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Normal weight individuals who develop Type 2 diabetes: the personal fat threshold

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Abstract

Type 2 diabetes (T2DM) is frequently regarded as a disease of obesity and its occurrence in individuals of normal body mass index (BMI) is often regarded as indicating a non-obesity-related subtype. However, the evidence for such a distinct, common subtype is lacking. The United Kingdom Prospective Diabetes Study (UKPDS) cohort of people diagnosed with T2DM in the 1970s and 1980s had a median BMI of only 28 kg/m^2. UKPDS data form the basis of current understanding of the condition even though one in three of those studied had a BMI of less than 25 kg/m^2. BMI, though, is a population measure and not a rigid personal guide. Weight loss is considered *de rigueur* for treating obese diabetic individuals, but it is not usually considered for those deemed to have a normal BMI. Given the new evidence that early T2DM can be reversed to normal glucose tolerance by substantial weight loss, it is important to explain why non-overweight people respond to this intervention as well as obese individuals. We hypothesize that each individual has a personal fat threshold (PFT) which, if exceeded, makes likely the development of T2DM. Subsequent weight loss to take the individual below their level of susceptibility should allow return to normal glucose control. Crucially, the hypothesized PFT is independent of BMI. It allows both understanding of development of T2DM in the non-obese and remission of diabetes after substantial weight loss in people who remain obese by definition. To illustrate this concept, we present the distribution curve of BMI at diagnosis for the UKPDS cohort, together with a diagram explaining individual behaviour within the population. The concept of PFT is of practical benefit in explaining the onset of diabetes and its logical management to the non-obese majority of people with T2DM.

Key words: aetiology, obesity, pathogenesis, Type 2 diabetes, weight loss

INTRODUCTION

Type 2 diabetes (T2DM) is a condition of relative insulin deficiency, in which hyperglycaemia develops when a person's β-cell function is no longer sufficient to meet their insulin requirement [1,2]. Insulin resistance is common in people with T2DM and exacerbated by obesity, but individuals with normal weight can develop T2DM if their β-cell function is sufficiently compromised [3]. The interplay between the degree of insulin resistance and the level of β-function is likely to contribute to the heterogeneity of T2DM presentation, especially in non-obese individuals [4,5].

The identification of monogenic causes of maturity onset diabetes of youth (MODY), which are unrelated to obesity, has reinforced the notion that 'classical' T2DM is linked to obesity and that all non-obese people may probably have a different diabetes subtype. The perceived relationship between T2DM and obesity, however, has not always been obvious. In the 1970s, when the average weight of the UK population was considerably less than at present, the Whitehall study showed only a small association between obesity and T2DM [6]. At that time it was considered that there was no major effect of obesity on the development of T2DM [6–8].

This article examines the scientific basis for the belief that the pathophysiology of T2DM may be driven by individual weight gain, rather than achieving a population-derived body mass index (BMI) threshold and that this may be reversible. It considers data on populations and individuals and examines possible explanations of the phenomena observed. We hypothesize that each individual could have a personal fat threshold (PFT) which determines their susceptibility to developing T2DM, in relation to their degree of β-cell function and insulin sensitivity. Gaining sufficient weight to cross their PFT will trigger the condition,

Abbreviations: BMI, body mass index; MODY, maturity onset diabetes of youth; PFT, personal fat threshold; T2DM, Type 2 diabetes; UKPDS, United Kingdom Prospective Diabetes Study

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whereas losing their 'excess weight' could return them to normal glucose tolerance.

IS THE ASSUMED PATHOPHYSIOLOGICAL DIFFERENCE IN NON-OBESE AND OBESE T2DM INDIVIDUALS REAL?

