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Positive selection of type 2 diabetes genotypes – the glycaemic threshold hypothesis

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ABSTRACT

The high prevalence of deleterious polygenic type 2 diabetes (T2D) is a paradox requiring explanation beyond food excess, inactivity and the obesity resulting from positive energy balance. Historically, hunting-foraging and later agrarian communities often manifested a converse negative energy balance due to nutritional deficit and/or high physical energy demand – both potentially resulting in hypoglycaemia. Since hypoglycaemia impairs both reproductive fitness and cognitive function, it is proposed that that by expressing resistance to hypoglycaemia, T2D phenotypes were subject to positive selection. The insulin resistance present in often-associated atherosclerotic cardiovascular disease, metabolic syndrome and polycystic ovarian disease may also explain their frequent coexistence and current prevalence.

Polygenic type 2 diabetes (T2D) – as defined by internationally-agreed blood glucose levels after overnight fasting and two hours after a glucose load [1] – accounts for around 90% of diabetes cases worldwide. Nevertheless there is a continuum: the term 'impaired glucose regulation' (IGR) – sometimes referred to as pre-diabetes – defines intermediate elevations of fasting and/or two-hour post-load blood glucose. The significance of IGR at age 45 has been confirmed by its lifetime 74% rate of progression to T2D [2], together with a 20–30% higher incidence of ischemic cardiovascular events within 10 years compared to normoglycaemic subjects [3].

Epidemiological data in both Europe [4] and Asia [5] reveal that within the age-group 70–79, 30% or more of many populations manifest IGR or T2D – an approximation of underlying T2D genotype prevalence. This is supported by lifetime risk estimates of 30–50% for IGR and T2D in Australia [6], the Netherlands [2] and the USA [7] and as high as 80% in indigenous Canadians [8]. This data identifies not only a serious and escalating global humanitarian and economic challengebut also an enigma: the persisting and paradoxical high frequency of deleterious underlying T2D genotypes.

While environmental factors of inactivity and nutritional excess – positive energy balance – are considered largely responsible for an approximate 10% global prevalence of T2D, twin studies identify the centrality of genetic factors. Around 50% of monozygotic co-twins of T2D subjects are found to be concordant for T2D at the time of their sibling's diagnosis; concordance rising to 76% after 15 years and 96% if IGR is included [9]. Furthermore, genome-wide association studies (GWAS) reveal at least 100 genes associated with T2DM, although these are estimated to still represent only around 10% of the genetic risk [10]. Individual alleles have been recently linked with a wide variety of individual biochemical processes relevant to blood glucose control. Nevertheless with the exception of uncommon monogenic maturity diabetes of the young (MODY), no single genotype has been associated with T2D or IGR.

Early interpretations

In 1962, Neel proposed his 'thrifty-genotype' hypothesis – that diabetes genotypes favoured physical survival based on energy storage as fat during food availability – energy later utilizable in times of famine [11]. His hypothesis led to the author's comparative evaluation of energy balance and metabolic studies in the spiny mouse (*Acomys cahirinus*), an Israeli desert rodent spontaneously developing T2D-similar diabetes in captivity [12,13]. In comparison with white mice, these studies did reveal survival elements, including 'thrift' – lower metabolic rate, higher temperature tolerance and maintenance of body weight despite lower food intake – without necessarily being able to relate this to the species' diabetic status. A later search for high prevalence diabetes in recently captive species from Argentina led to the discovery of further T2D-manifesting burrowing rodents, including the degu (*Octodontomys gliroides*) and particularly the tuco-tuco (*Ctenomys*

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talarum), which manifests T2D-typical lens, renal and neuropathic changes [14].

Characterization of high T2D prevalence in Australian aboriginal [15] and other urbanised indigenous populations added some weight to Neel's concept of selective T2D genotype survival in earlier populations, rendered deleterious by rapidly-evolving positive energy balance. The thrifty genotype hypothesis has since been widely discussed but not well supported [16], in particular by genomic studies [17]. A 'drifty genotype' alternative has been proposed [16] together with an epigenetic 'thrifty phenotype' process that links low birth weight to T2D development in later life [18]. The validity of these hypotheses has been widely discussed [19] but no biological mechanisms have been identified. Neel's concept of resistance to famines has been considered extreme, given their infrequency: intermittent or seasonal energy deficit a more likely challenge.

