

Lean diabetes mellitus: An emerging entity in the era of obesity

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Received: August 29, 2014

Peer-review started: August 29, 2014

First decision: October 14, 2014

Revised: November 18, 2014

Accepted: February 4, 2015

Article in press: February 9, 2015

Published online: May 15, 2015

Abstract

Much has been published on the characteristics of type 2 diabetes mellitus and its association with the epidemic of obesity. But relatively little is known about the incidence of lean diabetes, progression of disease and fate of the patients with low-normal body mass index (< 25). Studies in developing countries have shown that the clinical characteristics of these patients include history of childhood malnutrition, poor socioeconomic status, relatively early age of onset and absence of ketosis on withdrawal of insulin. In the United States, recent studies showed that the lean,

normal weight diabetes is not rare especially among minority populations. They showed that these patients are mainly males, have higher prevalence of insulin use indicating rapid beta cell failure. They might have increased total, cardiovascular and non cardiovascular mortality when compared to obese diabetic patients. In this review, the epidemiologic and clinical features of lean diabetes are presented. The potential causal mechanisms of this emerging diabetes type that may include genetic, autoimmune, acquired and behavioral factors are discussed. The need for studies to further elucidate the causation as well as specific prevention and treatment of lean diabetes is emphasized.

Key words: Lean diabetes; Beta cell failure; Ketosis resistant diabetes of young; Obesity paradox; Sarcopenic obesity

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Core tip: Little is known about lean diabetes (patients with low-normal body mass index). Studies in developing countries have shown that these patients have history of childhood malnutrition, poor socioeconomic status and early age of onset with absence of ketosis. In the United States, recent studies showed that the lean, normal weight diabetes is not rare especially among minorities. These patients are mainly males and have higher prevalence of insulin use indicating rapid beta cell failure. They might have increased total, cardiovascular and non cardiovascular mortality when compared to obese diabetic patients. The potential causal mechanisms of this diabetes type may include genetic, acquired and behavioral factors.

George AM, Jacob AG, Fogelfeld L. Lean diabetes mellitus: An emerging entity in the era of obesity. *World J Diabetes* 2015; 6(4): 613-620 Available from: URL: <http://www.wjgnet.com/1948-9358/full/v6/i4/613.htm> DOI: <http://dx.doi.org/10.4239/wjd.v6.i4.613>

INTRODUCTION

The prevalence of diabetes mellitus (DM) has increased exponentially over the past decade globally. In the United States, nearly 26 million adults have diabetes with over 9 million being prediabetic. The numbers are expected to double by 2050. Nearly 35% of American adults are obese putting them at an increased risk for the development of Diabetes. Healthy people 2020 initiative has stressed the importance of reduction in obesity to lower the incidence of this morbid condition among the United States population^[1].

Since early times obesity has been a well known risk factor for diabetes. However, beyond the classical obesity related type 2 diabetes and other well defined types of diabetes like type 1, Maturity onset Diabetes of the Young, Gestational diabetes, *etc.*, there is a renewed interest in the underweight or normal weight lean diabetes that is emerging also in the developed countries like United States. This review will focus on the low-normal weight diabetes that is so far not well characterized and defined. More importantly, this review will highlight the differences in the clinical features of diabetes mellitus in normal body weight patients in the United States in comparison to the classical obese diabetes. The evidence related to the profile, peculiarities, morbidity, mortality and pathogenesis associated with lean type diabetes will be described.

DIABETES IN LOW BODY WEIGHT GROUP (BODY MASS INDEX < 18 KG/M²)

Though recognized as a distinct entity early on, very little attention has been paid to the qualitative changes associated with it. Any "atypical diabetes" syndrome which did not meet the classical American Diabetes Association or World Health Organization Classification suffered from imprecise definitions which led to a group of complex phenotypes^[2]. Further studies have been undertaken only recently shedding much insight into their disease burden, progression and natural history. Adult onset diabetes with body mass index (BMI) < 25 was initially placed under the category of "malnutrition related diabetes mellitus" in a subcategory termed "protein deficient pancreatic diabetes"^[3]. Later this syndrome was noted to be similar to that originally described as "Jamaica type Diabetes", a term used to represent around 5% of Caribbean diabetics^[4]. Similar clinical syndromes were subsequently described in regions of south Asia and Africa and has acquired various names; "Tropical Diabetes, Mixed onset type Diabetes, Phasic insulin dependent Diabetes, J type Diabetes, Z type Diabetes, M type or type 3 Diabetes, Ketosis resistant growth onset type Diabetes"^[5].