It is widely believed that non-obese people with T2DM have less insulin resistance but a greater β-cell defect than those who are overweight or obese [3,5,9,10]. However, insulin resistance also increases as a function of increasing BMI whether or not an individual is dysglycaemic [11]. Accordingly, to determine the effect of insulin resistance on the development of T2DM, comparisons need to be made between people matched for BMI. When this is done, it can be seen that people with T2DM have modestly greater insulin resistance at any level of BMI, but that there is no greater insulin resistance in obese than in non-obese people with T2DM, relative to their BMI matched normoglycaemic peers [12]. This is also seen when people with T2DM are compared with BMI matched late-onset auto-immune diabetes [13]. The apparent enigma of the sometimes higher-fasting plasma insulin levels seen in obese individuals with T2DM, compared with their non-diabetic counterparts, is explained when the compensatory fasting hyperglycaemia of obesity is taken into account [14,15]. Equally, test meals elicit similar increases in plasma C-peptide in non-obese and obese people with T2DM (2.5- and 1.8-fold respectively) [16]. Concepts of β-cell impairment have been swayed by the lower fasting plasma insulin in non-obese compared with obese people with T2DM. Just as for the normoglycaemic population, this merely reflects their lower degree of insulin resistance. However, direct measurement of β-cell response to a glucose challenge shows the more relevant abnormality of T2DM. The first phase insulin response to an intravenous glucose challenge is absent in T2DM, whatever the BMI, and in impaired glucose tolerance no effect of BMI has been demonstrated on either first- or second-phase insulin secretion [16].

The concept that non-obese people with T2DM have lesser degrees of insulin resistance and greater β-cell impairment has been extrapolated to therapeutic decisions. The American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) guidelines note that 'Common practice has favoured metformin in heavier patients' [17] and it is assumed that non-obese patients will respond less-well to the glucose-lowering effect of metformin. This assumption has been examined and disproven with the improvement in HbA_{1c} (glycated haemoglobin) between matched non-obese and obese groups with T2DM given metformin shown to be almost identical [18,19].

POPULATION DATA: NO DISTINCT SUBCATEGORY OF NON-OBESE T2DM

The BMI frequency distribution for the 5102 people with newly diagnosed diabetes, enrolled between 1977 and 1991 into the United Kingdom Prospective Diabetes Study (UKPDS) [20] is shown in Figure 1. These data have not previously been published as a distribution curve. The curve is unimodal with a slight skew to the right showing that only a minority have a BMI greater than 35 kg/m^2. There is no interruption of the smooth left-hand side of the distribution curve, suggesting that there is no dichotomy and that a separate entity of non-obese T2DM is either too small to visualize or absent. It is also notable that 36% had a BMI less than 25 kg/m^2. The distribution observed is right-shifted from that of a contemporaneous adult UK population in which 64% had a BMI less than 25 kg/m^2 [21]. From today's perspective, it is remarkable that so many people with newly diagnosed T2DM had normal BMIs. Nevertheless, given that the risk of T2DM rises steeply at higher BMI's and that higher BMI's are now more prevalent, it is not surprising that the association between obesity and T2DM is much more evident today.

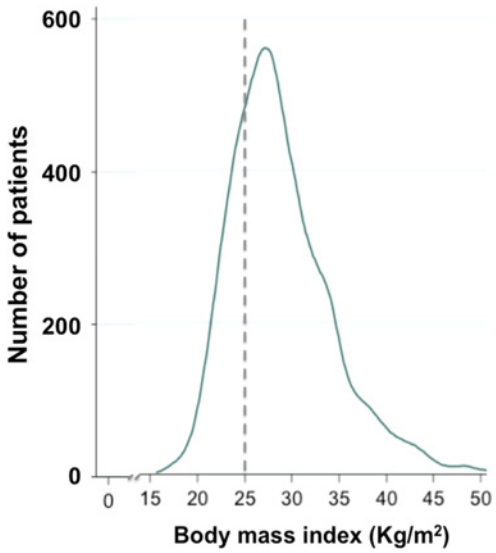

Figure 1 Population BMI distribution frequency plot for the entire 1977–1991 UKPDS cohort with newly diagnosed diabetes

