweeteners; more would be required, at nearly twice the calories of current food choices.

Absent confirmation in real-world diets characterized by moderate fructose use and mixtures of sugars, the conclusion of Cirillo et al. that fructose has a meaningful role in inducing the metabolic syndrome must be considered speculation.

Conflict of interest statement. The author is a consultant to the food and beverage industry in nutritive sweeteners, including HFCS and sucrose. His professional associations, past and present, include individual food industry companies as well as such organizations as the American Chemical Society, American Council on Science and Health, Calorie Control Council, Corn Refiners Association, Institute of Food Technologists and International Life Sciences Institute.

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Reply

Sir,
Dr White raises the clinical relevance of the experimental and human studies showing that fructose can induce inflammation and features of metabolic syndrome. Fructose (0.25 mM) induces intercellular adhesion molecule-1 (ICAM-1) expression and ATP depletion in endothelial cells [1]; similar serum concentrations are routinely achieved following a sugary meal in humans [2]. A diet in 20% fructose raises sICAM-1 levels in rats [1], and a diet of 25% fructose raises sICAM-1 in humans [3]; this is not distinct from diets of 15–20% fructose seen in the upper quintile of society [2]. A diet of 25% fructose was able to induce insulin resistance, dyslipidaemia and increased intra-abdominal fat in overweight adults [4]. Recent reports suggest that at least 16% of the studied American populations, especially adolescents and children, are consuming over 25% of daily energy requirements from sugar-sweetened beverages. While most experimental studies use higher doses of fructose, this is done so that we can see effects in days to weeks, not months to years. Rats fed 15% fructose do develop insulin resistance, but it takes months [5]. The reason why we give pure fructose is that by doing so we can separate its effects from glucose; however, the combination is actually worse since glucose stimulates fructose absorption. Some studies show that fructose can induce features of metabolic syndrome more effectively when combined with glucose [6].

Throughout the world, there has been a marked increased intake of fructose, with the primary sources being from table sugar (sucrose) or high fructose corn syrup (HFCS). Intake correlates with the epidemic of obesity and metabolic syndrome; experimental studies show that fructose can induce features of the metabolic syndrome, and the cellular mechanisms are now being elucidated. We recommend a tax on sugar and HFCS with the aim of reducing the intake by 60%; the millions of dollars from the tax could support medical research, and the billions saved in health care costs would boost our ailing economies.

Conflict of interest statement. R.J.J. and Y.S. are listed as inventors on patent applications by the University of Florida related to the role of fructose in hypertension and metabolic syndrome. Dr Johnson has also written a book on fructose for the lay public (Rodale Press, 2008).