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Major Pathophysiology in Prediabetes and Type 2 Diabetes: Decreased Insulin in Lean and Insulin Resistance in Obese

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Context: Lowering of body mass index (BMI) to ≥25 kg/m^2 as obesity by ADA suggests insulin resistance as a major mechanism of impaired glucose metabolism (IGM) in Asians. However, glimepiride, an insulin secretagogue, delayed onset of type 2 diabetes (DM2) from prediabetes (PreDM), indicating decreased insulin secretion (IS) as a major factor in lean (L; BMI < 27 kg/m^2) subjects with IGM.

Objective: Assessment of IS and insulin resistance (IR) in L and obese (Ob; BMI ≥ 27 kg/m^2) subjects with euglycemia (N), PreDM, and new onset DM2.

Subjects: Seventy-five men and 45 women ages 36 to 75 years were divided into six groups: LN, LPreDM, LDM2, ObN, ObPreDM, and ObDM2.

Methods: Determination of IS by insulinogenic indices (I/G) at fasting (FI/FG), first phase (ΔI/ΔG), and cumulative responses over 2 hours of OGTT (CRI/CRG), and IR by FIXFG, ΔIXΔG, and CRIXCRG. Changes in IS and IR for PreDM and DM2 were calculated as % fall and % rise, respectively, from levels in N.

Results: All indices of IS and IR were lower ($P < 0.05$) in L than corresponding Ob groups ($P < 0.05$). Moreover, decline in IS and rise in IR were progressive from N to PreDM ($P < 0.05$) and DM2 ($P < 0.05$) in both groups. However, the declines in IS were greater ($P < 0.05$) than rises in IR in LPreDM and LDM2. Whereas, the rises in IR were higher ($P < 0.05$) than declines in IS in ObPreDM and ObDM2.

Conclusion: In L, major mechanism of IGM is declining IS and not rising IR documented among Ob.

Freeform/Key Words: prediabetes, type 2 diabetes, insulin sensitivity, insulin secretion, obese, lean

The American Diabetes Association (ADA) lowered body mass index (BMI) from ≥27 kg/m^2 to ≥25 kg/m^2 as a diagnostic criterion of obesity in the Asian American population [1]. Thus, the ADA probably continues to indicate insulin resistance as a major pathophysiologic mechanism of altered glucose metabolism in Asian subjects as among lean population in the United States. However, by older criteria, the same population would be considered lean as still recognized in non-Asian Americans [1]. In a recent study, glimepiride, an insulin secretagogue, was documented to delay progression from prediabetes (PreDM) to type 2 diabetes (DM2) in more lean subjects and for a longer duration of time in comparison with treatment with metformin in an obese non-Asian population [2]. It is plausible that better efficacy of glimepiride in lean subjects was induced by its capacity to reverse the decline in insulin secretion, which may be the major pathophysiologic factor in these subjects in contrast

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; DM2, type 2 diabetes; OGTT, oral glucose tolerance test; PreDM, prediabetes.

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to insulin resistance, a well-established mechanism in obese subjects manifesting deranged glucose metabolism, including PreDM and DM2. Therefore, indices of insulin secretion, as well as insulin resistance, were determined in lean (BMI < 27 kg/m^2) and obese (BMI ≥ 27 kg/m^2) subjects with normal glucose tolerance, PreDM, and new onset DM2.

1. Subjects and Methods

The study was approved by Research and Development Committee as well as the Human Studies Subcommittee at the Veterans Affairs Medical Center, Des Moines, Iowa, 50310.

