An Atypical Form of Diabetes Among Individuals With Low BMI

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PATHOPHYSIOLOGY/COMPLICATIONS

OBJECTIVE

Diabetes among individuals with low BMI (<19 kg/m^2) has been recognized for >60 years as a prevalent entity in low- and middle-income countries (LMICs) and was formally classified as "malnutrition-related diabetes mellitus" by the World Health Organization (WHO) in 1985. Since the WHO withdrew this category in 1999, our objective was to define the metabolic characteristics of these individuals to establish that this is a distinct form of diabetes.

RESEARCH DESIGN AND METHODS

State-of-the-art metabolic studies were used to characterize Indian individuals with "low BMI diabetes" (LD) in whom all known forms of diabetes were excluded by immunogenetic analysis. They were compared with demographically matched groups: a group with type 1 diabetes (T1D), a group with type 2 diabetes (T2D), and a group without diabetes. Insulin secretion was assessed by C-peptide deconvolution. Hepatic and peripheral insulin sensitivity were analyzed with stepped hyperinsulinemic-euglycemic pancreatic clamp studies. Hepatic and myocellular lipid contents were assessed with ^{1}H-nuclear magnetic resonance spectroscopy.

RESULTS

The total insulin secretory response was lower in the LD group in comparison with the lean group without diabetes and the T2D group. Endogenous glucose production was significantly lower in the LD group than the T2D group (mean ± SEM 0.50 ± 0.1 vs. 0.84 ± 0.1 mg/kg · min, respectively; $P < 0.05$). Glucose uptake was significantly higher in the LD group in comparison with the T2D group (10.1 ± 0.7 vs. 4.2 ± 0.5 mg/kg · min; $P < 0.001$). Visceral adipose tissue and hepatocellular lipids were significantly lower in LD than in T2D.

CONCLUSIONS

These studies are the first to demonstrate that LD individuals in LMICs have a unique metabolic profile, suggesting that this is a distinct entity that warrants further investigation.

Diabetes and its complications have reached epidemic proportions globally. The burden of adult diabetes is predicted to rise from 537 million cases in 2021 to 783 million cases by 2045 with ∼80% of those affected living in low and middle-income countries (LMICs) (1). The existence of a unique form of diabetes among individuals with low BMI was first reported by Hugh-Jones in 1955 on encountering a group of patients in Jamaica who eluded classic descriptions of type 1 (T1D) or type 2 (T2D)

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diabetes (2). Thereafter, cases of individuals with low BMI and diabetes (LD) have been documented in many other LMICs, including Bangladesh, Nigeria, India, Ethiopia, Korea, Thailand, and Uganda (3–10), with original reports from India suggesting a prevalence of ~23% (11). This entity was formally recognized by the World Health Organization (WHO) in 1985 as a distinct form of diabetes entitled "malnutrition-related diabetes mellitus" (MRDM) (12). Early reports of this form of diabetes had documented a number of common characteristic features, including a history of malnutrition in early childhood or in utero with persistence of low BMI (typically <19 kg/m^2) in adulthood; early onset of diabetes (age <30 years); predominantly male prevalence (~85%); absence of ketonuria or ketosis despite uncontrolled blood glucose levels (fasting plasma glucose >200 mg/dL); high insulin requirements, >60 IU/day or 2.0 units/kg day; and an increased risk of diabetes complications (7,13). While high insulin requirements in these very lean individuals suggest insulin resistance, this has never been rigorously studied.

The WHO report of 1999 suggested that MRDM be deleted from the classification of diabetes due to lack of substantial evidence proving that malnutrition or protein deficiency per se causes diabetes (14). However, subsequent epidemiologic data continued to support this entity as a unique and fairly prevalent form of diabetes. The estimates of MRDM among patients with diabetes in India and Iran have ranged from ~6 to 21%, after exclusion of patients with visible pancreatic pathology (15–18). Maiti et al. (16) recently reported that underweight individuals (BMI <18.5 kg/m^2) with diabetes in rural India were twice as likely to present with glucose levels >270 mg/dL than those with normal or increased BMI. Among >4,700 individuals with insulin-requiring diabetes in rural Ethiopia, mean BMI was 16.7 kg/m^2 for men and 16.5 kg/m^2 for women, with a two-to-one male predominance (7), and nearly all patients were ketosis resistant (16). The investigators subsequently proposed that most of the subjects they studied in Ethiopia were likely to have a nonautoimmune form of diabetes, which they proposed to be MRDM (19). In a recent systematic review of atypical forms of diabetes, investigators noted that the prevalence of T1D might be overestimated among underweight individuals from LMICs, whose clinical features they considered to be consistent with the original definition of MRDM. This suggests that many such individuals may be inappropriately treated and highlights the need for further investigation to characterize diabetes in low-resource settings (20).

Patients with LD from LMICs often have limited access to appropriate testing and therefore may be misclassified as having T1D. This has significant therapeutic implications, considering that the treatment guidelines for T1D are complex, requiring multiple daily insulin doses and intense management of various medical parameters. This is especially important as affordability, access to, and appropriate handling of insulin are challenging in many LMICs (3–8,11). Furthermore, insulin therapy can lead to hypoglycemia, especially in patients with food insecurity (3–8,11). Thus, a correct assessment of patients' metabolic defects could allow practitioners to appropriately tailor their clinical management and perhaps avoid unnecessary insulin therapy. In this study we therefore used state-of-the-art methodologies to define the metabolic characteristics of the poorly understood entity of MRDM, rigorously "phenotyping" a group of individuals (LD) who met the WHO classification of this condition. This was uniquely possible at Christian Medical College, Vellore (CMC), in Vellore, India, where such sophisticated studies could be performed in subjects likely to have MDRM. Such studies are necessary to ultimately develop appropriate treatment strategies for this poorly understood condition.

