**Name of journal: World Journal of Diabetes**

**ESPS Manuscript NO: 13718**

**Columns: Minireviews**

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

George AM *et al*. Lean diabetes mellitus

Amrutha Mary George, Amith George Jacob, Leon Fogelfeld

**Amrutha Mary George, Amith George Jacob, Leon Fogelfeld,** Division of Endocrinology, John H Stroger Hospital of Cook County, Chicago, IL 60612, United States

**Author contributions**: George AM, Jacob AG and Fogelfeld L contributed to this work.

**Open-Access:** This article is an open-access article which selected by an in-house editor and fully peer-reviewed by external reviewers. It distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Correspondence to:** **Leon Fogelfeld, MD, Head,** **Professor** of Medicine Rush University, **Endocrinology Fellowship Program Director**, Division of Endocrinology, John Stroger Hospital of Cook County, 1901 W Harrison Street, W.Polk (room 811), Chicago, IL 60612, United States. lfogelfe@cchil.org

**Telephone:** +1-312-8640539

**Fax:** +1-312-8649734

**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:**

**Published online:**

**Abstract**

Much has been published on the characteristics of type 2 diabetes mellitus (DM) 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

# © The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

**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; In press

**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 *et al*[6] as “Ketosis Resistant Diabetes of the Young (KRDY)”. This category includes a broad subset of patients mostly of Asian and African ethnicity. The following criteria were suggested for the diagnosis of KRDY[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; (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 US 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 (TCFFL2) and a genetic defect of ATP sensitive potassium channel Kir6.2 (or KCN JII) are associated with defective insulin secretion. Carriers of TCFFL2 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[59].

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[45,46] 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[47]. 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 has higher mortality than adults who were overweight or obese[48]. 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[48]. 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*[48] 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 ≥ 25).

  Further research into this obesity paradox by Tobias *et al*[55] 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[55]. The increased mortality among lean diabetic smokers has been observed in the general population as well[49-52] and further studies are needed to address whether they represent an effect modification or is secondary to bias[53]. 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[54].

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 cardiopulmonary 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[56]. A study on veterans has also supported this view[57]. 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[58] 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 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.

**REFERENCES**

1 **Florez H**, Castillo-Florez S. Beyond the obesity paradox in diabetes: fitness, fatness, and mortality. *JAMA* 2012; **308**: 619-620 [PMID: 22871873 DOI: 10.1001/jama.2012.9776]

2 **Balasubramanyam A,** Yajnik CS, Tandon N. Non-traditional forms of diabetes worldwide: Implications for translational investigation. *Trans Endocrinol Metab* 2011; **2:** 43-67 [DOI: 10.1210/TEAM.9781879225824.ch2]

3 World Health Organization 1985 Diabetes Mellitus: Report of a WHO Study Group. Geneva: WHO Technical Report Series 727

4 **Hugh-jones P**. Diabetes in Jamaica. *Lancet* 1955; **269**: 891-897 [PMID: 13264638 DOI: 10.1016/S0140-6736(55)92530-7]

5 **Hoet JJ**, Tripathy BB. Report of the International Workshop on types of Diabetes Peculiar to the Tropics. *Diabetes Care* 1996; **19**: 1014 [PMID: 8875102]

6 **Ahuja MM.** Diabetes-special problems in developing countries. *Bull Deliv Health Care Diabetics Devel Countries* 1980; **1:** 5-6.

7 **Lester FT**. A search for malnutrition-related diabetes mellitus among Ethiopian patients. *Diabetes Care* 1993; **16**: 187-192 [PMID: 8422774 DOI: 10.2337/diacare.16.1.187]

8 **Das S.** Lean type 2 diabetes mellitus: Profile, peculiarities and paradox. *Hypertension* 2008; **8:** 26-4

9 **Alemu S**, Dessie A, Seid E, Bard E, Lee PT, Trimble ER, Phillips DI, Parry EH. Insulin-requiring diabetes in rural Ethiopia: should we reopen the case for malnutrition-related diabetes? *Diabetologia* 2009; **52**: 1842-1845 [PMID: 19565213 DOI: 10.1007/s00125-009-1433-5]

10 **Fekadu S**, Yigzaw M, Alemu S, Dessie A, Fieldhouse H, Girma T, Trimble ER, Phillips DI, Parry EH. Insulin-requiring diabetes in Ethiopia: associations with poverty, early undernutrition and anthropometric disproportion. *Eur J Clin Nutr* 2010; **64**: 1192-1198 [PMID: 20664624 DOI: 10.1038/ejcn.2010.143]

