Lean Type 2 Diabetes Mellitus

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1 Introduction

Type 2 diabetes is increasing in epidemic proportions across the globe. Obesity is generally considered to be the major contributor to the epidemic of diabetes mellitus. In NHANES 1999–2002 study from USA around 55% of diabetics were obese (Eberhardt & Ogden, 2004) The focus in the Western world remains on the more prevalent overweight or obese patient, but a significant proportion of diabetes cannot be attributable to obesity using current criteria. A large proportion of patients with type 2 diabetes are ‘lean or underweight.’ In the Diabetes and Informatics (DAI) study in Italy involving over 13,000 patients with type 2 diabetes, approximately 25% had a body mass index (BMI) ≤ 25 kg/m² and rates of obesity were 23% in men and 37% in women (Mannucci et al. 2004). Likewise, in a study involving 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 (Daousi & Casson, 2006).

There is some controversy, however, as to what exactly defines a lean patient with type 2 diabetes. There is uncertainty regarding the 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 (National Heart, Lung, and Blood Institute Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, 1998). In South Asians, 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 (Deurenberg-Yap et al.,

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2000; Vikram et al., 2003). For the same level of waist circumference compared with Caucasians, Japanese subjects have a larger mass of adipose tissue (Kadowaki et al., 2006).

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. International Diabetes Federation (IDF) have set a separate cut-off for anthropometric parameters for South Asians distinct from the Caucasians (Alberti et al., 2006).

2 Prevalence

In 1965 Tripathy and Kar from India highlighted the fact that 27% of elderly diabetics were lean (Tripathy & Kar, 1965). Several other studies from India also have reported a prevalence rate of lean diabetes ranging from 3.5%–18.1% (Chaudhary et al., 2013; Das et al., 1995; Mohan et al., 1997; Mukhyaprapana et al., 2004).

In NHANES 1999–2002 study from USA around 15% of diabetics were lean, although in this study the diabetics were not categorized into type 1 or type 2 (Eberhardt & Ogden, 2004).

At the Cook County Diabetes Center (CCDC), serving minority population in Chicago, 13% of 18,000 patients with diabetes mellitus were lean (BMI < 25 but > 17 kg/m²) (Coleman et al., 2014).

There are also several studies reporting lean type 2 diabetes from many Asian countries. In a study from China, 5.8% of newly referred type 2 diabetics were lean using a BMI cut-off of 18.5 kg/m² (Chan et al., 2004). In another study from China of 1000 type 2 diabetic patients, 58% had a BMI less than 25 kg/m² (Taniguchi et al., 2000). A Japanese study of 111 untreated type 2 diabetes reported 8% of the patients were lean using a BMI cut-off of 21.5 kg/m² (Lu et al., 2006). The preferred cut-off for Asians/Indians to define as lean or underweight is a BMI of 18.5 kg/m² (International Diabetes Institute, 2000).

3 Risk factors

In a study from US which compared lean diabetes patients to their obese counterparts, 56% of lean patients reported having a first degree relative with diabetes compared to 62% in the obese diabetes group (p < 0.001). In the lean group, 30.5% were current smokers and 5.7% had a history of alcoholism compared to 22% and 2.4%, respectively, in the obese population (p < 0.001). There was a higher prevalence of pancreatitis: 3.6% in the lean diabetics compared to 0.9% in obese patients (p < 0.001) (Coleman et al., 2014).

A region on chromosome 21q has been identified to contribute to type 2 diabetes mellitus in lean individuals (Iwasaki et al., 2003). Further examination of this region led to the identification of KCNJ15 (potassium inwardly-rectifying channel, subfamily J,
member 15) as a susceptibility gene (Okamoto et al., 2010). KCNJ15 is linked to dysfunctional glucose-stimulated insulin secretion (GSIS) in lean Japanese patients with type 2 diabetes (Okamoto et al., 2012). Other studies have also shown that lean type 2 diabetics have a stronger genetic predisposition. A variant (rs8090011) in the LAMA1 gene was more strongly associated with type 2 diabetes in lean cases than in obese cases (Perry et al., 2012). TCF7L2 also has a stronger effect in non-obese cases compared to obese cases (Tsai et al., 2010).