RESEARCH DESIGN AND METHODS

Study Design

These comprehensive metabolic studies were performed in the Department of Endocrinology at CMC in collaboration with the Global Diabetes Institute, Albert Einstein College of Medicine. Approval to conduct the study was obtained from the institutional review boards for ethics in research of both institutions. The study protocol was conducted in accordance with the Declaration of Helsinki, and informed consent was obtained from the participants of the study (21).

Study Participants

Screening efforts were particularly directed toward identifying subjects likely to have MRDM. Given the background of this clinical disorder, the patients were characterized by a lower socioeconomic status (SES) and low BMI (BMI up to 19.5 kg/m^2). Screening was undertaken at CMC's diabetes specialty clinics, in addition to the Low Cost Effective Care Unit and other health care facilities serving low-SES patients within the catchment area of CMC. For metabolic consistency, study participants were all South Indian males aged 19–45 years with diabetes of at least 1 year's duration and moderate glycemic control (HbA_{1c} 8–10% [63.9–85.8 mmol/mol]) and without micro- or macrovascular complications. A total of 272 subjects were screened, and 73 of these were included in the study. The study population (n = 73) was comprised of the five groups with the characteristics defined below. Scoring for SES was done with a validated scoring scale for Indians (22). A detailed outline of the study design with exclusion criteria can be found in Supplementary Fig. 1.

We used the WHO classification for MRDM from 1999 to carefully select subjects for the LD group. These subjects were studied in parallel with groups of individuals who fit classic descriptions of T1D and T2D. We used rigorous criteria to exclude T1D subjects from the LD group based on immunogenetic analysis and other criteria. These included C-peptide responses to a standard mixed-meal tolerance (MMTT) test as well as excluding individuals with a history of ketoacidosis and seropositivity to GAD-65 and islet antigen 2 (IA-2) antibodies. The ultimate "proof" that LD individuals do not have T1D is the fact that the measures of insulin secretion by C-peptide deconvolution differ markedly from the response in the T1D group. Considerable effort was made to match the duration of diabetes across the three groups with diabetes. LD subjects were similar in age to subjects without diabetes.

LD (n = 20)

We aimed to recruit patients with diabetes having BMI ≤19 kg/m^2, history of low birth weight, or episodes of malnutrition since childhood, documented with a standardized questionnaire-based dietary recall method (23) on at least one occasion, with no history of ketoacidosis,

no pancreatic pathology on imaging, GAD-65 and IA-2 antibody negativity, and a preserved C-peptide response (>0.5 ng/mL) to standard MMTT. These subjects did not have a family history of diabetes or significant micro- or macrovascular complications and were negative for all known mutations in the candidate genes for maturity-onset diabetes of the young (MODY) and lipodystrophy. While we carefully selected subjects with characteristics consistent with MRDM, we use the terminology "low BMI diabetes" as a more general term given the withdrawal of the formal WHO designation of MRDM.

T1D (n = 15)

For classification of T1D, patients had diabetes and a history of documented ketoacidosis, positive GAD-65 or IA-2 antibodies, and absence of C-peptide response (< 0.5 ng/mL) to standard MMTT.

T2D (n = 13)

For classification of T2D, patients were included who had diabetes, BMI between >23 and <30 kg/m^2, no history of ketoacidosis, negative GAD-65/IA-2 antibodies, and presence of C-peptide response (>0.5 ng/mL) to a standard MMTT.

Lean (n = 16) and Overweight (n = 9) Subjects Without Diabetes

Age- and BMI-matched (to LD and T2D, respectively) healthy individuals with normal glucose tolerance, normal HbA_{1c}, and absence of familial history of diabetes within three generations who were in generally good physical health without a history of chronic medication use, alcoholism, or smoking were recruited to the group of lean subjects without diabetes (lean non-DM) and the group of overweight subjects without diabetes (overweight non-DM).

Study Techniques

Baseline Investigations

All subjects underwent anthropometric measurements including BMI, waist circumference, and waist-to-hip ratio measurements and were classified as lean, nonobese, or obese based on the 2013 guidelines of the National Institute for Health and Care Excellence (24) (details available in Supplementary Materials). Laboratory investigations included serum electrolytes, serum urea and creatinine, liver function tests, lipid profile, HbA_{1c}, blood glucose measurements, challenged C-peptide levels, and GAD-65/IA-2 antibody assays. In addition, all participants underwent abdominal ultrasonography in the fasting state to rule out anomalies of the liver, spleen, and pancreas.

Genetic Screening

Using next-generation sequencing techniques, genetic screening for MODY and lipodystrophy was performed on a panel of 13 genes for MODY and 6 genes for lipodystrophy including insulin resistance/lipodystrophy (*LMNA*, *AGPAT2*, *BSCL2*, *PPARG*, *INSR*, and *ZMPSTE24*) genes for all patients within the LD group (25,26) (details available in Supplementary Materials).

Stabilization of Glucose Concentrations

Given the strong evidence for the importance of correcting glucotoxicity on insulin secretion and resistance both in humans (27–29) and animals (30,31), glycemic control was intensified in all subjects with diabetes for 2 weeks prior to metabolic studies. This was followed by an overnight insulin infusion to maintain euglycemia prior to the hyperinsulinemic-euglycemic clamp study procedure. All subjects were monitored meticulously to ensure uniformity of diet and duration of fasting prior to clamp procedures. This protocol is described in Supplementary Materials.

