EDITORIAL

Is caffeine protective against Type 2 diabetes?

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Type 2 diabetes (T2D) is a complex metabolic disease with serious complications and its prevalence is now reaching epidemic proportion worldwide with minorities and those from developing countries bearing the largest burden of disease and premature mortality [1–3]. The fundamental basis of T2D pathogenesis involves impaired insulin action and secretion. Obesity is the most important risk factor that can be modified with comprehensive lifestyle interventions to significantly reduce diabetes risk [4]. Nonetheless, whether, how, and to what extent specific dietary components may offer beneficial effects on diabetes risk remain uncertain. Now a series of recent observational studies have indicated that promising modifiable lifestyle factors may include intake of caffeinated coffee and/or caffeine. Coffee is one of the most frequently consumed beverages worldwide, perhaps in large part owing to the psychosomatic effects of caffeine [101], although coffee also contains many other components such as vitamins, minerals, alkaloids and phenolic compounds. To date, a number of prospective studies conducted among mainly European men and women have demonstrated an inverse association between coffee consumption and T2D risk [5–9]. In the most recent systematic review, Huxley and colleagues summarized findings from 18 studies involving 457,922 participants and reported that those who drank between three and four cups per day had approximately 25% lower T2D risk compared with those drinking two or fewer cups per day (relative risk: 0.76; 95% CI: 0.69–0.82) [9].

Several mechanistic explanations have been put forth relating a myriad of components such as magnesium, potassium, chlorogenic acid and caffeine to improved insulin sensitivity and β-cell function [10].

Caffeine (1,3,7-trimethylxanthin) is a xanthine alkaloid rich in coffee, tea and chocolates derived from cocoa beans. One recent study in rats reported that caffeine may protect pancreatic β-cells against natural toxins such as streptozotocin [11]. Several studies in rodents have also demonstrated that caffeine increases resting metabolic rate [12–14] and decreases body

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weight [15]. Recently, Greenberg and colleagues observed that the inverse association between coffee intake and T2D risk only applied to those who had previously lost weight [16], suggesting the important role of weight loss relating coffee intake to T2D risk. However, few have directly assessed caffeine intake in relation to obesity or T2D risk in humans [5,6,17]. In a crossover study of 40 participants, caffeinated coffee consumption of 1 l per day for 4 weeks increased fasting insulin levels compared with coffee abstinence, but did not decrease fasting glucose levels, raising concern of the acute impairment of insulin sensitivity [18]. However, in a nonrandomized clinical trial of 47 participants, caffeinated coffee consumption of eight cups per day for 4 weeks led to favorable changes in inflammatory markers, 6% increase in serum adiponectin levels and 8% decrease in serum IL-18; although no changes were seen for markers of glucose metabolism [19]. In addition, several large cohort studies reported that plasma markers of systemic inflammation were prospectively associated with T2D risk [20,21], supporting the notion that chronic inflammation are antecedents of T2D. Taken together, these findings suggest that mediating systemic inflammation may be another possible mechanism whereby caffeinated coffee may exert its protective effect against T2D risk. However, the long-term effects of caffeine on glucose metabolism remain uncertain as there is no randomized control trial directly evaluating the glycemic or metabolic effects of caffeine on body weight and T2D risk.

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In a recent prospective study of postmenopausal women, we found that both caffeinated coffee and caffeine were inversely associated with T2D risk [6]. The multivariable-adjusted odds ratios for T2D were 0.47 (95% CI: 0.23–0.94) comparing those with four or more cups per day of caffeinated coffee to nondrinkers, and 0.56 (95% CI: 0.27–1.15) for women consuming more than 500 mg per day compared with 50 mg or less per day of caffeine [6]. Importantly, those who consumed caffeinated coffee and caffeine were positively associated with plasma levels of sex hormone-binding globulin (SHBG) [6,22,23], a protein that has been independently and prospectively associated with increased T2D risk in men and women [24,25]. SHBG is synthesized primarily in the liver and is classically thought to bind androgens with high affinity and estrogens with low affinity, thereby regulating the bioavailability of these sex steroids [26]. Interestingly, some studies have found that SHBG may bind to its own receptors on the plasma membranes of a variety of cells exerting its direct metabolic effects [27]. By contrast, there was no significant association between decaffeinated coffee intake and T2D risk (odds ratio: 0.72; 95% CI: 0.19–2.69); nor was there any relationship between decaffeinated coffee and SHBG levels. Therefore, these molecular epidemiologic studies suggest that caffeine may affect SHBG metabolism in the liver and influence the plasma levels of SHBG [23]. In addition, we found that the inverse associations of caffeinated coffee and caffeine intakes with risk of T2D were substantially attenuated after adjusting for SHBG levels [6]. Furthermore, carriers of the rs6259 minor allele or noncarriers of the rs6257 minor allele of the *SHBG* gene (previously reported to be predictive of diabetes risk) who consumed two cups or more per day of caffeinated coffee had lower risk of T2D in directions corresponding to their associated plasma SHBG levels [6]. More importantly, the T2D risk predicted by low SHBG levels remained significant using a Mendelian randomization analysis [25], a finding that was subsequently confirmed in a large consortium of case–control studies [28]. Taken together, these findings support the notion that caffeine intake may affect T2D risk via alteration of SHBG metabolism.

In conclusion, a large number of prospective cohort studies have demonstrated a consistently significant inverse relation between coffee intake and T2D risk. Whether this relationship was causal remain debatable owing to the nature of observational studies. The causality argument has been strengthened in recent molecular epidemiologic work linking the SHBG genotype and phenotype to the relationship between coffee intake and diabetes risk. In our view, a modest amount of coffee intake can indeed be incorporated into a healthy lifestyle that includes exercise and weight reduction for diabetes prevention. However, it is important to note that caffeinated coffee and caffeine intakes may have adverse effects, such as arrhythmias, dyslipidemia, pregnancy complications and drug interactions [29]. Ultimately, the balance of risk and benefits associated with caffeine needs to be evaluated in future intervention trials. In the meantime, prudence dictates that those who

do not currently drink coffee should not pick up the habit simply for lowering T2D risk.

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