11 **Mohan V**, Vijayaprabha R, Rema M, Premalatha G, Poongothai S, Deepa R, Bhatia E, Mackay IR, Zimmet P. Clinical profile of lean NIDDM in South India. *Diabetes Res Clin Pract* 1997; **38**: 101-108 [PMID: 9483373 DOI: 10.1016/S0168-8227(97)00088-0]

12 **Sutjahjo A**, Taniguchi H, Hendromartono A, Baba S. High frequency of autonomic as well as peripheral neuropathy in patients with malnutrition-related diabetes mellitus. *Diabetes Res Clin Pract* 1988; **5**: 197-200 [PMID: 3219990 DOI: 10.1016/S0168-8227(88)80088-3]

13 **Samal KC**, Das S, Agarwal BN, Panda NC, Tripathy BB. Nutritional status and profile of NIDDM of recent onset. *J Diab Assoc India* 1998; **28:** 99-101

14 **Zimmet PZ**, Tuomi T, Mackay IR, Rowley MJ, Knowles W, Cohen M, Lang DA. Latent autoimmune diabetes mellitus in adults (LADA): the role of antibodies to glutamic acid decarboxylase in diagnosis and prediction of insulin dependency. *Diabet Med* 1994; **11**: 299-303 [PMID: 8033530 DOI: 10.1111/j.1464-5491.1994.tb00275.x]

15 **Mohan V**, Deepa R, Bhatia E, Singh AK, Hitman GA, Zimmet PZ, MacKay IR. Antibodies to pancreatic islet cell antigens in diabetes seen in Southern India with particular reference to fibrocalculous pancreatic diabetes. *Diabet Med* 1998; **15**: 156-159 [PMID: 9507918 DOI: 10.1002/(SICI)1096-9136(199802)15: 2<156: : AID-DIA533>3.0.CO; 2-E]

16 **Garg MK**, Tripathy D, Shah P. Patients with malnutrition related diabetes mellitus are as insulin sensitive as insulin dependent diabetics. *J Assoc Physicians India* 1999; **47**: 1145-1148 [PMID: 11225212]

17 **Huh KB**, Lee HC, Kim HM, Cho YW, Kim YL, Lee KW, Lee EJ, Lim SK, Kim DH, Yoon JW. Immunogenetic and nutritional profile in insulin-using youth-onset diabetics in Korea. *Diabetes Res Clin Pract* 1992; **16**: 63-70 [PMID: 1576933 DOI: 10.1016/0168-8227(92)90136-F]

18 **Abu-Bakare A**, Taylor R, Gill GV, Alberti KG. Tropical or malnutrition-related diabetes: a real syndrome? *Lancet* 1986; **1**: 1135-1138 [PMID: 2871387 DOI: 10.1016/S0140-6736(86)91846-5]

19 **Moses SGP,** Kannan V. The clinical profile of undernourished diabetics aged 30 or less with associated complications in Madras, India.Diabetes Mellitus in Asia. *Excerpta Medica, Amsterdam* 1976: 259-262

20 **Hagroo AA**, Verma NP, Datta P, Ajmani NK, Vaishnava H. Observations on lipolysis in ketosis-resistant, growth-onset diabetes. *Diabetes* 1974; **23**: 268-275 [PMID: 4207364]

21 **Malik TK**, Kumar V, Ahuja MM. Degree of acetonaemia following epinephrine infusion to determine biochemical characterization of diabetes mellitus. *Indian J Med Res* 1974; **62**: 80-85 [PMID: 4216570]

22 **Rao RH**, Vigg BL, Rao KS. Suppressible glucagon secretion in young, ketosis-resistant, type "J" diabetic patients in India. *Diabetes* 1983; **32**: 1168-1171 [PMID: 6418596 DOI: 10.2337/diab.32.12.1168]

23 **Zamboni M**, Mazzali G, Zoico E, Harris TB, Meigs JB, Di Francesco V, Fantin F, Bissoli L, Bosello O. Health consequences of obesity in the elderly: a review of four unresolved questions. *Int J Obes (Lond)* 2005; **29**: 1011-1029 [PMID: 15925957 DOI: 10.1038/sj.ijo.0803005]

24 **Kanan K.** Lean Type II diabetes mellitus-a distinct entity. *Kapur A* 1993: 147-51.