"Stepped Up" Euglycemic-Hyperinsulinemic Pancreatic Clamp Studies

Prior to the clamp procedure, subjects underwent a 12-h preparatory phase during which euglycemia (~90 mg/dL) was attained with use of a variable insulin infusion algorithm monitored with hourly glucose measurements. Hepatic and peripheral insulin sensitivity were assessed with "stepped" euglycemic-hyperinsulinemic pancreatic clamp studies. The entire procedure was divided into three interconnected phases, namely, the basal phase, low phase, and high phase, spanning a total duration of 6 h (Fig. 1). Throughout the 6-h clamp duration, plasma glucose concentration was maintained at basal levels (~90 mg/dL) with meticulously adjusted exogenous infusion of 20% dextrose and a stable infusion of glucoregulatory hormones. The detailed protocol for the clamp studies conducted in the study subjects has previously been outlined (32) and is also detailed in Supplementary Materials.

Glucose Turnover

Estimation of deuterated glucose in serum and plasma samples was performed at the Albert Einstein College of Medicine, with measurements by gas chromatography–mass spectrometry as previously described (32). Glucose R_a and R_d, or glucose uptake (a measure of peripheral insulin sensitivity), were calculated with Steele's steady-state equation (33). Rates of endogenous glucose production (EGP) (a parameter of assessing hepatic insulin resistance) were determined by subtraction of rates of glucose infusion from the tracer-determined R_a. Data for glucose turnover represent mean values during the final 60 min of the "low insulin" step of the clamp (t = 180–240 min) and the "high insulin" step of the clamp (t = 300–360 min).

Insulin Secretion Assessed With MMTT

The participants in the LD, T1D, and T2D groups were monitored regularly for achieving glycemic control prior to the MMTT. Fructosamine levels were measured to ensure correction of glucotoxicity prior to the MMTT. The participants were provided with a standardized meal and snack to consume the night prior to the MMTT and were instructed to remain fasting after 10:00 P.M. to minimize the metabolic variability between tests. All participants underwent the MMTT 1 week prior to the clamp, after correction for glucotoxicity. On the day of the MMTT, participants in the LD and T2D groups discontinued oral antidiabetes medications and insulin. We initially performed an MMTT in a few T1D participants (n = 5) after stopping their insulin. However, due to the potential risk of acute hyperglycemia and ketosis following withdrawal of insulin, the MMTT procedures were only performed in n = 5 T1D patients. Following an overnight fast, the participants) were administered a mixed meal of Ensure (Abbott Healthcare Pvt Ltd, Mumbai, India, a nutritional supplement (carbohydrate 54%, fat 32%, and protein 14%), 6 scoops (54 g of the meal/219 kcal) dissolved in plain water (maximum 360 mL water) consumed over 5–10 min. Blood samples were obtained through an indwelling

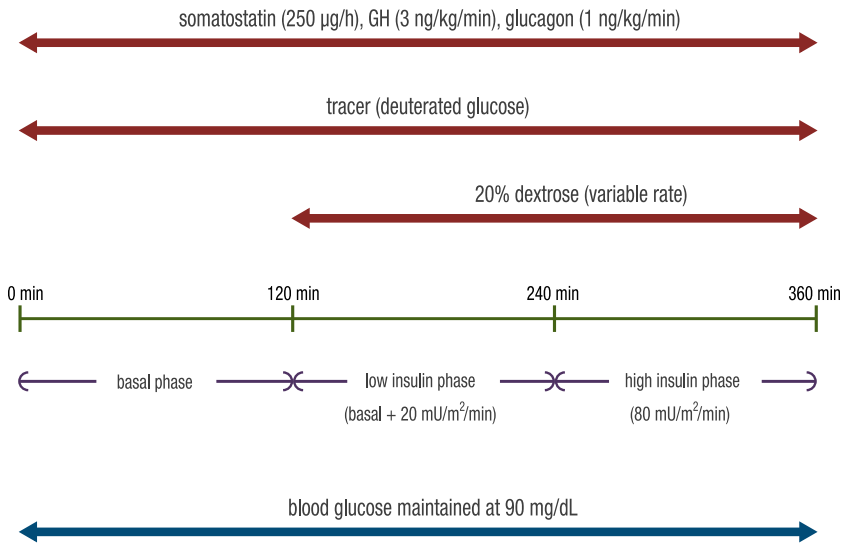

Figure 1—Schematic representation of the euglycemic-hyperinsulinemic clamp procedure. GH; growth hormone.

intravenous catheter in the fasting state (0 min) and 15, 30, 45, 60, 90, 120, 150, and 180 min following the meal for measurement of glucose, insulin, glucagon, and C-peptide levels. Plasma triglycerides and free fatty acid (FFA) levels were measured in the fasting state and at 60, 120, and 180 min. We calculated insulin secretion from the C-peptide deconvolution studies from area under the curve (AUC) measurements using the trapezoidal method (34,35). Further specific details of the 3-h MMTT can be found in Supplementary Materials.