4 Pathophysiology

Normal weight people with type 2 diabetes often have better insulin sensitivity, but greater insulin secretory deficits, compared with overweight/obese patients. Nevertheless, some degree of insulin resistance is a frequent characteristic feature of normal weight people with type 2 diabetes (DeFronzo et al., 2004). There are some reports of reduced glucose transporters in diabetics. Garvey et al. (1988) reported that the numbers as well as the intrinsic activity of glucose carriers are reduced in adipose tissue of obese Type 2 diabetic patients. Similarly there is a reduction in the number of GLUT 4 in the plasma membrane fraction of skeletal muscle of lean diabetic patients in the basal state (Vogt et al., 1992). In contrast, Handberg et al. (1990) and Pedersen et al. (1990) did not find a significant alteration in the GLUT 4 number in human skeletal muscle of diabetic patients or control subjects in the basal state.

Glucose storage is severely impaired in lean type 2 diabetes and a decrease in non-esterified fatty acid levels enhances muscle glucose oxidation and non-oxidative glycolysis but not glycogen synthesis. Changes in glycogen synthase action, which results in dysregulation of glucose storage in skeletal muscle after meal ingestion is probably the main alteration of glucose metabolism in lean type 2 diabetic subjects (1996).

Lean type 2 diabetics have been demonstrated to have a 41% deficit ($P < 0.05$) in relative β-cell volume compared with non-diabetic lean individuals. Obese type 2 diabetics have a 63% ($P < 0.01$) deficit in relative β-cell volume compared to non-diabetic obese subjects. Frequency of β-cell apoptosis is increased 10-fold in lean and 3-fold in obese type 2 diabetes compared with non-diabetic lean and obese individual respectively, ($P < 0.05$) (Butler et al., 2003). Several studies have evaluated patients of lean type 2 diabetes using either clamps or homeostatic model assessment (HOMA). There are also studies where C-peptide is measured in basal state and/or after stimulation.

4.1 C-peptide Studies

Mohan et al. (1997) found no significant difference in the fasting or stimulated C-peptide levels between lean and obese diabetics. Diabetes in lean Japanese patients is associated with a low level of fasting insulin in addition to reduced peripheral glucose uptake and elevated endogenous glucose production (Takahara et al., 2011). These data suggest that this disorder in normal-weight individual results from impaired insulin secretion and action.
Interestingly in the study by Das et al. (1995), mean basal insulin is lower in lean type 2 diabetics but there is no significant difference in basal C-peptide value compared to obese type 2 diabetics. Lean type 2 diabetics have a significantly lower rise in serum insulin level after oral glucose load as well as after 1mg IV glucagon compared to obese patients. But C-peptide did not differ significantly between the two types, suggesting similar reserve in beta cell function. The disparity between serum insulin and c-peptide level in lean type 2 diabetics may be due to greater extraction of insulin by liver. However, in another study by Das et al. (2007), mean values of fasting insulin and fasting C-peptide in lean and normal body weight individuals respectively did not differ significantly. Even though total proinsulin immunoreactivity (PIM) is significantly elevated in lean type 2 diabetic patients compared with lean control subjects, fasting insulin, c-peptide, ratio of intact proinsulin to PIM are comparable between the obese and lean type 2 diabetes. But after glucagon stimulation, PIM levels are significantly elevated in the diabetic subjects; more pronouncedly in the obese diabetic patients. The ratio of PIM to insulin or C-peptide during the test is significantly elevated in both lean and obese diabetic patients; more pronouncedly in the lean group (Roder et al., 1999). In the study by Chan et al. (2004), serum C-peptide was lowest in the underweight and highest in overweight patients.