25 **Bhatia E**, Baijal SS, Kumar KR, Choudhuri G. Exocrine pancreatic and beta-cell function in malnutrition-related diabetes among north Indians. *Diabetes Care* 1995; **18**: 1174-1178 [PMID: 7587854 DOI: 10.2337/diacare.18.8.1174]

26 **Goswami R**, Kochupillai N, Gupta N, Kukreja A, Lan M, Maclaren NK. Islet cell autoimmunity in youth onset diabetes mellitus in Northern India. *Diabetes Res Clin Pract* 2001; **53**: 47-54 [PMID: 11378213 DOI: 10.1016/S0168-8227(01)00235-2]

27 **Coleman NJ**, Miernik J, Philipson L, Fogelfeld L. Lean versus obese diabetes mellitus patients in the United States minority population. *J Diabetes Complications* 2013; **28**: 500-505 [PMID: 24581791]

28 **González-Chávez A**, Simental-Mendía LE, Elizondo-Argueta S. Elevated triglycerides/HDL-cholesterol ratio associated with insulin resistance. *Cir Cir* 2011; **79**: 126-131 [PMID: 21631973]

29 **Boizel R**, Benhamou PY, Lardy B, Laporte F, Foulon T, Halimi S. Ratio of triglycerides to HDL cholesterol is an indicator of LDL particle size in patients with type 2 diabetes and normal HDL cholesterol levels. *Diabetes Care* 2000; **23**: 1679-1685 [PMID: 11092292 DOI: 10.2337/diacare.23.11.1679]

30 **Giannini C**, Santoro N, Caprio S, Kim G, Lartaud D, Shaw M, Pierpont B, Weiss R. The triglyceride-to-HDL cholesterol ratio: association with insulin resistance in obese youths of different ethnic backgrounds. *Diabetes Care* 2011; **34**: 1869-1874 [PMID: 21730284 DOI: 10.2337/dc10-2234]

31 **St-Onge MP**, Janssen I, Heymsfield SB. Metabolic syndrome in normal-weight Americans: new definition of the metabolically obese, normal-weight individual. *Diabetes Care* 2004; **27**: 2222-2228 [PMID: 15333488 DOI: 10.2337/diacare.27.9.2222]

32 **Holman RR**. Long-term efficacy of sulfonylureas: a United Kingdom Prospective Diabetes Study perspective. *Metabolism* 2006; **55**: S2-S5 [PMID: 16631806 DOI: 10.1016/j.metabol.2006.02.006]

33 **UK Prospective Diabetes Study Group.** U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* 1995; **44**: 1249-1258 [PMID: 7589820 DOI: 10.2337/diab.44.11.1249]

34 **Vaag A**. On the pathophysiology of late onset non-insulin dependent diabetes mellitus. Current controversies and new insights. *Dan Med Bull* 1999; **46**: 197-234 [PMID: 10421979]

35 **Butler AE**, Janson J, Soeller WC, Butler PC. Increased beta-cell apoptosis prevents adaptive increase in beta-cell mass in mouse model of type 2 diabetes: evidence for role of islet amyloid formation rather than direct action of amyloid. *Diabetes* 2003; **52**: 2304-2314 [PMID: 12941770 DOI: 10.2337/diabetes.52.9.2304]

36 **Ritzel RA**, Butler AE, Rizza RA, Veldhuis JD, Butler PC. Relationship between beta-cell mass and fasting blood glucose concentration in humans. *Diabetes Care* 2006; **29**: 717-718 [PMID: 16505537 DOI: 10.2337/diacare.29.03.06.dc05-1538]

37 **Vaag A**, Jensen CB, Poulsen P, Brøns C, Pilgaard K, Grunnet L, Vielwerth S, Alibegovic A. Metabolic aspects of insulin resistance in individuals born small for gestational age. *Horm Res* 2006; **65 Suppl 3**: 137-143 [PMID: 16612127 DOI: 10.1159/000091519]

38 **Hermann TS**, Rask-Madsen C, Ihlemann N, Domínguez H, Jensen CB, Storgaard H, Vaag AA, Kober L, Torp-Pedersen C. Normal insulin-stimulated endothelial function and impaired insulin-stimulated muscle glucose uptake in young adults with low birth weight. *J Clin Endocrinol Metab* 2003; **88**: 1252-1257 [PMID: 12629115 DOI: 10.1210/jc.2002-021550]

