The lean patient with type 2 diabetes: characteristics and therapy challenge

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Introduction

Obesity is considered to be a key driving force behind the worldwide epidemic of type 2 diabetes (1,2). Approximately 58% of type 2 diabetes may be attributable to an increase in obesity (based upon an increase in body mass index (BMI)), although this varies from almost 90% in North America to < 40% in Southeast Asia (1,2). Thus, whereas the focus in the Western world remains on the more prevalent overweight or obese patient, a significant proportion of cases on a global basis may not be attributable to obesity using current criteria, particularly in many Asian countries (1), where a large proportion of patients with type 2 diabetes are considered to be ‘lean’ by traditional standards.

What exactly defines a lean patient with type 2 diabetes and which measures and thresholds of obesity categorise patients best are evolving issues. The influence of ethnicity, age and diabetes phenotype on anthropomorphic measures and their impact on the pathophysiological characteristics of diabetes, notably insulin secretion and insulin resistance, are all issues that have received attention. Pathophysiological heterogeneity may be even more marked among lean patients with type 2 diabetes, whereas insulin resistance and insulin secretory dysfunction are present in the majority of overweight/obese patients, the relative contributions appear to be less well defined in non-overweight patients. As such, treating the lean patient with type 2 diabetes may pose a particular challenge.

This review highlights the current definitions, epidemiology and pathophysiology relevant to the non-overweight patient with type 2 diabetes. It discusses the potential challenges in treating this patient group and considers optimal treatment strategies in clinical practice.

What defines a lean patient?

Standard definitions of overweight and obesity are based upon BMI – for instance, in Western countries, adults with a BMI of 25–29.9 kg/m² are considered overweight, those with a BMI ≥ 30 kg/m² are considered to be obese and individuals with a BMI of 18.5–24.9 kg/m² are considered to be normal weight (i.e. ‘lean’) (3). People classified as overweight or obese (i.e. those with a BMI ≥ 25 kg/m²) are considered to be at increased risk of developing associated comorbid conditions, including, among others,
hypertension, dyslipidaemia, type 2 diabetes and coronary heart disease.

Only a minority of patients with type 2 diabetes in Western countries are not classed as overweight or obese by these traditional criteria. For instance, in the NHANES 1999–2002 study from the USA, only around 15% of people with diabetes were not overweight, whereas approximately 55% were obese (4). However, as the NHANES data did not discriminate between diabetes type, the rates of overweight are likely to be even higher for type 2 diabetes alone, as people with type 1 diabetes generally have a lower BMI (5). A similar pattern is seen in European studies – in the Diabetes and Informatics (DAI) study in Italy, which involved a sample of over 13,000 patients with type 2 diabetes, approximately 25% had a BMI ≤ 25 kg/m² and rates of obesity were 23% in men and 37% in women (6). Likewise, in a recent sample of over 2700 people with type 2 diabetes attending a secondary care diabetes clinic in the UK, 14% had a BMI ≤ 25 kg/m² and 52% were obese (5). There is little evidence on rates of overweight/obesity in type 2 diabetes at the point of diagnosis (i.e. prior to the influence of interventions, etc.). However, in a US study of 1300 subjects ≥ 30 years of age with diabetes, 20% of those diagnosed with diabetes in 1985–1989 were not overweight at diagnosis, although rates of normal weight were on a downward trend from ~30% 10–15 years earlier (7).

Nevertheless, there is some controversy as to what exactly defines a lean patient with type 2 diabetes. Several factors may contribute to the uncertainty in this area, including choice of the most appropriate parameters and their thresholds for defining overweight and obesity, the influence of different patient characteristics, such as ethnicity and age, and the possible presence of distinct diabetes phenotypes. For instance, people who are not overweight by traditional weight criteria (i.e. BMI) may have an increased percentage of body fat, particularly the more metabolically active intra-abdominal fat that can be assessed clinically by measuring waist circumference (3). Increased visceral intra-abdominal fat is particularly notable in people with type 2 diabetes, as it is associated with decreases in both β-cell function and insulin sensitivity (8,9). In NHANES 1999–2000, approximately 8% of US adults with normal BMI (18.5 to < 25 kg/m²) had a ‘high-risk’ waist circumference [i.e. > 102 cm (men) or > 88 cm (women)] (10). In the DAI study, which included only people with type 2 diabetes, 38% of men and 74% of women exceeded these waist circumference values (6). A recent consensus by the International Diabetes Federation (IDF) has set more stringent waist circumference thresholds for identifying ‘high-risk’ abdominal obesity as a central component of the metabolic syndrome (≥ 94 cm and ≥ 80 cm Europid men and women respectively), as well as some ethnicity-specific criteria (11).