Centrality of reproductive and cognitive fitness

In discussing natural selection, Darwin identified determinants of physical survival and mating success, and the central role of reproductive fitness [20]. Similar determinants apply to selection for disease as for evolutionary survival. Thus Corbett et al. recently presented a 'fertility first' hypothesis to explain the high prevalence of four very common genetically-determined syndromes – polycystic ovarian disease, the metabolic syndrome, atherosclerotic cardiovascular disease and T2D – a concept of historical genotype survival advantage based on relative reproductive fitness [21]. No biological mechanisms were proposed. The relevance of physical and social cognitive functioning to natural selection has also been emphasized [22,23], but underlying biological mechanisms have received little attention.

The present paper argues that a) hypoglycaemia is a common occurrence in states of negative energy balance; b) this hypoglycaemia compromises both cognitive and reproductive function, and c) by expressing resistance to hypoglycaemia, T2D phenotypes have selectively maintained cognitive and reproductive function and thereby a survival advantage that has led to the current T2D epidemic.

Cognitive and reproductive function and their relationships to glucose metabolism

Glucose is the primary fuel of the metabolically expensive, disproportionately-large human brain. Thus a wide variety of cognitive activity in normal subjects is impaired by hypoglycaemia, including psychomotor function, immediate and delayed visual and verbal memory as well as spatial awareness, working memory and reaction time [24]. The anatomical sites of these dysfunctions have not been clarified and the levels of serum glucose at which cognitive dysfunction occurs vary. The above cognitive impairments were observed at a glucose concentration of 2.5 mmol/l, but other studies have reported impairment already at 3.0 mmol/l [25] and even 3.6 mmol/l [26]. In addition, repeated hypoglycaemia – as may have been a common phenomenon in foraging and agrarian communities – has been shown to diminish hypoglycaemia counter-regulatory mechanisms [27], potentially further impairing cognitive function.

The effect of hypoglycaemia on reproductive function is more complex. Negative energy balance due to under-nutrition and/or over-exercise affects reproduction in both sexes largely by impairing hypothalamic gonadotropin releasing hormone (GnRH) pulse generation [28]. The mediators are a complex of peripherally and centrally derived peptides of adipose and intestinal origin, together with neuropeptides and neurotransmitters [29]. These respond to reduced levels of oxidisable nutritional substrates – including fatty acids, but predominantly glucose [30].

Almost 100 years ago, anovulation was reported in pigeons given hypoglycaemic doses of the then newly-identified insulin [31]. Later, McClure investigated anovulation and foetal resorption in food-deficient mice and then cattle, and showed that hypoglycaemia with secondary suppression of gonadotropin was its likely cause. Either glucose feeding or gonadotropin restored normal ovulation [32]. More specifically, these studies demonstrated that 2-deoxyglucose (2DG) – a glucokinase inhibitor that causes intracellular glycopenia – resulted in anovulation and the death of tubal ova. These important observations have now been confirmed in other species [33]. Glucose sensing relevant to reproduction has been identified in both the ventromedial hypothalamus and the hindbrain by intra-ventricular 2DG infusion studies [34]. There are further potentially redundant sensing and effector mechanisms linking hypoglycaemia to defective reproduction, including a direct impairment of ovarian function [35].

Neuro-endocrine reaction to negative energy balance is rapid. Independent of any diminution of adipose-tissue mass, a prompt release of its peptide hormone leptin inhibits the hypothalamic-pituitary-gonadal (HPG) axis: a teleologically-relevant response ensuring that energy-expensive reproduction is prevented in the absence of adequate nutrition. Although this inhibition is reversible by leptin administration, its effect is opposed by 2DG – underlining the importance of glucose availability for normal HPG function [36].

After an original report of luteinizing hormone (LH) suppression by hypoglycaemia [37], a quantitative assessment in healthy men using hyperinsulinaemic hypoglycaemic clamp techniques revealed progressive LH inhibition commencing already with blood glucose reduction from 5.2 to 4.2 mmol/l [38]. Prompt suppression of serum LH (approx 45%) and of testosterone (approx 35%) occurred at a mean glucose level of 2.9 mmol/l; an effect shown to be independent of the action of necessarily high serum insulin levels. LH is indeed highly reactive to fasting – even the omission of a single missed evening meal [39] – and its fall is readily preventable by minimal oral glucose supplementation [40]. Thus not only cognitive but also reproductive function is highly glucose-dependant.

