New wine in old bottle: liver and diabetes

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Received: 30 September 2013 / Accepted: 3 October 2013 / Published online: 13 October 2013
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There is a long and intimate relationship between the liver and carbohydrate metabolism; could there be more to this than is already known? Insulin has important effects on carbohydrate metabolism; it suppresses gluconeogenesis and induces glycogenesis and lipogenesis [1]. Recent evidence suggests that the hypothalamus can modulate the secretion of insulin and hepatic glucose flux through the autonomic nervous system [2], and by fatty acid oxidation. There is an intriguing concept that a feed-forward mechanism exists to facilitate weight gain involving the brain, liver and other organs [3]: in conditions of energy excess, hepatic glucose metabolism increases expression of glucokinase and feeds back to the central nervous system through the vagus nerve, leading to inactivation of brown adipose tissue sympathetic nerves. Thereby thermogenesis is decreased and deposition of adipose tissue occurs. This has been called the ‘thrifty mechanism operating on the whole body’ [3]. When excess food is available, this evolutionarily conserved homeostasis favours adiposity. Novel hepatic regulatory pathways involving carbohydrate metabolism are being identified such as solute carrier family 30 member 8 gene (SLC30A8) that influences insulin clearance by the liver [4], FoxO1/3/4 transcription factors [5] and mitochondrial exhaustion [6].

Liver disease and diabetes mellitus often coexist. Among 14,523 adults with chronic hepatitis B, a significantly higher cumulative incidence of cirrhosis (RR=3.43, 95 % CI=2.62–4.49) was found among those with newly diagnosed diabetes [7]. Even after adjustment for possible confounding factors, diabetes

remained an independent predictor for cirrhosis, suggesting that subjects with chronic hepatitis B who develop diabetes are prone to develop cirrhosis of liver. Nonalcoholic fatty liver disease (NAFLD), a common cause of chronic liver disease is associated with metabolic syndrome, and is an independent risk factor for the development of type 2 diabetes mellitus [8]. Insulin resistance plays a role in its pathogenesis. A recent study reported that individuals with NAFLD had higher prevalence of metabolic syndrome and lower levels of [25-(OH)D [9]. Among patients with chronic hepatitis C virus from South-east Asia, increasing age, obesity and HCV genotype 3 independently predicted type 2 diabetes in HCV seropositive patients [10].

How could the two be related? A number of hypotheses were proposed: DNA from the gut microbiota, identified in the liver and adipose tissue could point to the existence of a ‘tissue microbiota’ [11], thereby opening up potential channels for therapy. Recently, mitochondrial biogenesis has been implicated in obesity and insulin resistance [12]. Epigenetic alterations may operate to transmit nutrient and metabolic changes into heritable gene expression. Aberrant metabolism and epigenetic alterations may thus be linked [13]. The association of the enzyme gamma-glutamyltransferase and atherosclerosis is being increasingly recognized [14].

In this issue of the *Journal*, Ho et al. published a report on the relation of the enzyme GGT and metabolic syndrome in a Taiwanese aboriginal population [15]. GGT is a hepatic enzyme that has an antioxidant role [16]. Earlier studies showed that GGT levels were a risk factor for insulin resistance. In a South African cohort (n:1198) indicators of insulin resistance increased with rising levels of GGT, suggesting that the enzyme could be used as a risk factor for development of metabolic syndrome [17]. Elevated levels of γ -glutamyltranspeptidase was associated with death due to cardiovascular and hepatic causes in older subjects from the Rancho Bernardo Study [18]. Similar prognostic value of GGT for metabolic syndrome was reported from China [19]. Increasing GGT even within the

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normal range predicted risk of metabolic syndrome in a Korean cohort, independent of the baseline level [20].

What is particularly interesting in the current study [15] is its replication in an isolated population of aboriginal members from Taiwan. In addition to GGT, butyrylcholinesterase (BChE) is another liver-derived enzyme [21] that is affected by quality and quantity of fat intake [22, 23]. BChE levels are also altered in type 2 diabetes mellitus, and show an inverse relation with serum cholesterol level [24]. A role for BChE in the expression of metabolic syndrome was proposed [25]. Other studies have suggested that BChE is associated with obesity, lipid levels and with insulin resistance [26]. In the Kansai Healthcare Study, elevated levels of serum BChE were independently associated with future risk of diabetes [27].

De Bona et al. studied the activities of BChE and of γ -glutamyltransferase in relation to oxidative stress markers in metabolic syndrome [28] because the two are related to its pathogenesis [6, 25]; 87 subjects were recruited (69 women), comprising 39 with metabolic syndrome (30 women) and 48 controls (39 women). Oxidative stress markers were assessed (non protein thiol groups, protein thiol groups, plasma ascorbic acid, lipid peroxidation, adenosamine deaminase, γ -glutamyltransferase and BChE). Metabolic syndrome was associated with elevated levels of both BChE (5.72 ± 1.40 vs 4.24 ± 1.30 ; $p < 0.001$) and γ -glutamyltransferase (0.58 ± 0.42 uKat/L vs 0.22 ± 0.15 uKat/L; $p < 0.001$).

This suggests that markers of oxidative stress in metabolic syndrome and diabetes mellitus may be identified by measuring BChE and γ -glutamyltransferase. BChE has been proposed to be a marker of low-grade systemic inflammation, often seen in insulin resistance syndrome [29]. Although it may not play a causal role, BChE has been suggested to modulate its expression [30], or be a secondary marker [31]. The ability of high serum lipids to induce stereoscopic alteration in its configuration could be a pathogenic mechanism [32].

New biology involving molecular genetics and bioinformatics provides new methods to gain insights into biological processes that help us understand physiological processes and thereby devise tools and therapy for clinical application [33–35].

Variant forms of the protein have been reported in some ethnic groups [36], suggesting they might have evolutionary significance analogous to the protective effect of sickle cell trait against malaria. A recent animal report documents that deficiency of PDCD4 (programmed cell death 4) could protect mice against diet-induced obesity, and may be a potential target for developing pharmacological agents [37]. On a more practical note, differential elevation of liver enzymes could be markers of different phenotypic associations of metabolic syndrome [38].

The association of liver and diabetes is still a virgin field, with exciting developments that could enhance our understanding of pathological processes and lead to newer prognostic markers and drugs.

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