Most recommended obesity thresholds assessing the risk of obesity-related diseases are based upon studies in Western (primarily Caucasian) populations (12,13). However, among populations in many countries (especially in Eastern Asia and Southeastern Asia) there may be a greater proportion of people (including those with type 2 diabetes), who are not considered overweight or abdominally obese using these ‘Western’ criteria (12–14). For example, in a recent sample of 1200 patients with type 2 diabetes in Taiwan, only 48% of men and 43% of women had a BMI ≥ 25 kg/m² (15). Similarly, in a recent sample of 1000 patients with type 2 diabetes in urban China, only 42% of men had a BMI ≥ 25 kg/m² and only 4% of men and 9% of women had a BMI ≥ 30 kg/m², whereas only 4.1% of men and 30% of women had a ‘high-risk’ waist circumference (> 102 or 88 cm respectively) (16). Several studies also suggest that percent body fat for a given BMI is higher among many Asian populations, particularly among people of South Asian origin (17,18). A recent study also suggests that Japanese subjects have a larger area of adipose tissue for the same level of waist circumference compared with Caucasian subjects (19). A higher percent body fat may explain why obesity-related diseases occur at lower levels of obesity measures in Asian populations (15). Accordingly, several authors have recommended lower waist circumference and BMI thresholds for defining levels of overweight/obesity and associated risk in various Asian populations (13,14,20,21). These recommendations have been ratified in some individual Asian countries (Japan and China), where guidelines incorporating lower thresholds have been established (22,23).

It is also worth noting that, although they are obese on average, patients diagnosed with type 2 diabetes at older ages tend to be less overweight – for instance, if diagnosed after the age of 45 years, patients may have a BMI six points lower on average than patients diagnosed before 45 years, whereas patients diagnosed after 70 years of age have an average BMI in the overweight rather than obese range (10 points lower than those diagnosed before 30 years) (24). However, intra-abdominal fat increases with age (9) and older patients may be more ‘metabolically obese’ with increased intra-abdominal fat, despite lower BMI (25).

Phenotypes other than ‘classic’ type 2 diabetes may influence anthropomorphic characteristics in
some patients, especially latent autoimmune diabetes in adults (LADA). This relatively poorly defined phenotype has characteristics of both type 1 and type 2 diabetes and may constitute 10% of all patients diagnosed with type 2 diabetes – diagnosis is based upon adult age at onset of diabetes, the presence of circulating islet autoantibodies [particularly those to glutamic acid decarboxylase (GAD)], and lack of a requirement for insulin for at least 6 months after diagnosis (26). Although it has not been established firmly, it is generally believed that LADA patients are lean at diagnosis, although some LADA patients can be overweight (26). In one study, LADA patients with the highest levels of GAD antibodies had significantly lower BMI (comparable with type 1 patients) than those with medium or low levels (27). In the UKPDS (which mostly included overweight patients), 12% of newly diagnosed patients with type 2 diabetes were either GAD positive or islet cell antibody positive, although the rate was highest in those aged 24–35 years (35%) and decreased with age (9% for age 55–65 years) (28). Antibody negative patients had significantly higher BMI in all age groups, although BMl and the difference relative to antibody positive patients decreased with age. In an Italian population-based cohort of 130 lean (BMI < 25 kg/m²) patients with newly diagnosed diabetes, aged 30–54 years, approximately 50% tested positive for GAD and/or islet cell antibodies, suggesting that this phenotype may be highly prevalent among lean patients (at least in this population) (29).

Thus, when considering whether a person with type 2 diabetes is ‘lean’, several factors need to be considered, including BMI, waist circumference and ethnicity, and appropriate threshold values should be used. Lean patients are also more likely to be older at diagnosis and possibly antibody positive, as well as having a tendency towards certain pathophysiological characteristics (see below).