Biochemical Assays

Plasma glucose levels were measured with use of the glucose oxidase method with a bedside glucose analyzer (Analox GM9D; Analox Instruments Ltd, Lunenberg, MA). Insulin, C-peptide, and human growth hormone were measured by a two-site chemiluminescent immunometric assay (IMMULITE 2000 immunoassay system; Siemens Healthcare Diagnostics Products Ltd, Llanberis, U.K.). Glucagon was measured using a competitive ELISA method employing a commerically available ELISA kit (ALPCO, Salem, NH). Plasma FFA levels were determined with an acyl-CoA oxidase method–based kit (Wako Diagnostics, Richmond, VA) on an automated modular analyzer (cobas 8000, Roche Diagnostics, Indianapolis, IN). Plasma glycerol levels were measured with a phosphorylation method–based calorimetric kit (Sigma-Aldrich, St. Louis, MO). Plasma lactate levels were estimated with enzymatic oxidation methods with commercial kits (cobas 8000). GAD-65 and IA-2 autoantibody positivity was analyzed with a quantitative sandwich immunoassay method (RSR Limited, Cardiff, U.K.) with an assay range of up to 5–2,000 units/mL for GAD-65 and up to 7.5–4000 units/mL for IA-2.

Imaging Procedures

Whole-body composition for body fat percentage, fat mass, lean mass, and truncal fat was assessed with a Hologic DEXA scanner (Hologic DEXA Discovery QDR 4500) (Coefficient of Variation [CV]: 4%). Data obtained from the regions of interest were analyzed with APEX software (version 4.0.2).

^{1}H-MRI and MRS (3 Tesla Intera Achieva magnetic resonance system; Philips Medical Systems, Eindhoven, Netherlands) using single-voxel stimulated echo acquisition mode was performed in the fasting state in all participants for the quantification of intramyocellular and extramyocellular lipids in the soleus and tibialis muscles of the leg along with hepatocellular lipids, visceral adipose tissue (VAT) volume, and subcutaneous adipose tissue (SAT) volume. Details of the DEXA and MRS methodologies can be found in Supplementary Materials.

Statistical Analysis

Descriptive statistics of the variables are presented in terms of mean and SEM when data are normally distributed or as median and interquartile range when data are not normally distributed. Normality of the data were tested with the Shapiro-Wilk test wherein a P value >0.05 was considered significant for normative distribution. One-way ANOVA or Kruskall-Wallis test with post hoc analysis was applied for comparisons between groups. Pearson or Spearman correlation analysis was applied to test for significance in correlations. A P value <0.05 was considered statistically significant. Statistical analysis was performed with STATA (version 16.0 for Windows (StataCorp, College Station, TX).

Data and Resource Availability

Data will be made available by the corresponding author if requested.

RESULTS

Participant Characteristics

This study included a total of 73 Asian Indian males: LD, $n = 20$; T1D, $n = 15$; T2D, $n = 13$; lean non-DM, $n = 16$; and overweight non-DM, $n = 9$. Only male participants were included in the study to minimize sex-specific variability and on the basis of the male predominance of MRDM. Demographic characteristics, anthropometry, and biochemical profiles at the point of screening are shown in Table 1. Mean BMI, hip circumference, and waist-to-hip ratio in the LD group were significantly lower in comparisons with the T1D group (all $P = 0.001$). No significant differences were observed in BMI in comparing LD and lean non-DM

Table 1—Anthropometric and biochemical profile (at the time of the screening) across groups

	LD (n = 20)	T1D (n = 15)	T2D (n = 13)	Lean non-DM (n = 16)	Overweight non-DM (n = 9)
Age (years)	41.5 (36.0, 42.5)	28.0 (25.0, 34.0)***	36.2 (32.0, 41.0)	26.0 (24.5, 37.0)**	41.0 (40.0, 41.0)
Height (cm)	164.5 ± 1.1	166.3 ± 1.7	167.6 ± 1.7	171.1 ± 2.0*	166.3 ± 2.0
Weight (kg)	49.6 ± 1.0	56.7 ± 1.3*	73.0 ± 1.5***	56.3 ± 2.7*	70.5 ± 1.9***
BMI (kg/m^2)	18.3 ± 0.2	20.5 ± 0.4***	26.0 ± 0.3***	19.1 ± 0.6	25.4 ± 0.35***
Waist circumference (cm)	74.0 (69.0, 75.5)	77.0 (72.0, 81.0)	96.0 (93.0, 99.0)***	72.0 (69.0, 81.0)	92.0 (90.0, 95.2)***
Hip circumference (cm)	77.5 (76.5, 82.0)	88.0 (87.0, 91.0)***	97.0 (95.0, 99.0)***	85.0 (81.5, 92.0)**	93.7 (92.8, 96.0)***
Waist-to hip ratio	0.91 (0.9, 1.0)	0.9 (0.9, 0.9)**	1.0 (1.0, 1.0)**	0.9 (0.8, 0.9)*	1.0 (1.0, 1.0)**
HbA_{1c} (%)	9.7 (7.8, 11.0)	9.3 (7.9, 9.9)	8.7 (8.5, 9.0)	5.1 (5.1, 5.3)***	5.4 (5.1, 5.5)***
Creatinine (mg/dL)	0.8 (0.7, 0.9)	1.1 (1.0, 1.1)***	1.0 (1.0, 1.1)**	1.0 (0.7, 1.1)*	1.1 (1.0, 1.1)**
Fasting glucose (mg/dL)	219.5 (143.0, 286.0)	214.0 (112.0, 347.0)	171.0 (149.0, 199.0)	84.0 (81.0, 88.5)***	90 (87, 93)***
Fasting insulin (μ/mL)	4.5 (3.0, 7.9)	6.9 (1.9, 14.2)	10.4 (2.1, 15.7)	2.1 (1.9, 4.7)*	9.1 (5.7, 10.3)
Fasting C-peptide (ng/mL)	1.2 (0.6, 1.6)	0.1 (0.1, 0.1)***	2.1 (0.8, 2.7)*	1.2 (0.8, 1.6)	1.7 (1.5, 2.4)*
Cholesterol (mg/dL)	156.0 (139.0, 200.0)	163.0 (135.0, 195.0)	198.0 (163.0, 204.0)	150.5 (130.0, 182.0)	178.0 (158.0, 201.0)
Triglycerides (mg/dL)	127.5 (84.0, 160.0)	68.5 (49.0, 82.0)**	204.0 (133.0, 267.0)*	87.5 (48.0, 138.5)*	117.0 (100.0, 162.0)
HDL (mg/dL)	35.0 (34.0, 44.0)	43.0 (41.0, 47.0)*	39.0 (29.0, 42.0)	44.5 (37.0, 56.0)*	39.0 (36.0, 43.0)
LDL (mg/dL)	105.1 ± 8.0	104.1 ± 9.2	122.9 ± 8.9	96.3 ± 7.3	128.1 ± 10.5