4.2 Clamp studies

In hyperinsulinemic euglycemic and hyperglycemic clamp study by Suraamornkul et al. (2010), lean patients had higher sensitivity to exogenous insulin. Insulin sensitivity was similar in lean type 2 diabetics compared to lean non-diabetic control subjects. First and second phase of insulin and C-peptide was significantly decreased in lean type 2 diabetics. Using the euglycemic insulin clamp with a D-[3-3H]glucose infusion 87.5% with a BMI less than 24.0 kg/m² were insulin sensitive, and 88.9% with a BMI greater than 28.5 kg/m² were insulin resistant (Banerji & Lebovitz, 1992).

Using hyperinsulinaemic euglycaemic clamp, diabetic patients with abdominal obesity has been shown to display peripheral insulin resistance in combination with defective insulin secretion, whereas non-obese diabetic patients showed only a secretory defect (Arner et al., 1991). Visceral abdominal fat area measured by DXA correlates inversely with insulin sensitivity determined by glucose infusion rate during euglycemic hyperinsulinemic clamp in lean subjects independent of percent total body fat similar to obese type 2 diabetic subjects (Rattarasarn et al., 2003).

In lean type 2 diabetics there is no impairment in hepatic but a slight reduction in extrahepatic insulin sensitivity but insulin release is markedly impaired (Pigon et al., 1996). Leg glucose uptake and oxidation is similar in lean type 2 diabetics with age, sex and relative weight controls. The combine net balance of lactate and Ala is lower in lean type 2 diabetics. Basal muscle glycogen synthase is lower in lean subjects but activated to a similar extent during hyperinsulinemic clamp study (Kelly et al., 1993).
4.3 Homeostasis Model Assessment Insulin Resistance (HOMA-IR)

HOMA-IR has consistently shown correlation to BMI. Eighty-eight percent of T2DM patients with a BMI \( \leq 27.0 \text{ kg/m}^2 \) were insulin-resistant, whereas 92% T2DM patients with a BMI \( < 21.5 \text{ kg/m}^2 \) are insulin-sensitive. Type 2 diabetic patients with midrange BMI (21.5 to 27.0 kg/m\(^2\)), are equally likely to be insulin-resistant or insulin-sensitive (Taniguchi et al., 2000). Lean type 2 DM demonstrated better beta cell function with homeostasis model assessment beta cells (HOMA-B) compared to normal body weight type 2 DM. Insulin resistance as assessed by HOMA-IR did not differ significantly between lean and normal body weight type 2 DM, suggesting that lean type 2 DM are actually a variant of the classic phenotype (Das et al., 2007). Moreover, HOMA-IR results were similar amongst underweight (< 18.5 kg/m\(^2\)), normal weight (18.5–23 kg/m\(^2\)) and overweight (\( \geq 23 \text{ kg/m}^2 \)) (Chan et al., 2004).

Another interesting facet of insulin-sensitive lean T2DM is normal non-insulin mediated glucose uptakes (NIMGU) but diminished glucose effectiveness at zero insulin (GEZI) (García-Estévez et al., 2002). This may have important bearing on the clinical presentation of such a phenotype.

5 Autoantibodies Markers

Coleman et al. (2014) evaluated islet cell antibodies in 53 out of 1784 lean diabetic patients, of which 89% tested negative. In an Italian population-based cohort of 130 lean (BMI < 25 kg/m\(^2\)) patients with newly diagnosed diabetes approximately 50% tested positive for GAD and/or islet cell antibodies, suggesting that this phenotype may be highly prevalent among lean patients (Bruno et al., 1999). In contrast to low reporting of anti-GADAbo amongst lean T2DM by Mohan et al. (1997) of 9.6%, Unnikrishnan et al. (2004) reported a much higher prevalence (25.3%) for the same. In the study by Mohan et al. (1997) number of lean diabetics testing positive for anti-GADAbo was not much higher than ideal body weight subjects (5.1%), or obese subjects (4.2%). Lean T2DM with anti-glutamic acid decarboxylase antibody (GADAbo) positivity are younger and have lower beta cell function (HOMA-B) as compared to the GADAbo-negative group, thus suggesting that the former group could have a slowly progressive form of type 1 diabetes or Latent autoimmune diabetes of adults (LADA) (Unnikrishnan et al., 2004).