Confirmatory information on the effect of population changes in BMI distribution over time is available. As subsistence farmers, the Pima Indians had neither excess obesity nor excess diabetes [22,23]. In 1940, after displacement from their traditional agricultural lifestyle, the prevalence was similar to that of the general US population [24]. Following inactivity, food oversupply and dramatic increase in rates of obesity, the prevalence of T2DM in adult Pima Indians rose to 38% [25]. Although there must be an underlying genetic basis for the high susceptibility to T2DM in this population, its development is conditional upon lifestyle [26]. This is demonstrated by contemporaneous comparison with ethnically identical Pima Indians living in Arizona and in Mexico [25]. Non-obese Pima Indians living in Mexico under nutritional conditions which limit adult weight gain, have a T2DM prevalence which is less than one-fifth that of their obese counterparts living in Arizona. In populations, the incidence and prevalence of T2DM rises or falls depending simply upon the state of the food supply as documented in Cuba in 1990–1996 and in Britain during the first and second world wars [27,28]. The

Nurses' Health Study has shown that there is a 4-fold increase in T2DM prevalence for women of BMI 23–25 compared with those of BMI less than 22 kg/m^2 as well as confirming that the prevalence increases steadily with higher BMIs [29].

Recently, a new perspective has been added by the demonstration that people with recent onset T2DM could regain normal glucose control and normal β-cell function when the fat content of the liver and the pancreas was decreased by a weight loss dietary regimen. This reversal of T2DM was found to be achievable equally readily by people with lower initial BMI [30,31]. Weight loss effectiveness studies in T2DM have typically excluded those with BMIs less than 25 kg/m^2 [32,33]. The UKPDS, however, included all newly diagnosed patients with T2DM who were treated with diet alone for their 3–4 month run-in period. During this time, 16% of the cohort achieved a fasting plasma glucose of <6.0 mmol/l, with no relationship between achieving fasting normoglycaemia and initial body weight. Indeed, with presenting plasma glucose of 8–10 mmol/l, normoglycaemia was achieved with a mean weight loss of 13% if body weight was normal, whereas a mean weight loss of 21% of body weight was required to achieve this in the whole cohort. Additionally, at 15 months into the study, fasting blood glucose depended upon the degree of achieved weight loss and not body weight at diagnosis. These data illustrate the good glycaemic response to weight loss in non-obese people with T2DM [34]. Following widespread popular interest in applying information on weight loss to reverse T2DM [35], the knowledge that people who are not overweight can successfully achieve this has reached a wide audience in the lay press [36].

INDIVIDUAL DATA COMPARED WITH POPULATION DATA

Figure 2 illustrates individual and population BMI data. Instead of a line graph summarizing the population BMI frequency distribution, as in Figure 1, the BMIs of a number of representative individuals with T2DM are depicted as red dots (Figure 2A). If the same individuals had been living in an environment of relative food scarcity, the prevalence of T2DM would be expected to be low and personal weight gain would not have occurred. In Figure 2(B), the normoglycaemic individuals in this notional slimmer state are shown in blue, together with their heavier T2DM alter egos shown in red. Viewed as a population, the rate of obesity has increased and the BMI distribution curve merely shifts to the right. But for every individual there is a finite increase in their body weight, whatever their starting point.

Figure 2(C) shows three such individuals from the upper panel who have early T2DM and BMIs of 36, 29 and 24 kg/m^2 respectively. One is obese by definition, one is overweight and one is normal weight. Each individual succeeded in losing 15 kg in weight and regained normoglycaemia [30]. All three, therefore, moved from their relative place in the red distribution to that in the blue and reversed their diabetes. In doing so, each must have crossed their PFT, above which glucose control is lost and below which it is normal. It can be seen that the effect of crossing the PFT is identical for any individual, wherever he or she is within the BMI distribution of the population. The person with the lowest BMI merely moves down to their appropriate position, which is still within the normal distribution of the lighter groups of individuals who do not have diabetes (Figure 2B, blue dots).