One hundred twenty non-Asian subjects, 75 men and 45 women (mean age, 51 $\pm$ 7 years; range, 36 to 75 years), participated in the study after obtaining informed consent. Subjects with PreDM and DM2 of recent onset prior to initiation of treatment referred to endocrinology clinic during a period of 2 years between 1 July 1985 and 30 June 1987 were enrolled. Age-matched lean and obese subjects with normal glucose tolerance were volunteers recruited among the employees of the medical center and the churchgoers attending morning mass at the local church. Inclusion criteria included ability to provide informed consent, normal renal and hepatic function, and absence of any other disorder, such as hypertension, coronary artery disease, *etc*., or presence of these disorders being stable while receiving stable daily dose of medications during 6 months prior to entry into the study. Postmenopausal women receiving stable hormone replacement and younger women using contraceptives in any form were included as well. Subjects with history of hospitalization for any reason or who had received steroids or immunosuppressive drugs by any route during 6 months prior to enrollment were excluded. Pregnant women were excluded as well. The subjects were classified into two groups: lean, BMI $<$ 27 kg/ m^2 and obese, BMI $\geq$ 27 kg/ m^2. Both groups of subjects were further divided into three subgroups: normal, PreDM, and DM2 as per the diagnostic criteria established by the ADA based on fasting plasma glucose and HbA1c concentrations determined on at least two separate occasions [1]. Plasma insulin and glucose were determined in all the participants after an overnight fast of 8 to 10 hours and again at interval of 15 minutes for 2 hours after ingestion of glucose 75 g (oral glucose tolerance test [OGTT]; [Figs. 1 and 2]). Subjects were requested to consume a regular diet containing at least 150 g carbohydrate for 3 days. Insulin secretion was determined by a previously well-established method: insulinogenic index: insulin/glucose (I/G) [3–5]. Insulin resistance was quantified by Insulin $\times$ Glucose product (I$\times$G) because this index has been used as a major denominator in previously well-established methods, *e.g.*, Homeostasis Model assessment (HOMA), Matsuda, Quicki, *etc.*, and validated to be reliable and accurate as correlated with insulin sensitivity index as quantitated by determination of plasma glucose disappearance rate over first 20 minutes during insulin tolerance test [6–11]. The markers of insulin secretion were determined at baseline, fasting insulin/fasting glucose (FI/FG), at the time of first peak of insulin, insulin rise from fasting level/glucose rise from the fasting concentration at the same time during OGTT (ΔI/ΔG), and the ratio of cumulative responses as calculated as a sum of the differences above the fasting levels at all the time points (CRI/CRG) up to 2 hours after ingestion of glucose after an overnight fast. We have documented cumulative response to be a precise, accurate, and reproducible expression of the integrated secretion as determined by area under the curve [4, 5, 12]. The indices of insulin resistance were determined at fasting (FIXFG), at the first peak of insulin rise during OGTT (ΔIXΔG), and over 2 hours of OGTT (CRIXCRG). Changes in all individual indices of insulin secretion for subjects with PreDM and DM2 were calculated by determination of % fall from normal subjects, whereas changes in all individual markers of insulin resistance were expressed as % rise from normal subjects. Plasma glucose was determined by a chemical analyzer (Technicon, Inc., San Francisco, CA) using glucose oxidase method. HbA1c was assessed using a commercial kit (Glycogel test kit, Pierce Chemical, Co. Rockford, IL). Plasma insulin was measured by using a well-established commercial kit provided by the Mayo Clinic laboratory (Rochester, MN). Interassay and intraassay coefficients of variation were 7% to 10% in our laboratory. Comparisons were conducted for indices of insulin secretion and resistance between lean and obese individual