Many of the overlapping categories described above could be lumped together under the term

coined by Ahuja^[6] as "Ketosis Resistant Diabetes of the Young (KR DY)". This category includes a broad subset of patients mostly of Asian and African ethnicity. The following criteria were suggested for the diagnosis of KR DY^[6]: (1) blood glucose > 200; (2) onset < 30 years of age; (3) BMI < 18 kg/m²; (4) absence of ketosis on insulin withdrawal; (5) poor socio-economic status or history of childhood malnutrition; and (6) insulin requirement > 60 units/d or 1.5 units/kg.

Although early age of onset and low BMI may raise suspicion for type 1 diabetes, the presence of islet cell specific antibodies has consistently been lower than those with type 1 diabetes across multiple population groups. It can be argued that the wasting or leanness noted in around 25%-50% of patients could represent the effects of long standing glycosuria^[7]. Though BMI mostly improved with weight gain following optimal glycemic control, the mean value remained within the definition of low body weight among both genders^[8]. Phenotypic similarities have been described from various other regions of the world with nearly all of them demonstrating a male preponderance with the most extensive data being described from Ethiopia^[9,10].

A study from India on around 10000 type 2 diabetics revealed that around 3.5% patients were lean with a BMI < 18.5, with the larger share of around 63% patients having ideal body weight at diagnosis. Age of diagnosis (45 ± 13) and smoking patterns were not significantly different among the lean, ideal body weight and obese groups, although a male preponderance was noted only in the former two. This study also highlighted the fact that HbA1c, fasting and postprandial blood glucose levels were higher among those in the lean group. Micro-vascular complications of Diabetes such as retinopathy, nephropathy and neuropathy were more common among the lean male patients presumed to be related to the higher plasma glucose and HbA1c levels^[11]. Other studies have also highlighted the higher incidence of peripheral neuropathy among lean diabetic males^[12], whereas hypertension and coronary artery disease tend to be more common in the obese group^[13]. A limitation of these studies were that auto antibodies were measured only in a very small number, thereby leaving a chance that the lean diabetics could represent type 1 diabetics^[14], although patients who had an abrupt onset, ketosis or ketoacidosis at any time or required insulin at time of diagnosis were excluded from the study to avoid bias. In whom C-peptide levels were measured, they were found to be significantly higher compared to the type 1 diabetics being followed at the respective centers. Moreover the results of islet cell antibodies and antibodies against Glutamic acid decarboxylase were not significantly different between the 3 groups^[15]. Nearly 48% of the lean NIDDM patients responded to diet or oral hypoglycemic agents after a mean duration of 9.2 ± 8.1 years, which is a clear distinction from type 1 diabetics. Symptomatic ketoacidosis was absent in this group^[11].

The pathophysiology and its distinction from classic

type 2 diabetes is still unclear and a subject of much debate. The key feature appears to be a defect in insulin secretory capacity as opposed to peripheral insulin resistance as noted in classical diabetes. Multiple studies have shown an association between lean diabetes, malnutrition in early years of life and poor socioeconomic status. Although prospective human studies are lacking, experiments done on rats and primates have shown that low protein diet in early life leads to decreased beta cell mass and insulinopenia. Insulin mediated glucose disposal appears to be similar in KRDY and type 1 Diabetic patients^[16]. These patients have fasting C-peptide levels intermediate between type 1 and type 2 diabetics^[17,18]. Despite the "decent" C-peptide levels suggesting a good beta cell reserve, the circulating insulin levels at baseline and post stimulation with insulin secretagogues (glucose, tolbutamide and amino acids) have been consistently lower in lean diabetics when compared to their obese counterparts^[8,19-24]. The 2 mechanisms that have been postulated to cause this are excessive extraction of insulin in the porto-hepatic circulation from raised glucokinase activity and hyperactive futile cycles of carbohydrate metabolism^[8]. Resistance to ketosis noted in these cases is due to a small but sufficient insulin secretory reserve which is absent in type 1 diabetics^[2]. They have also been noted to have lower fasting plasma free fatty acid and ketone levels and a blunted response to catecholamines further delaying the development of ketoacidosis^[19-21]. The occurrence of fat malabsorption in a small subset of patients contributes evidence to an exocrine defect in KRDY patients^[25].

Auto-antibodies can be present in anywhere between 2%-25% of KRDY patients. Glutamic acid decarboxylase (GAD), tyrosine phosphatase like protein (IA-2) or high mobility group box transcription factor SOX-13 (ICA-12) antibodies are commonly found, though co-occurrence of GAD and IA-2 was observed in only 4.7% of lean patients compared to 22% type 1 diabetics^[26]. Any single antibody by itself is neither sensitive nor specific to distinguish between the phenotypes of type 1 or type 2 diabetes as GAD or ICA positivity has been reported even in 4%-13% of obese type 2 diabetics^[8]. In summary the primary etiology appears to be depressed beta cell function most likely due to malnutrition in utero and early infancy in addition to autoimmune modulations. However more studies are needed on this front to unearth the metabolic, hormonal and immunological characteristics of lean type 2 diabetics.