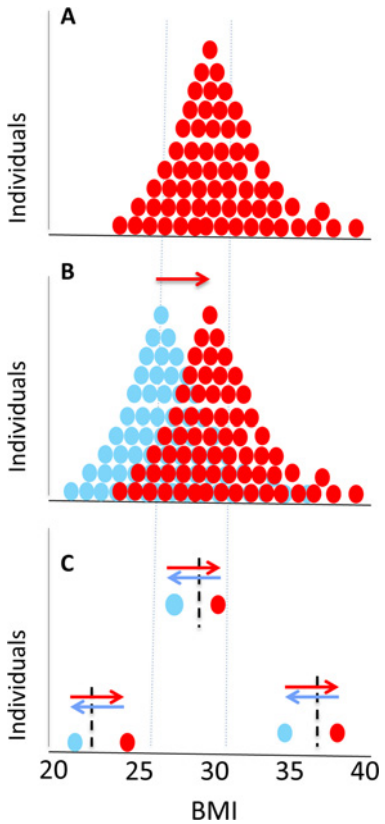

Figure 2 The presonal fat threshold versus popultation metric
(**A**) Representative frequency distribution of BMI for a group of individuals with T2DM. (**B**) Frequency distribution of BMIs in blue for the individuals depicted in (**A**) before they gained weight. The red frequency distribution, when diabetes had developed, is right shifted (red arrow) and usually interpreted as indicating a higher prevalence of obesity. (**C**) Three illustrative individuals from (**B**) are shown demonstrating their relative positions within the population BMI distribution. One is obese, one overweight and one normal weight. Weight loss of 15 kg in each case resulted in return to normal glucose tolerance although their classification by the population measure of BMI did not change. It is hypothesized that each individual has a PFT (dotted line) above which excess fat is stored within the liver and the pancreas. This individual susceptibility has no relationship to BMI despite the higher probability of diabetes being precipitated in the obese range. For each individual, moving to the right of their PFT triggers T2DM (red arrows) and moving to the left of the line restores normal glucose tolerance (blue arrows).

Viewed from a population perspective, individuals may have a BMI considerably greater than 30 kg/m^2 or less than 25 kg/m^2 but are still a part of the overall BMI frequency distribution. If the whole population distribution of BMI shifts to the right, as has occurred in Western society in the last few decades, then people who are thought not to have excess fat, when categorized by conventional BMI metrics, behave not according to their BMI status

but behave according to whether they are carrying more fat than they can tolerate individually. Personal excess fat is overlooked in less heavy individuals when population metrics are applied to individuals.

MECHANISMS UNDERLYING THE PFT

The physiological mechanisms underlying an individual's susceptibility to develop T2DM at a particular weight must be considered. Four critical factors may be identified. First, accumulation of liver fat can now be seen as pivotal [31], but the extent of this varies considerably at any weight or BMI [37]. Secondly, the susceptibility of individuals to develop hepatic insulin resistance at any given level of liver fat accumulation is variable even though the biochemical mechanism is understood [38]. The variable effect is illustrated by one known genetic influence in that individuals with the G-allelle of patatin-like phospholipase 3 gene have a higher liver fat level but normal hepatic insulin sensitivity [39]. It is likely that complex polygenetic traits also contribute to this. The third and fourth factors relate to the same considerations in the pancreas: extent and susceptibility to adverse effects of fat accumulation. Pancreas fat levels are raised in T2DM [30,40] and fall as normal insulin secretion is restored by a very low calorie diet [30]. It is known that chronic exposure to excess fatty acids decreases glucose-mediated insulin secretion by the β-cells [41]. However, there is considerable overlap in pancreas fat levels between normal and Type 2 diabetic individuals suggesting differing susceptibility [31]. Extent of visceral fat accumulation is a surrogate marker for intra-organ fat excess, but is not pathophysiologically related to adverse metabolic consequences [42,43]. Overall, the PFT for any one person is hypothesized to be determined both by extent of intra-hepatic and intra-pancreatic fat accumulation and by susceptibility to the local biochemical effects of lipid excess.