Data are means ± SEM or median and interquartile range (25th, 75th percentile). All of the biochemical measures including baseline glucose, C-peptide, and insulin were taken after intensive correction of glucotoxicity for 2 weeks prior to the clamp procedure, while HbA_{1c} was obtained at the time of screening. Asterisks indicate values that are significantly different in comparison with the LD group. *$P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

groups. However, waist-to-hip ratio was higher in the LD group compared with the lean non-DM group, despite matching for BMI ($P = 0.03$). Among biochemical variables, mean ± SEM blood corpuscular volume (81.4 ± 5.1 fL) and hemoglobin (13.5 ± 1.3 gm/dL) levels were significantly lower in the LD group compared with the lean non-DM group ($P = 0.01$). Mean HbA_{1c} and fasting glucose levels did not significantly differ among the three groups with diabetes, and mean triglyceride levels were significantly higher in the LD group compared with the lean non-DM ($P = 0.02$) and T1D ($P = 0.01$) groups. Fasting C-peptide levels were significantly higher in the LD group when compared with the T1D group ($P = 0.001$) but significantly lower than in the T2D group ($P = 0.05$). The patients of the LD group were negative for pathogenic mutations in 13 genes for MODY and genes for lipodystrophy, namely, the *LMNA*, *AGPAT2*, *BSCL2*, *PPARG*, *INSR*, and *ZMPSTE24* genes. Information on the clinical treatment received by the groups with diabetes (LD, T1D, and T2D) at point of recruitment in the study can be found in Supplementary Fig. 2*A*–*C*.

Insulin Secretion in Response to MMTT

We assessed insulin secretion using C-peptide deconvolution during a MMTT. The first-phase insulin secretory response (0–15 min) and the total insulin secretory response to MMTT were significantly lower in the LD group compared with the lean non-DM and the T1D groups. Of note, the AUC for insulin secretion rate was significantly lower in the LD subjects than in the T2D subjects (all $P < 0.05$) and demonstrated a markedly blunted rise in insulin secretion in response to the meal (Fig. 2*A* and Supplementary Table 1). As for the surrogate indices of insulin resistance during the MMTT, mean values of the Matsuda index (a measure of hepatic and peripheral insulin sensitivity), disposition index, and insulinogenic index were all significantly lower in the LD group relative to T2D, reflecting greater insulin sensitivity in the LD than in the T2D group, whereas HOMA of insulin resistance was significantly higher in comparison with the lean non-DM group (Supplementary Table 1). The mean glucose levels in the LD group were significantly higher than in the lean non-DM group at all time points (Fig. 2*B*).

Insulin Action During the Clamp Study

Rate of EGP was significantly lower in the LD group compared with the T2D group, suggesting comparatively less hepatic insulin resistance (0.50 ± 0.1 vs. 0.84 ± 0.1 mg/kg · min, respectively; $P < 0.05$) (Fig. 3*A*). Insulin-stimulated glucose uptake (R_d, peripheral insulin sensitivity) was significantly higher in the LD compared with the T2D group (R_d 10.1 ± 0.7 vs. 4.2 ± 0.5 mg/kg · min; $P < 0.001$) (Supplementary Tables 2 and 3).

The R_d value during the high phase of the clamp study was significantly higher in the LD group than in the T2D group, suggesting lower peripheral insulin resistance (Fig. 3*B*). After adjustment for lean body mass, glucose uptake was significantly higher in the LD group than the T2D group (Supplementary Table 2). R_d demonstrated significant negative correlations with truncal fat mass ($r = -0.66$, $P = 0.004$) and total fat mass ($r = -0.64$, $P = 0.004$) in the LD group (Supplementary Fig. 3*A* and *B*).