But as reported in several studies, vast majority of lean type 2 diabetes are antibody negative, (Bruno et al., 1999; Mohan et al., 1997; Unnikrishnan et al., 2004) and their c-peptide level is not significantly different from obese type 2 diabetics (Das et al., 1995; 2007; Mohan et al., 1997) suggesting that they are a distinct clinical entity from LADA. Another differential diagnosis to be considered is maturity onset diabetes of the young (MODY) which typically have one or more of the following: a strong family history of diabetes, onset of diabetes in the second to fifth decade, insulin independence, absence of features of insulin resistance and absence of β-cell autoimmunity (Thanabalasingham & Owen, 2011).
6 Clinical features and Complications

6.1 Gender

There is a definite male preponderance in lean type 2 diabetes mellitus. (Arnab et al., 2006; Coleman et al., 2014; Das et al., 1995; Mohan et al., 1997; Mukhyaprapana et al., 2004; Punyakrit et al., 2011) In contrast, 70% of obese diabetics were females, whereas 65% of lean diabetics were males in the study by Mukhyaparna et al. (2004) Coleman et al. (2014) working on US population 62% of lean T2DM were males. Among obese patients only 48% were male.

6.2 Age

As demonstrated by several Indian studies, mean age of lean T2DM ranges from 45–58 years (Das et al., 1995; Mohan et al., 1997; Mukhyaprapana et al., 2004; Punyakrit et al., 2011). In the study from USA, the mean age of onset of lean type2 diabetes was 44 years which is similar to obese diabetics (Coleman et al., 2014). Similarly, Mohan et al. (1997), did not observe any significant differences in the age at diagnosis among lean, ideal weight and obese type 2 diabetics. However in the study by Mukhyaparna et al. (2004), the mean age of onset of diabetes in lean diabetics was significantly higher compared to the mean for obese diabetics. But in the Thai study by Rattarasarn et al. (2003), the mean age of lean type 2 diabetics was lower than of obese type 2 diabetics, which of course, was not significantly different.

6.3 Glycemic Status

Mean fasting, post-prandial or 2 hr postchallenge blood glucose higher among lean patients (Das et al., 1995; Mohan et al., 1997; Mukhyaprapana et al., 2004). HbA1c level was also significantly higher in the lean group compared to obese (Chan et al., 2004; Coleman et al., 2014; Das et al., 1995; Mohan et al., 1997).

6.4 Blood Pressure

Hypertension was seen in 12% of lean type 2 diabetics (Punyakrit et al., 2011). In another Indian study, incidence of hypertension in lean diabetics was 16.2%, whereas it was 39.09% in normal weight 41.6% in over weight and 61.5% in obese diabetics (Mukhyaprapana et al., 2004). Both systolic and diastolic blood pressure were significantly lower in the lean T2DM compared to ideal body weight and obese groups (Chan et al., 2004; Mohan et al., 1997). Coleman et al. (2014) also reported that lean diabetes patients had lower blood pressure compared to obese.

6.5 Lipid Profile

There is no gross abnormality in lipid profile among lean diabetics (Punyakrit et al.,
Lipid profile was more favorable in lean diabetics compared to obese in some studies (Arnab et al., 2006; Das et al., 1995). Serum cholesterol and triglycerides levels were the lowest in the lean group and were progressively higher in the ideal body weight and obese groups ($P < 0.001$) (Mohan et al., 1997). Serum triglyceride showed increasing, while HDL-C showed decreasing trends across different BMI groups (Chan et al., 2004). Serum TG/HDL ratio was significantly lower in the lean as opposed to the obese T2DM subjects (Coleman et al., 2014). Glycaemic control did not influence lipid metabolism in lean NIDDM patients, BMI < 25 kg/m$^2$ in men and < 27 kg/m$^2$ in women (Ikeda et al., 1991).