39 **Jensen CB**, Storgaard H, Dela F, Holst JJ, Madsbad S, Vaag AA. Early differential defects of insulin secretion and action in 19-year-old caucasian men who had low birth weight. *Diabetes* 2002; **51**: 1271-1280 [PMID: 11916955 DOI: 10.2337/diabetes.51.4.1271]

40 **Ozanne SE**, Jensen CB, Tingey KJ, Storgaard H, Madsbad S, Vaag AA. Low birthweight is associated with specific changes in muscle insulin-signalling protein expression. *Diabetologia* 2005; **48**: 547-552 [PMID: 15729577 DOI: 10.1007/s00125-005-1669-7]

41 **van Abeelen AF**, Elias SG, Bossuyt PM, Grobbee DE, van der Schouw YT, Roseboom TJ, Uiterwaal CS. Famine exposure in the young and the risk of type 2 diabetes in adulthood. *Diabetes* 2012; **61**: 2255-2260 [PMID: 22648386 DOI: 10.2337/db11-1559]

42 **Kim JY**, Song EH, Lee HJ, Oh YK, Park YS, Park JW, Kim BJ, Kim DJ, Lee I, Song J, Kim WH. Chronic ethanol consumption-induced pancreatic {beta}-cell dysfunction and apoptosis through glucokinase nitration and its down-regulation. *J Biol Chem* 2010; **285**: 37251-37262 [PMID: 20855893 DOI: 10.1074/jbc.M110.142315]

43 **Zhang L**, Curhan GC, Hu FB, Rimm EB, Forman JP. Association between passive and active smoking and incident type 2 diabetes in women. *Diabetes Care* 2011; **34**: 892-897 [PMID: 21355099 DOI: 10.2337/dc10-2087]

44 **Saxena R**, Gianniny L, Burtt NP, Lyssenko V, Giuducci C, Sjögren M, Florez JC, Almgren P, Isomaa B, Orho-Melander M, Lindblad U, Daly MJ, Tuomi T, Hirschhorn JN, Ardlie KG, Groop LC, Altshuler D. Common single nucleotide polymorphisms in TCF7L2 are reproducibly associated with type 2 diabetes and reduce the insulin response to glucose in nondiabetic individuals. *Diabetes* 2006; **55**: 2890-2895 [PMID: 17003358 DOI: 10.2337/db06-0381]

45 **Lund SS**, Tarnow L, Stehouwer CD, Schalkwijk CG, Frandsen M, Smidt UM, Pedersen O, Parving HH, Vaag A. Targeting hyperglycaemia with either metformin or repaglinide in non-obese patients with type 2 diabetes: results from a randomized crossover trial. *Diabetes Obes Metab* 2007; **9**: 394-407 [PMID: 17391168 DOI: 10.1111/j.1463-1326.2007.00713.x]

46 **Turner R**, Stratton I, Horton V, Manley S, Zimmet P, Mackay IR, Shattock M, Bottazzo GF, Holman R. UKPDS 25: autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. UK Prospective Diabetes Study Group. *Lancet* 1997; **350**: 1288-1293 [PMID: 9357409 DOI: 10.1016/S0140-6736(97)03062-6]

47 **Vaag A**, Lund SS. Non-obese patients with type 2 diabetes and prediabetic subjects: distinct phenotypes requiring special diabetes treatment and (or) prevention? *Appl Physiol Nutr Metab* 2007; **32**: 912-920 [PMID: 18059616 DOI: 10.1139/H07-100]

48 **Carnethon MR**, De Chavez PJ, Biggs ML, Lewis CE, Pankow JS, Bertoni AG, Golden SH, Liu K, Mukamal KJ, Campbell-Jenkins B, Dyer AR. Association of weight status with mortality in adults with incident diabetes. *JAMA* 2012; **308**: 581-590 [PMID: 22871870 DOI: 10.1001/jama.2012.9282]

49 **Berrington de Gonzalez A**, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, Moore SC, Tobias GS, Anton-Culver H, Freeman LB, Beeson WL, Clipp SL, English DR, Folsom AR, Freedman DM, Giles G, Hakansson N, Henderson KD, Hoffman-Bolton J, Hoppin JA, Koenig KL, Lee IM, Linet MS, Park Y, Pocobelli G, Schatzkin A, Sesso HD, Weiderpass E, Willcox BJ, Wolk A, Zeleniuch-Jacquotte A, Willett WC, Thun MJ. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med* 2010; **363**: 2211-2219 [PMID: 21121834 DOI: 10.1056/NEJMoa1000367]