Comparative data from populations of different ethnicity reveal substantial ethnic differences in the susceptibility to develop diabetes depending upon the burden of fat. A large population study has observed that the equivalent degree of risk for a Caucasian of BMI greater than 30 kg/m^2 is expressed in South Asians at 25.2 kg/m^2 and at 27 kg/m^2 in African/Caribbeans [44]. Within the ethnic groups, genetic polymorphisms, which are associated with non-alcoholic fatty liver disease, can be identified [45]. Liver fat content is strongly correlated with insulin sensitivity also in people of Asian ethnicity [46] and predicts future onset of T2DM [47].

TESTING THE HYPOTHESIS

The PFT hypothesis could best be tested in those at highest risk for developing diabetes. The most homogenous group of individuals who would be closest to their PFT are those who have just reversed their diabetes and are normoglycaemic with a normal first-phase insulin response [30]. The defining characteristic for T2DM is inadequate β-cell insulin secretion and the restoration or loss of a first-phase insulin response can be used as the most direct index of reversal or return of the diabetic pathophysiology. It has been postulated that this is a consequence of the excess fat acting at the level of the β-cells [31,48,49].

Our hypothesis predicts that β-cell insulin responses in normal BMI and obese individuals with T2DM who have just completed an 8-week low-calorie liquid diet will be similar and identically affected by exposure to excess lipid metabolites. Both first-phase and total insulin secretory responses could be tested on two separate days, once after overnight intralipid infusion and once after saline infusion. Matched controls with no personal or family history of T2DM would also be studied. The lack of effect of triacylglycerol (triglyceride) over-provision on insulin secretion in those not susceptible to diabetes and the distinct effect upon people at risk of T2DM has been demonstrated previously [50]. The stepped insulin secretion tests described by Lim et al. [30] should be used in order that the first phase and total insulin responses could be quantified directly. We hypothesize that in both normal BMI and obese groups, β-cell function will be similarly returned to the diabetic state of absent first phase insulin response by over-provision of triacylglycerol and that there will be no such effect upon the controls. The return of a normal first-phase response from the characteristically absent response in T2DM remains the most striking aspect of Lim's paper and this is the essence of being above or below the PFT.

DISCUSSION

The PFT concept is of practical use in explaining the need for weight loss to individuals with T2DM, even if they are not obese. For any one person, the degree of susceptibility to the adverse effects of excess fat varies and their T2DM susceptibility cannot be known unless their PFT is exceeded. Once T2DM is triggered, substantial weight loss will be needed to reverse it. This hypothetical PFT for a person could be determined by careful observation during a weight loss intervention and would be the BMI at which their first-phase insulin response became normal. Following publication of Lim's study, individuals now report normal glucose control for up to 3 years to date [35,36]. It is notable that in the LookAhead, weight loss was 8.6% by 1 year declining to 4.7% by 4 years. Even this modest weight loss brought about return of normoglycaemia sustained for at least 2 years in 9.2% of the group and, in keeping with the PFT hypothesis, the weight gain was associated with a fall in rate of sustained remission of diabetes to 3.5% [32].

In normal weight individuals presenting with possible T2DM, it is essential to exclude MODY and slow onset Type 1 diabetes, even though most will have an ultimate diagnosis of classical T2DM. Recognition that T2DM has similar pathophysiology, irrespective of BMI classification, is an important step in determining the most appropriate management for the individual patient. The concept of a PFT is of practical benefit in explaining both the onset of diabetes and its logical management to all people presenting with T2DM.

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