6.6 Microvascular Complications

In the study by Punyakrit et al. (2011), from India, prevalence of peripheral neuropathy (70%) and retinopathy (25%) is higher among the lean diabetic patients as compared to macrovascular complications. Thirteen patients (13%) were suffering from nephropathy. Such a trend of higher prevalence of retinopathy among lean patients compared to ideal body weight and obese groups have been observed by others also. There was no significant difference in the occurrence of nephropathy between the groups. Among males with T2DM, peripheral neuropathy was more common in lean compared to obese, but no such difference was noted among females (Mohan et al., 1997).

However, Mukhyaparna et al. (2004) did not find any difference in the prevalence of microvascular complications among lean, overweight and obese T2DM, something similar to a study from USA by Coleman et al. (2014).

6.7 Macrovascular Complication

The prevalence of macrovascular complication was very low in lean type 2 diabetics; 1% had coronary artery disease and 2% had cerebrovascular accident (Punyakrit et al., 2011). In another Indian study also, ischemic heart disease was very low (2.7%) among lean type 2 diabetics, whereas it was 13.84% in normal weight 12% in over weight 23.07% in obese diabetics (Mukhyaparna et al., 2004). Coronary heart disease prevalence was lower in lean group, but there was no difference in prevalence of stroke and peripheral arterial disease (Coleman et al., 2014).

However, there was no significant difference in the prevalence of myocardial ischaemia or myocardial infarction between lean, ideal weight and obese T2DM from sex in the study by Mohan et al. (1997) The prevalence of peripheral vascular disease (PVD) was surprisingly higher among the lean patients of male sex compared to the obese group. However, the overall number of patients with PVD in the study was low.

6.8 Infections

Incidence of tuberculosis was very high in lean diabetics (26.6%) whereas tuberculosis was seen in 4% on of normal weight diabetics (Mukhyaparna et al., 2004). Eight percent of patients had foot or systemic infections (Punyakrit et al., 2011).
7 Response to treatment

In a randomized, single-blind, long-term study comparing unmeasured diet to exchange-type, calorically defined diet among lean T2DM the effect on fasting blood glucose, serum triglyceride, cholesterol, and weight was similar (Ikeda et al., 1991). Nearly 48% of the lean T2DM patients still responded to diet or oral hypoglycemic agents up to a mean duration of around 9 years (Mohan et al., 1997). A higher percentage of lean (49%) versus obese (44%) patients required the use of insulin for glycemic control ($p = 0.001$) (Pontiroli et al., 1992). In a Chinese study there were more subjects in the underweight group (41.3%) who were treated with insulin compared to normal weight (13.9%) and overweight (8.2%; $p < 0.001$) (Chan et al., 2004).

Secondary oral hypoglycemic agent (OHA) failure was seen in 27% (Punyakrit et al., 2011). Patients with secondary failure to sulphonylurea, similar to their responsive counterparts, failed to show insulin secretory response to intravenous glucose. But in comparison they have significantly reduced but not complete absence of insulin response to tolbutamide and glucagon. Amount of glucose metabolized and insulin sensitivity is also reduced in lean subjects (Pontiroli et al., 1992).

8 Conclusion

A large chunk of type 2 diabetes patients are lean, the prevalence depending upon the population studied and the cut-off level used. There is a higher preponderance among males in contrast to female preponderance among obese. Most clamp studies show insulin secretory defect as the predominant defect in contrast to predominant insulin resistance in obese. Nearly half of these patients still respond to OHA even after a mean duration of around 10 years. Compared to obese type 2 diabetes they have a lesser prevalence of macrovascular complications.

References


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