Glucose responses to negative energy balance

In healthy non-diabetic subjects, fasting results in remarkably consistent glucose nadir values: a typical reference 72-hour study demonstrated blood glucose decreasing from a mean 5.5 mmol/l to a nadir mean of 3.7 mmol/l [41]. Significantly, 30% of values fell below 3·3mmol/l, and thus well within the range known to both suppress LH and impair cognitive function.

In comparing fasting non-diabetic with T2D subjects in published studies, predictable and progressive blood glucose reductions are seen in both. However, mean blood glucose levels in T2D remain consistently 1.0–4.0 mmol/l higher than in non-diabetic subjects [42], even after 14 days of starvation [43]. Similar potentially informative studies in patients with IGR or monozygotic co-twins discordant for T2D are not available. However, the author's comparative animal studies on pre-diabetic *Acomys cahirinus* referred to earlier showed that during a 72-hour fast, mean basal blood glucose of 6·7mmol/l in both species fell to 4.3 mmol/l in spiny mice – a significantly higher nadir than the mean 3.4 mmol/l in weight-matched white mice [13]. A similar 1.0 mmol/l mean glucose differential was recorded when another spontaneously diabetic species, the captive Egyptian sand rat (*Psammomys obesus*) was compared to matched Wistar laboratory rats during fasting [44].

These studies suggest a subtle but important multispecies resistance to fasting-induced hypoglycemia (RFH) linked to the T2D genotype(s). Identifying a similar link in human T2D diabetes is difficult. However, a study by Vaag et al. [45] in normally glucose-tolerant identical co-twins of T2D subjects did reveal insulin resistance. Comparative extended fasting studies in such individuals may be one of the few ways of identifying the phenomenon of genetically-dependant hypoglycaemia resistance in man.

The other component of negative energy balance – physical exercise – is an equally relevant hypoglycaemic factor [46]. Thus blood glucose below 2.5 mmol/l was identified in one third of healthy subjects

exercised to 65% of $VO_{2\ max.}$ [47]. In another study, healthy subjects exercised to only 49% of $VO_{2\ max}$ reduced their mean blood glucose to 2.6 mmol/l [48].

It is likely that naturally-occurring seasonal or other survival challenges in historical hunter-gatherer and agrarian populations would have involved both exercise and nutritional elements leading to hypoglycemia that cannot be easily reproduced experimentally. However, significant hypoglycaemia – occasionally even fatal – occurs in anorexia nervosa, a psychological disorder characterised by under-nutrition, often accompanied by over-exercise [49]. In a consecutive series of 25 such hospitalized patients, 44% registered blood glucose levels below 3.3 mmol/l with 12% below 2.2 mmol/l [50]. It is relevant that cognitive function and brain structure in anorexia nervosa have been shown to be abnormal, remaining so even years after diagnosis [51]. Although additional mechanisms may influence reproduction during negative energy balance, present evidence supports a central role of hypoglycaemia, acting through a hypothalamic glucose/LH 'gatekeeper' which may itself be anomalous in T2D.

Beyond T2D, atherosclerotic cardiovascular disease, metabolic syndrome and polycystic ovarian disease are highly prevalent in most populations, with insulin resistance a feature common to all four entities [24]. Although such resistance to insulin has not been shown to necessarily equate with the putative RFH, there may be parallels between these entities and the positive selection of T2D genotypes [52]. In addition, other hyperglycaemic syndromes genetically unrelated to T2D may have been historically subject to positive selection through RFH. These include anomalies of glucose-6-phosphatase and glucokinase and the fasting hyperglycemias linked to the G6PC2 gene, as well as monogenic maturity-onset diabetes of the young (MODY).

Summary and further evaluation

The collective studies summarized here support a hypothesis underlying the paradoxically high population prevalence of T2D: namely historical cognitive- and reproduction-favourable T2D genotype survival based on hypoglycaemia-resistance: maintenance of normoglycaemia in the face of negative energy balance. Given such high T2D genotype prevalence, their positive selection may also underlie the evolutionary survival of *Homo sapiens* and other mammalian species in which T2D is being increasingly reported. Specific studies are needed to further characterise the glucose-LH gatekeeper by hypoglycaemic clamping [39], both in persons with and without T2D. In addition, the differential response to extended fasting requires further assessment, comparing non-diabetic with prediabetic subjects: the offspring of conjugal T2D subjects and of discordant monozygotic T2D twins.

Conflict of interest statement

There is no conflict of interest.

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Appendix A. Supplementary data

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