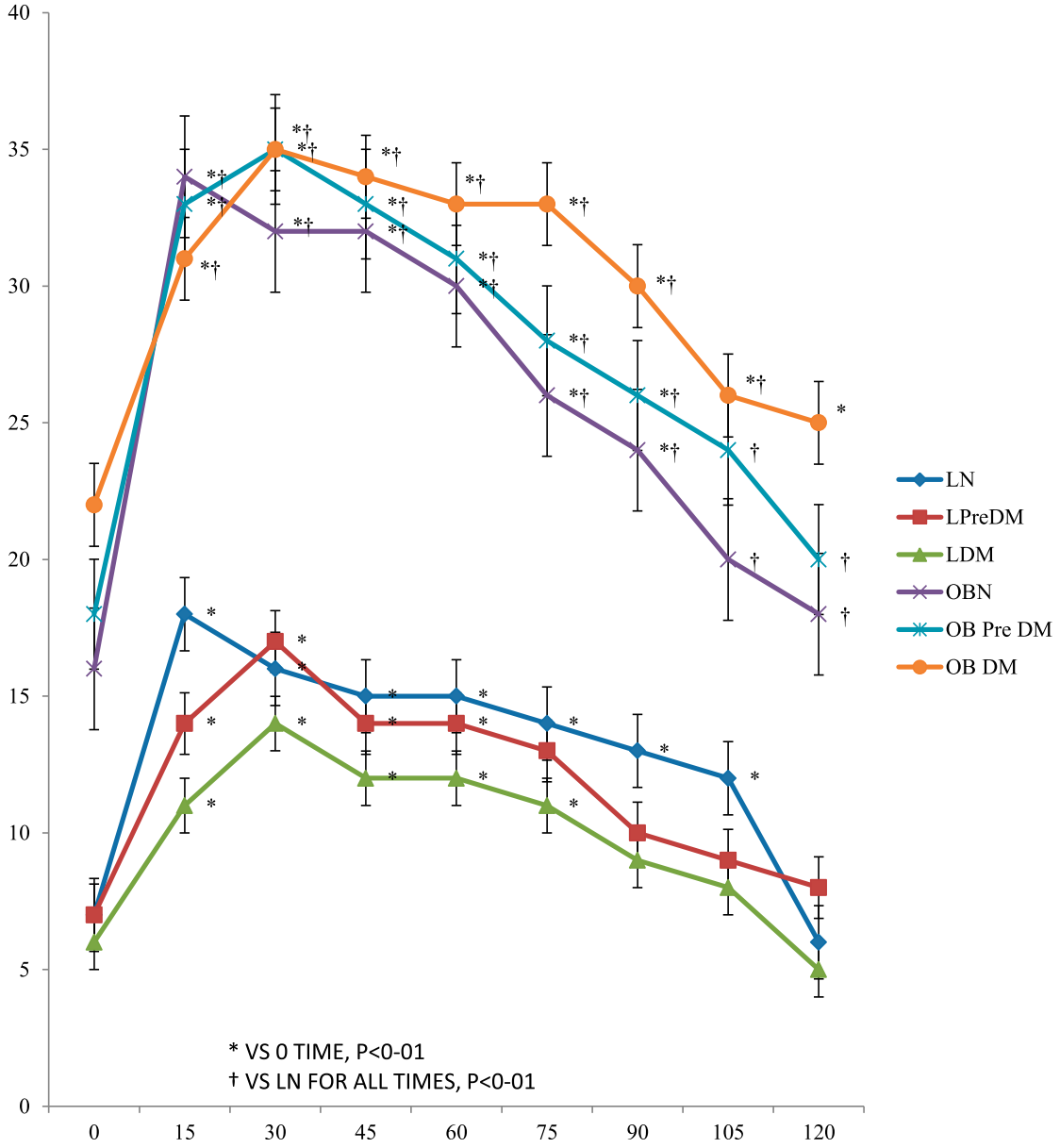

Figure 1. Plasma insulin concentration after an overnight fast and again at intervals of 15 minutes for 2 hours during 75-g OGTT.

subgroups, *e.g.*, normal, PreDM, and DM2. Comparisons were also performed for the same indices between subgroups, *e.g.*, normal vs PreDM vs DM2 among lean and obese groups. Finally, the degree of decline in insulin secretion in lean subjects was compared with the magnitude of rise in insulin resistance in obese subjects with worsening glucose tolerance from normal subjects to subjects with diabetes. Statistical methods used for these comparisons were paired Student *t* test and analysis of variance. All data are reported as mean ± standard error of mean (SEM).

2. Results

Insulinogenic indices (I/G) determined at fasting, at first peak of insulin rise, and during entire 2 hours declined progressively from normal population to subjects with PreDM and