DIABETES IN NORMAL BODY WEIGHT GROUP (BMI 18-24.9)

The term "lean" has been described variously in different studies. The major distinction seems to originate from the geographic region where the study was conducted. Those from developing countries use a BMI < 18 to describe leanness whereas studies

performed in the United States describe lean patients to have a BMI ranging from 18-24.9.

A study cohort of 18000 patients with type 2 diabetes in Chicago, United States showed that around 13% belonged to this group, with ideal body weight defined as a BMI ranging from 17-25. The study failed to demonstrate a significant difference between the age of diagnosis (43 ± 13) between the lean and obese diabetics, and corroborated the previous finding of male preponderance among the lean group (62%). Asians were shown to have a five-fold higher prevalence in the lean group (17% vs 4%). Environmental insults such as use of alcohol and cigarette smoking were more common among lean diabetics. As confirmed by various other studies, glycemic control was worse among lean diabetics and coronary complications more prevalent among the obese with no significant difference noted among micro-vascular complications^[27].

The major pathophysiology in this group appears to be rapid beta cell failure as opposed to insulin resistance. This was highlighted by the fact that lean individuals had both a higher prevalence and early initiation of insulin use^[27]. They were also noted to have lower TG/HDL ratios, which is an indirect marker of lower insulin resistance^[28-30]. In diabetics, central obesity (waist circumference > 102 cm in males and 88 cm in females by NCEP) correlates with the degree of insulin resistance^[31]. In the above cohort, 96.9% of the lean males did not have central obesity which points away from insulin resistance causing hyperglycemia^[27].

The key defect responsible for hyperglycemia in the lean diabetics is impaired pancreatic insulin secretion^[32-34] which is partly due to a reduced beta cell mass as demonstrated *via* autopsies^[35,36]. The more severe beta cell dysfunction in these patients may be functional rather than structural as beta cell mass was noted to be equally reduced in both lean and obese patients^[34]. Lean healthy Caucasian subjects born with a low birth weight have been demonstrated to develop several physiological defects of type 2 diabetes such as decline of insulin secretion, reduced muscle glucose uptake, reduced insulin stimulated glycolysis, lower fasting plasma glycerol levels and increased fat accumulation more prematurely than expected^[37-40]. Dutch Famine Study has also proven that a brief period of malnutrition during postnatal period or early childhood increases the risk of diabetes^[41]. These findings have been further validated in Asian populations too.

In addition, there was a higher prevalence of smoking, alcoholism and pancreatitis in the lean group in the Chicago study^[27]. Chronic alcohol consumption induces pancreatic beta cell dysfunction and apoptosis^[42]. Exposure to passive and active smoking are positively and independently associated with the risk of diabetes^[43]. Whether the pronounced male prevalence among the lean is due to inherent genetic differences or unhealthy life style that can promote beta cell failure in comparison to females is still a matter of debate.

Genetic modulators might also predispose to reduced beta cell function in the lean body weight group. Polymorphisms of transcription factor FL2 gene (TCF7L2) and a genetic defect of ATP sensitive potassium channel Kir6.2 (or KCN JII) are associated with defective insulin secretion. Carriers of TCF7L2 gene polymorphism were also shown to be leaner and more insulin sensitive as compared with other type 2 diabetics^[44]. Genetic scores for insulin resistance have shown association of lower subcutaneous fat mass and ectopic fat deposition highlighting the role of impaired adipose expandability and body fat distribution even among lean type 2 diabetic individuals^[45].

Higher prevalence of Asians in the lean group could be from greater intrauterine insults and under-representation of overweight and obesity amongst them based on standard Body Mass Index definitions available. GAD antibodies though less frequently noted^[46,47] may play a role in the autoimmune destruction of beta cells. It remains to be proven whether occurrence of these antibodies is merely secondary to the loss of beta cell function as compared to an etiological agent in itself^[48]. The role of genetics and autoimmunity in lean diabetics needs to be further elucidated prior to drawing more concrete conclusions in this group.