50 **Zheng W**, McLerran DF, Rolland B, Zhang X, Inoue M, Matsuo K, He J, Gupta PC, Ramadas K, Tsugane S, Irie F, Tamakoshi A, Gao YT, Wang R, Shu XO, Tsuji I, Kuriyama S, Tanaka H, Satoh H, Chen CJ, Yuan JM, Yoo KY, Ahsan H, Pan WH, Gu D, Pednekar MS, Sauvaget C, Sasazuki S, Sairenchi T, Yang G, Xiang YB, Nagai M, Suzuki T, Nishino Y, You SL, Koh WP, Park SK, Chen Y, Shen CY, Thornquist M, Feng Z, Kang D, Boffetta P, Potter JD. Association between body-mass index and risk of death in more than 1 million Asians. *N Engl J Med* 2011; **364**: 719-729 [PMID: 21345101 DOI: 10.1056/NEJMoa1010679]

51 **Manson JE**, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE, Hennekens CH, Speizer FE. Body weight and mortality among women. *N Engl J Med* 1995; **333**: 677-685 [PMID: 7637744 DOI: 10.1056/NEJM199509143331101]

52 **Pischon T**, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, van der Schouw YT, Spencer E, Moons KG, Tjønneland A, Halkjaer J, Jensen MK, Stegger J, Clavel-Chapelon F, Boutron-Ruault MC, Chajes V, Linseisen J, Kaaks R, Trichopoulou A, Trichopoulos D, Bamia C, Sieri S, Palli D, Tumino R, Vineis P, Panico S, Peeters PH, May AM, Bueno-de-Mesquita HB, van Duijnhoven FJ, Hallmans G, Weinehall L, Manjer J, Hedblad B, Lund E, Agudo A, Arriola L, Barricarte A, Navarro C, Martinez C, Quirós JR, Key T, Bingham S, Khaw KT, Boffetta P, Jenab M, Ferrari P, Riboli E. General and abdominal adiposity and risk of death in Europe. *N Engl J Med* 2008; **359**: 2105-2120 [PMID: 19005195 DOI: 10.1056/NEJMoa0801891]

53 **Manson JE**, Stampfer MJ, Hennekens CH, Willett WC. Body weight and longevity. A reassessment. *JAMA* 1987; **257**: 353-358 [PMID: 3795418 DOI: 10.1001/jama.1987.03390030083026]

54 **Manson JE**, Bassuk SS, Hu FB, Stampfer MJ, Colditz GA, Willett WC. Estimating the number of deaths due to obesity: can the divergent findings be reconciled? *J Womens Health (Larchmt)* 2007; **16**: 168-176 [PMID: 17388733 DOI: 10.1089/jwh.2006.0080]

55 **Tobias DK**, Pan A, Jackson CL, O'Reilly EJ, Ding EL, Willett WC, Manson JE, Hu FB. Body-mass index and mortality among adults with incident type 2 diabetes. *N Engl J Med* 2014; **370**: 233-244 [PMID: 24428469 DOI: 10.1056/NEJMoa1304501]

56 **Fogelholm M**. Physical activity, fitness and fatness: relations to mortality, morbidity and disease risk factors. A systematic review. *Obes Rev* 2010; **11**: 202-221 [PMID: 19744231 DOI: 10.1111/j.1467-789X.2009.00653.x]

57 **Kokkinos P**, Myers J, Faselis C, Doumas M, Kheirbek R, Nylen E. BMI-mortality paradox and fitness in African American and Caucasian men with type 2 diabetes. *Diabetes Care* 2012; **35**: 1021-1027 [PMID: 22399701 DOI: 10.2337/dc11-2407]

58 **Wing RR**, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM, Espeland MA, Evans M, Foreyt JP, Ghazarian S, Gregg EW, Harrison B, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jakicic JM, Jeffery RW, Johnson KC, Kahn SE, Kitabchi AE, Knowler WC, Lewis CE, Maschak-Carey BJ, Montez MG, Murillo A, Nathan DM, Patricio J, Peters A, Pi-Sunyer X, Pownall H, Reboussin D, Regensteiner JG, Rickman AD, Ryan DH, Safford M, Wadden TA, Wagenknecht LE, West DS, Williamson DF, Yanovski SZ. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013; **369**: 145-154 [PMID: 23796131 DOI: 10.1056/NEJMoa1212914]

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



**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.

**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 years, 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.