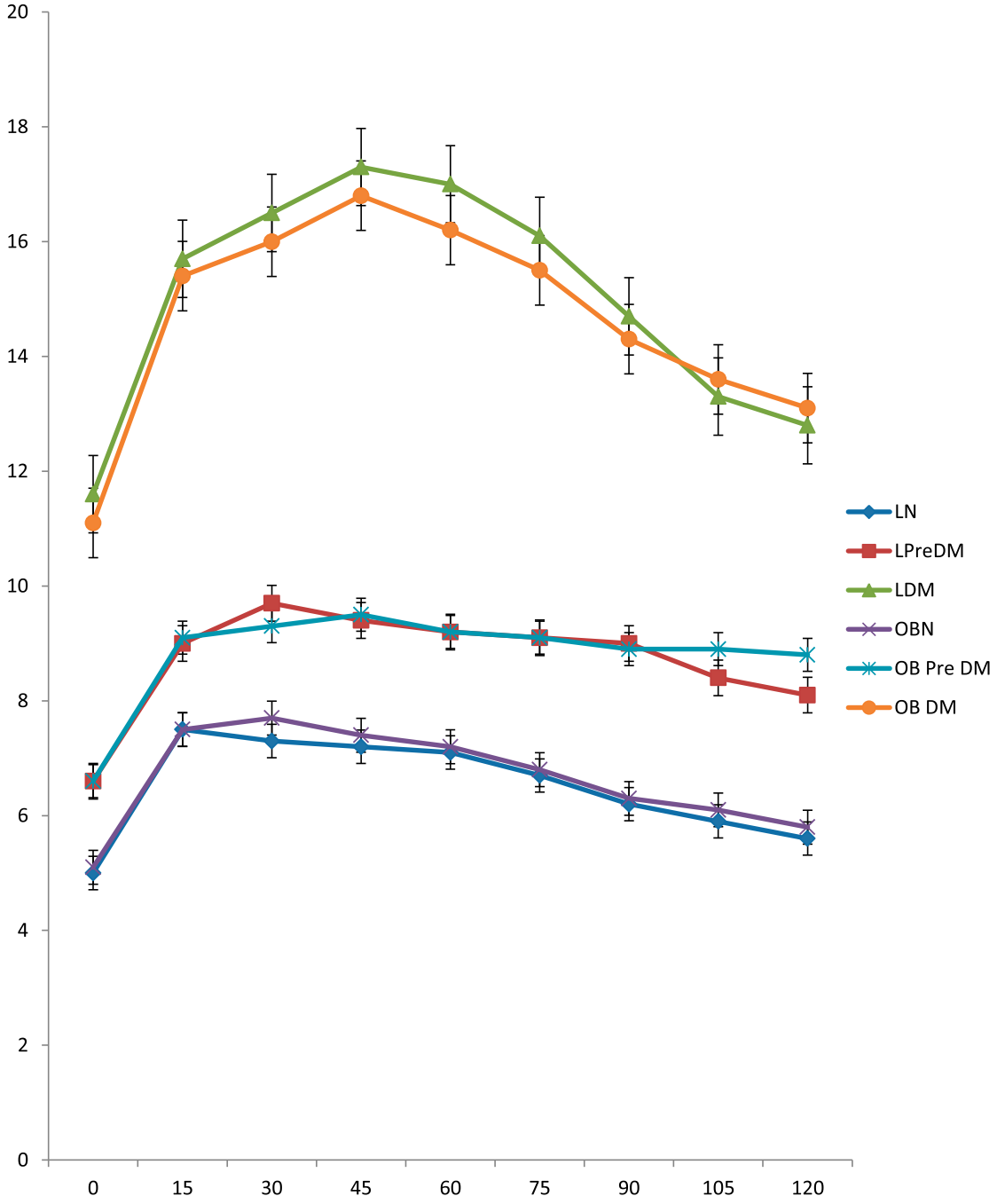

Figure 2. Plasma glucose concentration after an overnight fast and again at intervals of 15 minutes for 2 hours during 75-g OGTT.

further to subjects with DM2 in both lean and obese groups with changes being statistically significant among individual groups (Tables 1–3). Simultaneously, the markers of insulin resistance, Insulin × Glucose products rose progressively in both the lean and obese groups from normal subjects to the highest degree in subjects with DM2 with intermediate rise in subjects with PreDM (Tables 1–3). Moreover, both the indices of insulin secretion and insulin resistance were significantly lower in all individual lean groups when compared with the corresponding obese groups (Tables 1–3). However, the declines in indices of insulin secretion (Δ I/G) were significantly greater than the rises in markers of insulin resistance (Δ IxG) in lean subjects with PreDM as well as DM2 (Table 4). In contrast, the rises in markers of insulin