**Pathophysiology in lean patients: insulin secretion vs. insulin sensitivity**

It is often presumed that normal weight people with type 2 diabetes have better insulin sensitivity, but greater insulin secretory deficits, compared with overweight/obese patients. It is well established that, in general, increasing obesity is associated with decreasing insulin sensitivity (30,31). Accordingly, in patients with type 2 diabetes, obesity (especially visceral obesity) is associated with greater hepatic and peripheral insulin resistance (32–34) (Figure 1). Nevertheless, it is generally accepted that at least some degree of insulin resistance is a frequent characteristic feature of normal weight people with type 2 diabetes (35). Data from the Insulin Resistance in Atherosclerosis study in almost 500 non-Hispanic whites, Hispanics and African-Americans suggest that, among non-obese patients with type 2 diabetes (with BMI < 30 kg/m²), the proportion of insulin-sensitive subjects is relatively low (4–10%; marginally < 5–14% seen across all BMI categories) (36). In the study by Gastaldelli et al. (34), for any given level of obesity, diabetes increased hepatic insulin resistance by approximately 50% (Figure 1). However, a few studies suggest lower rates of insulin resistance among lean patients. A small study by Banerji and Lebovitz (37) suggested that 90% of African-American patients with BMI < 24 kg/m² were insulin sensitive, whereas 90% of those with BMI > 28.5 kg/m² were insulin resistant. Similarly, a small Scandinavian study showed that patients with abdominal obesity displayed peripheral insulin resistance alongside defective insulin secretion, whereas non-obese patients with diabetes showed only a secretory defect (38). A study in 16 non-obese (BMI < 27 kg/m²) Spanish patients with type 2 diabetes, identified six insulin-sensitive and 10 insulin-resistant patients and both groups had severely impaired insulin secretion (39). However, the varying BMI thresholds used in these studies complicate comparisons. Some studies also suggest that LADA patients may be insulin resistant, but this has not been investigated thoroughly (26).

Among several non-Western populations, rates of insulin resistance in patients with type 2 diabetes appear to be particularly low. For instance, in a sample of 267 Korean patients with BMI < 25 kg/m², only 24% were insulin resistant (40). In a sample of 111 Japanese patients, 15/17 (88%) with a BMI
> 27.0 kg/m² were insulin resistant, whereas only 3/38 (8%) of patients with a BMI < 21.5 kg/m² and 27/56 (48%) of patients with a BMI of 21.5–27.0 kg/m² were insulin resistant (41). However, in a study of 521 newly referred Chinese patients in Hong Kong, the insulin resistance index was similar in patients with a BMI < 18.5 kg/m², 18.5–23 kg/m² or > 23 kg/m² (42).

Unlike insulin resistance, impaired insulin secretion is found uniformly in patients with type 2 diabetes in all ethnic populations (35). Studies looking at insulin and C-peptide levels suggest that lean patients may have greater insulin secretory deficits (43,44). Altered pro-insulin/insulin ratios may also indicate greater β-cell dysfunction in lean patients relative to obese patients (44). However, as insulin secretion and insulin resistance are dynamically linked (because of β-cell compensation), it is difficult to assess them independently in patients with differing levels of insulin resistance (e.g. lean vs. obese) (45). There is a hyperbolic constant relationship between insulin sensitivity and insulin secretion in glucose-tolerant individuals – insulin-resistant individuals secrete more insulin and vice versa (45). Insulin secretion will also depend upon the prevailing level of glycaemia (35) and at higher levels of glycaemia, the difference in insulin secretion between overweight and non-overweight individuals is attenuated (46). When insulin secretion is assessed relative to the underlying insulin resistance, β-cell function in overweight individuals (BMI > 27 kg/m² in men or > 25 kg/m² in women) with normal glucose tolerance, impaired glucose tolerance or type 2 diabetes is superimposable on that of lean individuals within the same category of glucose tolerance, suggesting that β-cell function is not lower in lean patients (46) (Figure 2). Nevertheless, more rapid treatment failure seen among leaner patients in the UKPDS would appear to suggest greater (or more rapidly declining) insulin secretory deficits in these patients. It should be noted that the presence of LADA patients may be a contributing factor in the UKPDS (28,47,48). Several studies suggest that patients with LADA may have greater insulin secretory deficits than patients with ‘classic’ type 2 diabetes (26,28,29).

Post-mortem studies show that obesity in non-diabetic humans is characterised by a 50% increase in relative pancreatic β-cell volume, reflecting β-cell compensation for insulin resistance (49). However, obese humans with type 2 diabetes had a 63% deficit in relative β-cell volume compared with non-diabetic obese subjects, whereas lean subjects with type 2 diabetes had a 41% deficit compared with lean non-diabetic subjects (because of increased apoptosis).

Hence, this aspect of β-cell dysfunction appears to be similar in lean and obese patients in the long term, at least.

Thus, when considering the pathophysiology of lean patients with type 2 diabetes, several characteristics arise – many lean patients will have some level of insulin resistance, although the proportion of insulin-sensitive patients may vary with ethnicity. On the other hand, all patients will have β-cell dysfunc-
tion, which might be more marked than that seen in overweight/obese patients.

**Glycaemic control in lean patients**

As with overweight patients, lifestyle interventions are a key component of therapy in lean patients with type 2 diabetes; however, pharmacotherapeutic intervention and need for multiple therapies may be required earlier in lean or non-obese patients (47,48,50). As there may be less need to avoid weight gain, more options are available for first-line pharmacotherapy in lean patients, including sulfonylureas, thiazolidinediones, metformin, α-glucosidase inhibitors, glinides and insulin therapy. Sulfonylurea monotherapy, which targets the insulin secretory deficit (the principle deficit in many lean patients), remains the first-line treatment of choice for many lean patients because of well-established efficacy and wide availability (51). However, these agents require sufficient β-cell function to be effective and may not be suitable in disease of long duration – early intervention is, therefore, paramount.

