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Letter to the Editor

Coffee intake, glucose metabolism and gene polymorphisms: response to Kawada

In his letter to the editor[1], Kawada stated that he had a concern about our study[2], related to type 2 diabetes mellitus (T2DM). His concern is, however, unclear as our study was in relation to coffee's effects on healthy people and did not examine any potential T2DM risk from coffee drinking.

Denden *et al.*'s[3] finding that the *rs762551* AA genotype is associated with higher coffee intake is a major confounder to the epidemiology associating higher coffee consumption with reduced T2DM risk, particularly when this is considered in conjunction with Platt *et al.*'s[4] finding that those with the AC and CC genotypes have been shown to have an increased risk of T2DM irrespective of how much coffee is consumed. It may be the case that it is in fact the C allele that is associated with increased risk of T2DM, and because carriers of the C allele self-select to consume less coffee, increased coffee consumption is erroneously associated with a reduced risk. However, this would appear to be in direct contradiction of our findings, as we observed a reduction in the postprandial glycaemic response following chronic consumption in those with the C allele, suggesting an improvement in glucose metabolism.

Caution is advised when interpreting the epidemiology related to coffee consumption and T2DM risk. Coffee consumption in these cases is generally determined based on FFQ. These FFQ do not usually gather information on size of serving or type of coffee. The amounts of the different coffee components that are suggested to be responsible for effects on glucose and lipid metabolism, such as chlorogenic acids, trigonnelline, kafestol, caffeine and melanoidins, vary massively depending on the type of bean, degree of roasting and preparation method – for example, boiling, filter, instant, espresso and so on[5,6]. This variation renders it inadvisable to report associations based on number of cups per day.

It is worth noting that in our study we recruited individuals who did not consume coffee on a regular basis and had low total caffeine intake (median intake 80 mg/week), and therefore we were able to test the effect of this genotype before the fast phenotype had been 'activated' by coffee/caffeine consumption. Furthermore, we controlled the amount of coffee consumed and removed variation from preparation methods by the use of instant coffee. We believe these to be key strengths of our study.

Kawada hypothesises that 'the advantage of the AA genotype for rapid caffeine metabolism would lead to diminish the suppression of insulin sensitivity by habitual coffee intake'; however, in our study, we did not find any suppression of insulin sensitivity, as measured by Matsuda index, in those with the AA genotype. Although the increase in postprandial glucose observed in this group may suggest reduced insulin sensitivity, the increased suppression of postprandial fatty acids, also observed in this group, would suggest the opposite. Furthermore, it should be emphasised that our participants were studied in a caffeine-free state, after 2 d without coffee, and thus the ability of those with the AA genotype to metabolise caffeine more rapidly is irrelevant under these conditions. It is possible that, over time, people may build tolerance to caffeine's effects; however, it is not known how long a period would be required. Indeed, just 7 d caffeine intake was sufficient to reverse its acute adrenalin-raising effect[7].

Kawada also states that 'glucose-lowering effect by chlorogenic acids (CGA) is explained by the suppression of hepatic glucose-6-phosphate activity'. Although this has previously been suggested as a potential mechanism, it is unlikely that sufficient CGA concentrations would be achieved *in vivo*. Arion *et al.*[8] demonstrated that *in vitro* chlorogenic acid, better described as 5-caffeoylquinic acid (5-CQA using IUPAC (International Union of Pure and Applied Chemistry) numbering[9,10]), was a competitive inhibitor of hepatic glucose-6-phosphatase. The lowest 5-CQA concentration studied was 200 μmol/l, and the concentration for 50 % inhibition was calculated as 260 μmol/l[8]. Hemmerle *et al.*[11] investigated 5-CQA and a range of structurally related compounds, including the naturally occurring 5-*p*-coumaroylshikimic acid, 5-*p*-coumaroylquinic acid and methyl-5-caffeoylquinate, which achieved 50 % inhibition of glucose-6-phosphatase *in vitro* at concentrations of 250, 230 and 1000 μmol/l, respectively. Bassoli *et al.* found that while 5-CQA (1 mmol/l) inhibited glucose-6-phosphatase *in vitro* by approximately 40 %, perfusion of rat liver with 5-CQA (1 mmol/l) failed to reduce glucose output arising from glycogenolysis. The 5-CQA solution entering the liver contained 720 (SEM 37) μmol/l and the output contained 702 (SEM 40) μmol/l, indicating limited uptake, and the authors suggested that the hepatocyte concentration achieved was insufficient to inhibit glucose-6-phosphatase[12].

Coffee beverage is almost certainly the richest dietary source of 5-CQA and related acyl-quinic acids, but a cup of coffee is extremely variable, with the acyl-quinic acids content varying almost 10-fold – 56–531 μmol[5,13]. Volunteer studies have shown that 5-CQA and its regio-isomers are found in plasma with a T_{max} that may be as short as 30 min but is extended by adding sugar or cream to the coffee[14]. Even giving volunteers

coffee beverage supplying 1262 μmol 5-CQA (4525 μmol total acyl-quinic acids) only generated a transient plasma C_{max} of 44 (SD 7) nmol/l for 5-CQA, accompanied by 43 (SD 10) nmol/l for 3-caffeoylquinic acid and 73 (SD 7) nmol/l for 4-caffeoylquinic acid[15]. Even if equi-potent, the total CQA regio-isomer concentration is only a transient 150 nmol/l – approximately three orders of magnitude lower than the lowest concentration observed *in vitro* to achieve 50 % inhibition of glucose-6-phosphatase. Therefore, while coffee and/or dietary acyl-quinic acids might have beneficial effects, inhibition of glucose-6-phosphatase seems unlikely to be the mechanism responsible.

In conclusion, we hope we have addressed any concerns raised in the original letter. We would like to re-emphasise the preliminary nature of this work and wholeheartedly agree with Kawada's conclusion that further work investigating the mechanisms underlying our results is warranted.

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