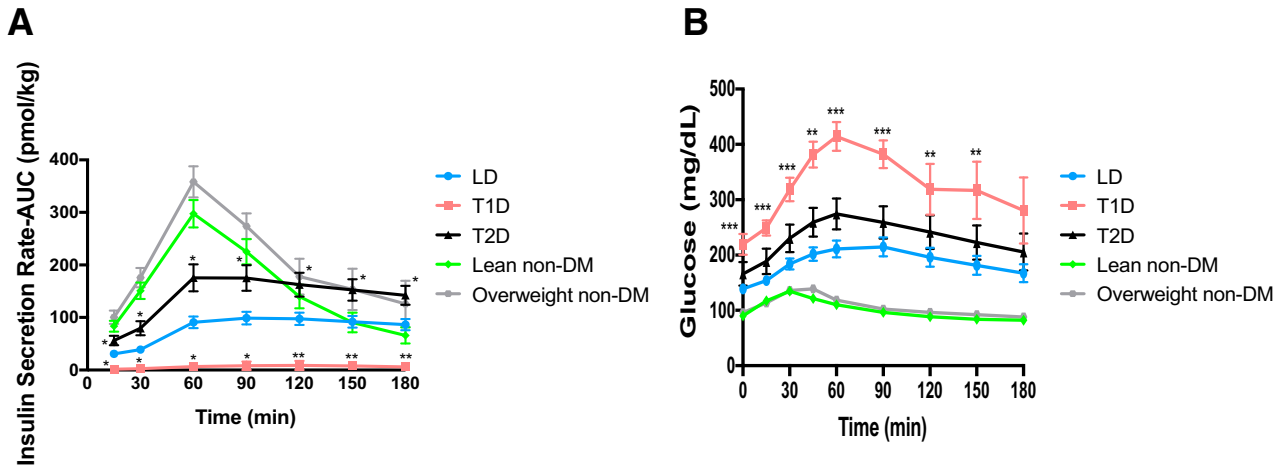

Figure 2—*A*: Insulin secretion AUC in response to MMTT across groups. *B*: Glucose levels during MMTT across groups. Data are presented as mean ± SEM. Asterisks indicate values that are significantly different for LD vs. T1D and T2D groups (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).

During the hyperinsulinemic-euglycemic pancreatic clamp, "steady-state" dynamics were attained during the low and high insulin phases as demonstrated by comparable atom percent excess and glucose levels across the study groups (Fig. 3*C* and *D*). Insulin, glucagon, and lactate levels were comparable across the study groups, confirming that steady hormone levels were maintained throughout the clamp studies. C-peptide levels remained suppressed throughout the low and high insulin phases of the clamp studies in response to somatostatin infusion in all groups relative to their fasting levels. Consistent with lower triglyceride levels at the time of the screening, FFA levels were significantly lower in the LD group compared with T2D during both the low and high insulin phases of the clamp studies ($P < 0.05$) (Supplementary Table 4). Therefore, the LD phenotype does not appear to be characterized by insulin resistance at the level of adipose tissue, although the rigorous correction of hyperglycemia may have reversed any original defects.

Body Composition Analysis

Body composition analysis by DEXA showed that total lean body mass was significantly lower in the LD subjects compared with the T1D, T2D, lean non-DM, and overweight non-DM subjects (all $P <$ 0.01). Truncal fat mass and total fat mass were significantly lower in the LD subjects compared with the T2D subjects and

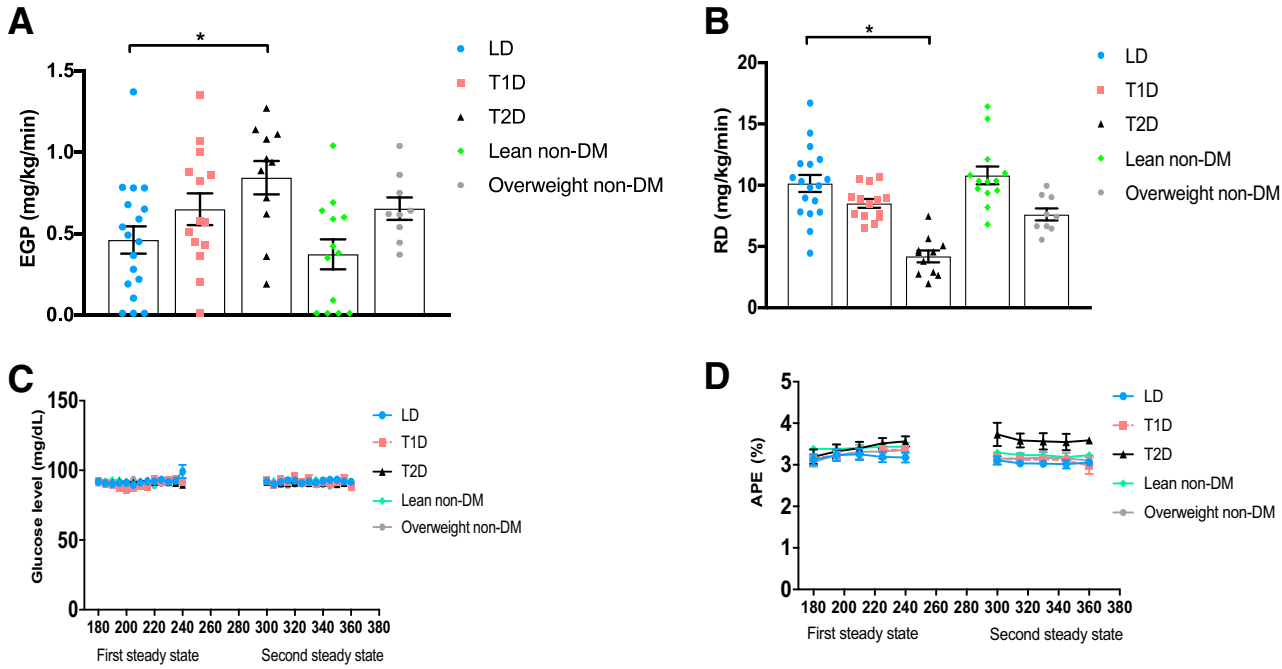

Figure 3—Clamp studies. *A*: EGP. *B*: Glucose uptake (R_d) during the clamp studies. *C*: Average glucose level during two steady states in each group. *D*: Average atom percent excess (APE) during two steady states in each group. Values are presented as mean ± SEM. Asterisks indicate values that are significantly different when compared to the LD group (*$P < 0.05$).

overweight non-DM subjects (all $P < 0.01$), while truncal fat mass was significantly higher in LD compared with T1D and lean non-DM subjects (all $P < 0.05$). Truncal lean mass was significantly lower in LD than in the T1D, T2D, and lean and overweight non-DM subjects (all $P < 0.05$) (Supplementary Table 4).