Although weight gain is less of a factor in lean patients, it may be preferable to use a newer sulfonylurea with less weight gain liability (e.g. glimepiride or a short-acting agent) (52). These newer sulfonylureas may also be associated with a lower incidence of hypoglycaemia (52) and lower risk of myocardial infarction than older sulfonylureas (53).

Agents from a different class are added when oral agent monotherapy fails, but there may be too little residual β-cell function by this point for the drug to work. Earlier combination therapy with agents that improve insulin resistance (e.g. metformin and thiazolidinediones) may help to prolong sulfonylurea efficacy, as many lean patients may also be insulin resistant. Furthermore, agents such as the thiazolidinediones (or possibly new agents such as the incretin mimetics) that show promise in preserving and improving β-cell function might be particularly relevant in lean patients in whom β-cell function may decline more rapidly (54,55). In view of the need to preserve β-cell function and avoid apoptosis, using a thiazolidinedione very early in the history of type 2 diabetes (i.e. as first-line monotherapy) may also be an effective approach in these patients, including those with GAD antibodies. Combination therapy can then be initiated if HbA1c exceeds 6.5–7.0%. At present, adding glimepiride or a short-acting sulfonylurea would appear to be the most appropriate combination strategy, although adding an incretin mimic, with the potential to enhance β-cell preservation further, may prove to be a valuable approach in the future (55).

Prolonged exposure of isolated human islets to different sulfonylureas has been shown to cause functional disturbances of the β-cell, although glimepiride seems to exert a milder negative impact compared with glibenclamide and chlorpropamide (56). Sulfonylureas in this study did not induce β-cell apoptosis, but this has been seen elsewhere with glibenclamide, which may have an adverse effect on β-cell mass (57). However, sulfonylurea-mediated closure of K_ATP channels is apparently not β-cell toxic per se (58). Furthermore, none of these in vitro trials have been reproduced in vivo. It is unclear whether such differences between sulfonylureas might translate into greater rates of β-cell decline with some drugs, although in the UKPDS, the loss of β-cell function occurred at the same rate in patients treated with sulfonylureas, metformin or conventional therapy (principally diet) (59).

**Conclusions: challenges for treating lean patients with type 2 diabetes**

It should be appreciated that relatively few patients with classic type 2 diabetes may in reality be considered as ‘lean’ in Western populations, especially if abdominal obesity is taken into account. Although the proportion of lean patients may appear much higher in some populations, the growing appreciation of ethnic-specific thresholds is likely to change this view. Nevertheless, more aggressive treatment may be required in less overweight patients (especially in the early stages). Combination treatment should be considered as early as possible to achieve glycaemic goals. Among lean patients, it may be particularly important to optimise combination treatment early while significant β-cell function still remains, with the possibility of β-cell preservation using an agent with demonstrated potential, such as a thiazolidinedione. This may be particularly relevant in patients with an autoimmune component.

It should also be appreciated that diabetes is a heterogeneous disorder that may manifest itself across a spectrum of phenotypes with poorly defined boundaries (e.g. from lean to obese, from autoimmune to non-autoimmune, from predominantly insulin deficient to predominantly insulin resistant). In practice, it can be difficult to judge whether insulin resistance or insulin deficiency is the predominant defect in less overweight patients. Therefore, although some ‘lean’ patients may be more insulin sensitive, targeting both insulin secretion and insulin resistance (e.g. with a sulfonylurea/thiazolidinedione combination) would appear to be a rational approach. Furthermore, glycaemic control might be an appropriate primary focus in lean patients,
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whereas multiple cardiovascular risk factors (e.g. dyslipidaemia and hypertension, as well as hyperglycaemia) are more likely to be the overall primary focus in obese patients who carry a higher cardiovascular risk as a result of increased prevalence of these factors (5). The impact of therapy on body weight may be less of a factor, but still needs to be considered, along with risk of hypoglycaemia, and selection of appropriate sulfonylureas to minimise these effects.

In conclusion, although less overweight (i.e. lean) patients with type 2 diabetes appear to have particular pathophysiological characteristics, there may be difficulty in determining specific underlying deficits to guide therapy choice in clinical practice. However, as there is a need to correct all metabolic defects, combination therapy that targets both insulin secretory dysfunction and insulin resistance would seem to be a rational approach in these patients. Furthermore, an emphasis on early optimal intervention with glucose-lowering agents, although clearly a major consideration for all people with type 2 diabetes, may be particularly relevant in lean patients.

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