Table 1. Fasting Plasma Insulin (I), Fasting Plasma Glucose (G), I/G, and IxG in Lean (L) and Obese (Ob) Subjects With Euglycemia (N), PreDM, and DM2

Subjects	Insulin (μ U/mL)	Glucose (mm/L)	I/G	IxG
LN	7 ± 1	5.0 ± 0.3	1.42 ± 0.08	36 ± 5
LPreDM	7 ± 1	6.6 ± 0.5^{ab}	1.08 ± 0.07^{ab}	45 ± 6^{ab}
LDM2	6 ± 1	11.6 ± 2.3^{ab}	0.52 ± 0.03^{abc}	68 ± 8^{abc}
ObN	16 ± 3^{a}	5.1 ± 0.3	3.31 ± 0.20^{a}	81 ± 8^{a}
ObPreDM	18 ± 4^{a}	6.6 ± 0.4^{a}	2.6 ± 0.18^{ab}	120 ± 12^{ab}
ObDM2	22 ± 5^{b}	11.1 ± 2.8^{abc}	1.9 ± 0.1^{abc}	239 ± 32^{abc}

$^{a}P < 0.01$ vs LN.
$^{b}P < 0.01$ vs LN for LPreDM and LDM2; vs ObN for ObPreDM and ObDM2.
$^{c}P < 0.01$ vs PreDM among both L and Ob groups.

resistance (Δ IxG) were significantly higher than the decline in indices of insulin secretion (Δ I/G) in obese subjects with PreDM as well as DM2 (Table 4).

3. Discussion

This study demonstrates that the decline in insulin secretion is greater than the degree of rise in insulin resistance in lean (BMI $<$ 27 kg/m^2) American subjects with PreDM and DM2 as expressed by well-established methods [3–12]. Alternatively, the progression of insulin resistance is markedly more pronounced as compared with the fall in insulin secretion as determined by the same techniques in obese (BMI $\geq$ 27 kg/m^2) American population manifesting both PreDM and DM2 [3–12]. The finding of the progressive decline in insulin secretion being greater than the progressive rise in insulin resistance in the lean American population in this study is consistent with the previous data in the literature documented in lean European subjects, as well as a lean Asian cohort with euglycemia, PreDM, and DM2 [13–24]. However, this study is unique as it shows a comparison of indices of insulin secretion and insulin resistance between lean and obese American subjects. Moreover, this study alone documents that the fall in insulin secretion in lean is significantly greater than the rise in insulin resistance in obese with worsening glucose tolerance from normal subjects to subjects with DM2. None of the previous studies have documented this finding. Moreover, efficacy of lifestyle change and/or metformin in delaying progression of PreDM to DM2 in Indian, Chinese, and European nonobese subjects as defined by average BMI $<$ 27 kg/m^2 was documented to be significantly lower in comparison with the obese population in the United States as expressed by mean BMI $>$ 27 kg/m^2 [25–34]. Addition of pioglitazone to lifestyle intervention also failed to improve outcomes in terms of delaying progression to DM2 in Indian subjects with PreDM [35]. However, none of these studies reported efficacy in lean and

Table 2. First Phase Insulin Rise (ΔI) at the Time of Peak Glucose Concentration (ΔG), ΔI/ΔG, and ΔIxΔG in Lean (L) and Obese (Ob) Subjects With Euglycemia (N), PreDM, and DM2

Subjects	ΔI (μU/mL)	ΔG (mm/L)	ΔI/ΔG	ΔIxΔG
LN	13 ± 4	2.5 ± 0.3	5 26 ± 0.68	31 ± 4
LPreDM	10 ± 3	3.9 ± 0.5^{ab}	2.59 ± 0.55^{ab}	39 ± 4^{ab}
LDM2	8 ± 3	6.2 ± 0.9^{ab}	1.31 ± 0.23^{abc}	50 ± 7^{abc}
ObN	18 ± 3^{a}	2.4 ± 0.4	7.43 ± 0.71^{ab}	44 ± 5^{ab}
ObPreDM	17 ± 3^{a}	3.8 ± 0.5^{a}	4.51 ± 0.36^{ab}	66 ± 9^{ab}
ObDM2	13 ± 4^{b}	6.5 ± 0.8^{abc}	2.17 ± 0.2^{abc}	83 ± 12^{abc}

$^{a}P < 0.01$ vs LN.
$^{b}P < 0.01$ vs LN for LPreDM and LDM2.
$^{c}P < 0.01$ vs ObN for ObPreDM and ObDM2.