On MRS imaging, the percentage of hepatocellular lipids in the LD group was significantly lower than in the T2D group but did not differ from the other groups ($P < 0.01$). Furthermore, the SAT and VAT volumes were significantly lower in the LD group than in the T2D and overweight non-DM groups ($P < 0.01$). In contrast, VAT-to-SAT ratio was significantly higher in the LD group than in the T1D and lean non-DM subjects (all $P < 0.01$) but lower than in the overweight non-DM group ($P < 0.05$). As for myocellular lipids, percentages of intramyocellular and extramyocellular lipids (tibialis anterior) did not significantly differ between the groups, although extramyocellular lipid (tibialis anterior) was significantly lower in the LD group in comparisons with the T2D subjects ($P < 0.05$) (Supplementary Table 5 and Supplementary Fig. 4).

Nutritional Profiles Between Groups

Dietary intake of proteins, calcium, and carotene was significantly lower in lean subjects with diabetes than in the lean non-DM group (all $P < 0.05$), while no significant differences were seen for any of the other macro- or micronutrients that were studied (Supplementary Tables 6 and 7).

CONCLUSIONS

This is the first study with use of state-of-the-art techniques to comprehensively characterize insulin secretion, hepatic and peripheral insulin sensitivity, whole-body composition, abdominal adipose tissue volume, and hepatic and intramyocellular lipid contents in individuals with LD. We further compared individuals with LD with subjects with T1D and T2D and with BMI-matched control subjects without diabetes. Prior to the procedure, glycemic control in the LD and T2D groups was similar, as evidenced by the fructosamine levels indicating absence of acute glucotoxicity. However, insulin secretory capacity was substantially lower in individuals in the LD group relative to T2D and control subjects without diabetes, yet still higher than in subjects with T1D. It is pertinent that the LD group demonstrated significantly lower mean values of the Matsuda index, the insulinogenic index, and the disposition indices in comparisons with the lean non-DM group. Consistent with previous reports (36), T2D subjects displayed a loss of first-phase insulin secretion and a slow return to baseline. Mean values of ISI and Matsuda index were higher in the LD group than in the T2D group. This can be attributed to a predominant insulin secretory defect and a probable lack of endogenous insulin resistance in the LD group. Notably, in the T2D group, the prominent feature is insulin resistance (32), leading to significantly lower mean values of the ISI and Matsuda index and higher value of HOMA of insulin resistance.

In the hyperinsulinemic-euglycemic clamp procedure, a significant positive correlation of SAT with low-phase EGP adds evidence regarding the possible role of SAT leading to decreased insulin sensitivity in the LD group. Notably, peripheral insulin sensitivity (R_d value) of the LD group did not differ from that of the T1D group or lean control subjects, suggesting that the LD group was more insulin sensitive than the T2D group.

Given the paucity of studies that have strictly adhered to the definition of MRDM, the exact prevalence rate, pathophysiology, and metabolic profile of this condition remain poorly understood (20,37). Previous clinical observations characterized lean patients with diabetes as insulin resistant based on high insulin requirements despite low BMI (7,11,38–43). A striking feature described in these studies is the complete absence of ketosis or ketonuria (44), which has been attributed to delayed mobilization of FFAs from adipose tissue and suppressed postprandial glucagon regardless of peripheral insulinopenia (45).

Other studies suggested an insulin secretory defect with reduced fasting insulin and C-peptide values and compromised insulin response in these individuals following oral glucose loading or in response to intravenous tolbutamide (40,46), although the rigorous methodologies are unique to this study. In a recent elegant study to identify subgroups of adult-onset diabetes in a Swedish cohort, investigators reported a novel cluster of patients with severe insulin-deficient diabetes (SIDD) characterized by negative GAD-65 antibody titers, relatively low BMI ($\sim$28.9 kg/m^2), low insulin secretion, a younger age of onset, and poor metabolic control (47). Such patients required a course of insulin therapy in addition to oral antidiabetes medications for glycemic control, and the majority of the patients were ketosis resistant (47). However, insulin resistance patterns established with focused physiological techniques and body composition profiles were not assessed, and the etiological mechanisms of SIDD remain to be explored. While our LD subjects also demonstrated predominant defects in insulin secretion, they were characterized by a very low BMI (mean 18.3 kg/m^2) and were ethnically Asian Indian. The results of our rigorous studies evaluating insulin action and whole body composition, including hepatocellular lipids and abdominal adipose tissue volumes, showed a unique metabolic phenotype that was distinctly different from T2D. This LD phenotype is likely also distinct from what was termed SIDD in a recent report of Asian Indians, who were characterized by a much higher BMI (24.9 kg/m^2) (48). However, the observations by Ahlqvist et al. (47) and the current results underscore the need to revisit the classification of diabetes and identify novel subgroups of diabetes.