THE OBESITY PARADOX AND SARCOPENIC OBESITY

Another interesting aspect is the occurrence of complications and increased rate of mortality in certain normal weight diabetes patients in comparison to their obese counterparts. This phenomenon is called the "obesity paradox". A pooled analysis done on 2625 participants from 5 longitudinal cohorts showed that normal weight adults at the time of incident diabetes had higher mortality than adults who were overweight or obese^[49]. This "obesity paradox" has also been previously noted in other studies on diabetics and in various other chronic conditions such as hypertension, end stage renal disease and heart failure. It is likely that lower body weight in the presence of obesity related metabolic disorders may just be a reflection of preexisting illness that may predispose to mortality^[49]. It is also known that despite having a leaner body mass, cigarette smokers are more insulin resistant, more likely to develop diabetes, and have a higher mortality from chronic lung disease and malignancies as compared with non-smokers. Carnethon *et al.*^[49] concluded that the elevated mortality in normal weight participants could not be entirely attributed to smoking, though a subgroup analysis demonstrated that there is no statistically significant difference between mortality in non-smoker adults of either cohort. A main limitation of this analysis was inability to assess the smoking burden and relatively low statistical power that limited the body mass index classification to 2 broad and

heterogeneous groups (BMI 18.5-24.9 and BMI \geq 25).

Further research into this obesity paradox by Tobias *et al.*^[50] in over 11000 participants, showed a J-shaped association between body mass index among all participants and in current or previous smokers. A direct linear relationship was observed in those who had never smoked. The lower mortality was observed among participants with a BMI of 22.4-24.9. The obesity paradox was therefore not observed in this study^[50]. The increased mortality among lean diabetic smokers has been observed in the general population as well^[51-54] and further studies are needed to address whether they represent an effect modification or is secondary to bias^[55]. In participants 65 years or older, a null or weaker linear association was observed, which was probably due to increased prevalence of co-existing chronic diseases and decreased validity of BMI as a measure of adiposity due to age related decline in muscle mass and wasting^[50,56].

A possible explanation for the observed obesity paradox could be sarcopenic obesity, defined as the presence of high body fat with reduced or normal lean body mass^[1]. The localization of adipose tissue particularly abdominal obesity, independent of total obesity is associated with increased risk of cardiovascular disease. Sarcopenic obesity reduces the cardio-pulmonary fitness and physical functioning possibly leading to premature death and could account for the higher mortality eventually seen in individuals who are normal weight at the time of diabetes onset^[23]. The sarcopenic obesity may also indicate a catabolic underlying illness that leads to increased mortality. This was further supported by a systematic review, which showed that all cause mortality was lower among those with a high body mass index and good aerobic fitness as compared with individuals of a normal body mass index and poor fitness^[57]. A study on veterans has also supported this view^[58]. Hence questions can be raised regarding the sufficiency of such a simplistic classification of diabetes into obese or non-obese groups solely based on BMI.

IS FURTHER WEIGHT LOSS RECOMMENDED IN LEAN DIABETICS?

Weight loss is recommended for all overweight or obese diabetics. Studies such as the diabetes prevention program outcome study (DPP) and Look AHEAD^[59] have primarily focused on weight management in overweight and obese individuals^[1]. Could such recommendation be also effective in lean diabetics? Some concerns may be raised that additional weight loss could worsen both bone loss and decrease further the lean body mass contributing further to sarcopenic obesity. In the Chicago study, it appeared that leaner individuals had worse beta cell failure. One can then postulate that lean diabetics is a special variant of type II diabetes whereby the failing beta cell cannot even

Table 1 Clinical differences between type 1, type 2, ketosis resistant diabetes of the young and lean type 2 variant diabetes

Clinical features	Type 1 diabetes	Type 2 diabetes	KRDY	Lean type 2 variant
Age of diagnosis	Can occur at any age, usually < 25	Usually > 25 yr, but increasing prevalence in adolescents	< 30 yr	Average age around 40 with male preponderance
Weight	Usually lean	Overweight and obesity	BMI < 18	BMI 18-25
Autoantibodies	Present	Absent	Variable	Absent
Family history of diabetes	5% to 10%	75% to 90%	Unknown	Around 50%
Insulin sensitivity	Normal	Decreased	Normal	Normal, in females might be decreased
Insulin dependent at diagnosis	Yes	No	40% at diagnosis	35% at diagnosis
Risk of ketoacidosis	High	Low	Low	Low

KRDY: Ketosis resistant diabetes of the young; BMI: Body mass index.