The state-of-the-art methodologies used in this study advance previous reports suggesting reduced insulin secretory capacity and ketosis resistance in LD subjects (13). LD subjects in the current study had a higher mean basal and peak postglucose level of insulin and C-peptide and absence of ketosis in comparisons with the T1D subjects. This suggests that insulin secretion was adequate to restrain ketogenesis in these individuals, yet insufficient to prevent postprandial glucose excursions (11). It has been speculated that this defect in insulin secretory capacity may be due to decreased β-cell mass, since epidemiological patterns reveal LD to be a disease that has a predilection for lower-income groups and rural populations of developing countries, where low-protein diets are prevalent (2). In our study, the participants were Asian Indians recruited from rural areas wherein the staple diet is rice and wheat based, with the LD group showing a significantly lower

dietary intake of protein in comparison with the lean non-DM group.

Maternal protein malnutrition has been studied in rodents, with reports of offspring born to these mothers having lower β-cell mass and decreased ability for β-cell regeneration. Remarkably, while early life malnutrition or starvation can predispose to T2D in adulthood (10,25,49,50), what distinguishes LD from T2D subjects is that the former remain underweight throughout their development (16). In humans, small-for-gestational-age neonates are noted to have a smaller fraction of islet cells and less pancreatic vasculature (51). While some clinical reports suggested that LD patients are insulin resistant (11), there is a paucity of sophisticated, dynamic studies evaluating insulin sensitivity in this group. Garg et al. (52) previously performed hyperinsulinemic-euglycemic clamps in LD individuals from Northern India, though without correcting for glucotoxicity or using glucose tracers to measure hepatic and peripheral insulin sensitivity. Since there is strong evidence in both animals (30,31) and humans (27–29) that correcting hyperglycemia ("glucotoxicity") would improve insulin secretion and resistance, we corrected hyperglycemia to eliminate the effects of glucose toxicity. The results of this study indicate that hepatic and peripheral insulin sensitivity in the LD group was similar in comparison with T1D and lean non-DM subjects, while the T2D subjects were more insulin resistant.

Results of body composition analysis revealed that total lean mass and truncal lean mass were significantly lower in the LD group, when compared with the lean non-DM group, which is why we were careful to correct glucose uptake for lean body mass. Serum triglycerides and VAT-to-SAT ratios were higher in the LD group than that in the lean non-DM group, while VAT volume was higher than in the T1D group. Furthermore, hepatocellular lipid content in the LD group was variable but significantly lower than in the T2D group, although it was similar to that in the T1D and non-DM groups. We also noted considerable variability for measures of body composition in the LD group, though the study was not powered to examine whether these measures were correlated with insulin sensitivity within the LD group. In a study of normoglycemic individuals with low BMI (mean 21.8 kg/m^2) who were malnourished in the first year after birth, the subjects had lower insulin sensitivity and higher abdominal adipose tissue volume. It was suggested that abdominal adipose tissue accounted for 65% of the variance in insulin sensitivity in malnourished individuals (53). It has been hypothesized that fetal malnutrition leads to increased VAT accumulation in lean individuals, driving higher glucose reserves in VAT and other insulin responsive tissues (54). However, functional studies on VAT biopsies are needed to ascertain whether the higher VAT volumes are leading to reduced peripheral sensitivity in some subjects in the LD group. While the association between VAT and impaired β-cell function and insulin sensitivity has been well documented in overweight or obese T2D subjects (30,31), its potential role in LD should ideally be elucidated in future studies including assessment of adipokines, inflammatory cytokines, and fat biopsies.

This study provides important and unique insights into the metabolic characteristics of the poorly understood entity of MRDM through rigorous "phenotyping" with use of state-of-the-art methodologies in a group of individuals who met the WHO classification of this condition. This was conducted at CMC, the only center in India with the capacity to perform these sophisticated studies. The rigorous nature of these metabolic studies limited the sample size and precluded the performance of concomitant large genetic studies. Future analyses with larger sample sizes might be helpful to explore the genetic basis for this condition. Additional studies are also needed to further characterize this unique phenotype and formulate evidence-based treatment strategies. Given the challenges around the cost and access to insulin globally, particularly in LMICs, minimizing or avoiding the use of insulin wherever clinically appropriate would be beneficial. Considering the insulin secretory defect, it is unclear whether, and to what extent, insulin secretagogues would be effective for glycemic control in these individuals.

Despite these strengths, this study had several limitations. Our study observations were cross-sectional, and therefore the cause and effect of this unique clinical entity could not be elucidated. Additionally, the study involved only male participants, and therefore the metabolic signature in females with LD could not be evaluated. Moreover, studying the incretin hormones and glucagon levels in the LD group would likely provide further insight into the metabolic etiology of this phenotype. A comparison of birth weights across the groups in the current study was not possible, given that the majority of our study subjects were from rural India, generally born at home or at a nearby primary health center more than three decades ago and hence lacking an official documentation of birth weights. Nevertheless, the current study is the first to provide a comprehensive assessment of the unique metabolic characteristics of LD patients.

In summary, this study is the first to comprehensively evaluate the metabolic profile of individuals with antibody-negative, ketosis-resistant LD without significant microvascular or macrovascular complications in comparison with individuals with clearly defined T1D and T2D from India. When glucose toxicity was corrected, this unique group of patients displayed a phenotype that is fundamentally different from T1D or T2D. Specifically, results of this study demonstrate that the cardinal physiologic feature of LD is a defect in insulin secretory capacity as opposed to insulin resistance, as had been previously suggested. Moreover, T2D is associated with an increase in hepatic glucose output and decrease in peripheral glucose uptake, neither of which is a prominent feature in LD, emphasizing that LD is unlikely to be a subtype of T2D. However, much remains to be learned about this distinctive metabolic entity, including its epidemiology, pathophysiology, natural history, and optimal treatment strategies, especially in low-resource clinical settings in LMICs.

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