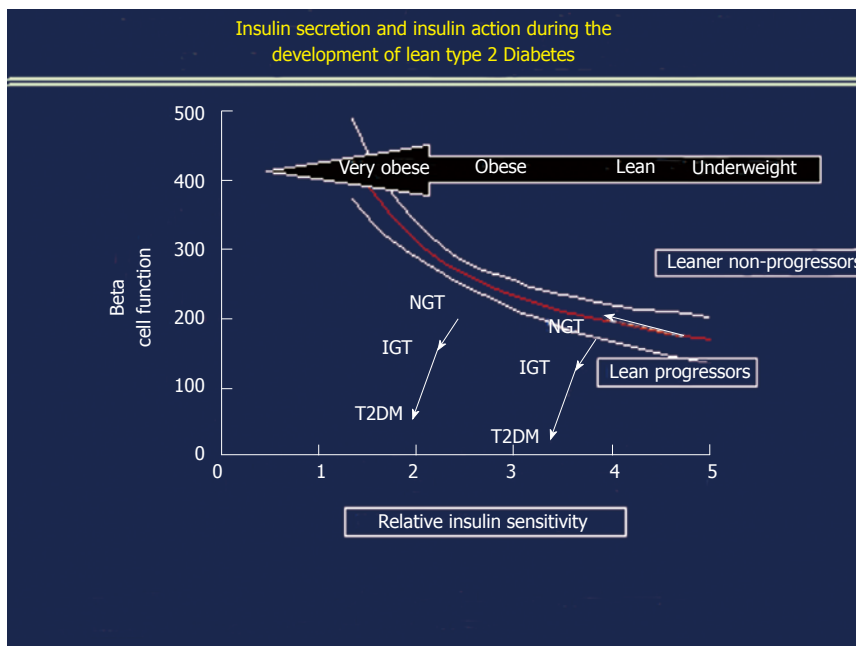


Figure 1 Pathogenetic model of development of lean type 2 diabetes. In the obese individuals the diabetes develops once the beta cell cannot cope with the insulin resistance conferred by the growing obesity. In the lean diabetes the early failure of the beta cells results in development of diabetes at much lower insulin resistance. It might be speculated that in individual with similar beta cell dysfunction but lower insulin resistance (lower weight) diabetes might not develop. NGT: Normal glucose tolerance; IGT: Impaired glucose tolerance; T2DM: Type 2 diabetes; Modified from Weyer *et al. J Clin Invest* 1999; 104: 787–794.

cope with the small amount of insulin resistance that lean body weight confers. Could then achievement of a lower body weight or lower adiposity in these patients prevent diabetes? Currently there is no answer to this intriguing hypothesis (Figure 1).

CONCLUSION

The patients with lean diabetes in comparison to classical obese type 2 diabetes (Table 1) are characterized by younger age at onset, earlier and more prevalent use of insulin, higher prevalence in males and higher rates of cigarette smoking and alcohol abuse. It was initially shown that patients with diabetes who are leaner have higher mortality rate in comparison to the obese (the obesity paradox). This was explained by the concept of sarcopenic obesity whereby these patients are metabolically obese with excess of adiposity but have decreased muscle mass (sarcopenia) which is the predisposing factor for the increased mortality. The obesity paradox however could not be confirmed in a most recent study in a larger cohort.

The underlying pathogenetic mechanism of lean diabetes has not yet been clarified and more studies are needed for its elucidation. It could be a completely new pathogenic entity, however there is a possibility that it may just be a variant of type 2 diabetes. In type 2 diabetes, the beta cells that are genetically destined to fail gradually over the years cannot cope with the increasing insulin resistance that is conferred by obesity. Lean diabetes might be a variant of these main operating pathogenic mechanisms. The difference is the much more pronounced beta cell failure that occurs earlier and results in more rapid exhaustion. Several potential mechanisms could be involved in the beta cell failure. The initial predisposing factors may be an adverse intrauterine or early postnatal environment with insufficient nutrients that result in a smaller beta cell mass. Then genetic predisposition of a more fragile beta cell mass may cause early destruction and apoptosis. Studies have showed that genetic markers of such fragility are more common in the lean than in obese diabetics. In addition, in developed countries like the United States, acquired insults like cigarette

smoking and alcoholism might be newly defined and significant pathogenetic contributors that could further weaken the beta cells. In these circumstances, even the little insulin resistance associated with lean body weight could precipitate diabetes (Figure 1). Recent study has also shown that genetically determined insulin resistance may also play a role in the pathogenesis of lean diabetes.

Considering the inadequacy of BMI in distinguishing leanness, future studies should investigate the complex interaction between body composition, amount and distribution of adipose tissue and physical functioning in determining the development of lean diabetes. In the meantime emphasis on modifiable risk factors like smoking and alcohol abuse that may further accelerate beta cell failure in lean patients may prevent further progression of the disease.

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P- Reviewer: Georgescu A, Kusmic C **S- Editor:** Song XX

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