Table 3. Cumulative Responses (CR) for Insulin and Glucose as Well as Insulin Secretion (CRI/CRG) and Insulin Resistance (CRIxCRG) Over 2 Hours of OGTT in Lean (L) and Obese (Ob) Subjects With Euglycemia (N), PreDM, and DM2

Subjects	CRI (μU/mL)	CRG (mm/L)	CRI/CRG	CRI x CRG
LN	53 ± 8	13.4 ± 0.9	4.2 ± 0.5	708 ± 48
LPreDM	43 ± 6^{ab}	18.7 ± 1.4^{ab}	2.3 ± 0.3^{ab}	819 ± 57^{ab}
LDM2	34 ± 5^{ab}	30.5 ± 2.5^{ab}	1.2 ± 0.1^{ab}	1040 ± 68^{ab}
ObN	89 ± 14^{a}	14.1 ± 1.1^{a}	6.2 ± 0.6^{ab}	1258 ± 71^{ab}
ObPreDM	86 ± 10^{ab}	19.8 ± 2.6^{ab}	4.5 ± 0.4^{ab}	1701 ± 87^{ab}
ObDM2	72 ± 10^{ab}	31.8 ± 3.1^{abc}	2.7 ± 0.4^{abc}	2293 ± 103^{abc}

$^{a}P < 0.05$ vs LN.
$^{b}P < 0.01$ for LPreDM and LDM2 vs LN and for ObPreDM and ObDM2 vs. ObN.
$^{c}P < 0.01$ vs PreDM among both L and Ob groups.

obese cohorts as individual groups. The less beneficial outcome treated with lifestyle change and/or metformin or pioglitazone in terms of delaying progression to DM2 in nonobese subjects with PreDM may indicate the decline in insulin secretion to be the major pathophysiologic mechanism rather than rising insulin resistance as described in this and other studies [13–24] because metformin and pioglitazone are documented to possess minimal or no substantial stimulatory influence on insulin secretion [36–38]. In contrast, the delay in the progression to DM2 in obese subjects with PreDM in the United States by metformin may be attributed to blunting of insulin resistance, which plays a dominant role in the obese subjects with PreDM as documented in several reports [39–43]. In fact, several other recent studies have concluded that β-cell dysfunction played a major role in progression to diabetes in lean Asian Indians with PreDM, whereas rising insulin resistance was the main pathophysiologic factor in progression to DM2 in obese US population of subjects with PreDM [44–46]. Finally, a greater efficacy of glimepiride, an insulin secretagogue, in delaying progression of PreDM to DM2 in more lean American subjects and for a longer duration in comparison with the use of metformin in an American obese population demonstrated in a recent report adds credence to this hypothesis [2].The better efficacy of glimepiride in the lean population in this study may be attributed to its well-established major ability to stimulate both the first and second phase insulin secretions, as well as it minor effect on enhancing insulin sensitivity [5, 47–53].

Therefore, the contribution of progressively rising insulin resistance is greater than the fall in insulin secretion in impaired glucose metabolism in American as well as other obese populations with PreDM and DM2. In contrast, the major pathophysiologic mechanism in onset of PreDM and its progression to DM2 in the lean American and other populations may be the progressive decline in insulin secretion, whereas insulin resistance may play a minor role. Thus, the ADA recommendation of initial treatment of lean American and non-American

Table 4. Changes in Indices of Insulin Secretion (% Fall) and Insulin Resistance (% Rise) in Lean (L) and Obese (Ob) Subjects With PreDM and DM2 From Corresponding Groups of Subjects With Euglycemia (N)

	% Fall From N	% Rise From N	% Fall From N	% Rise From N
Subjects	ΔI/ΔG	ΔI x ΔG	CRI/CRG	CRI x CRG
LPreDM	51 ± 6^{a}	26 ± 3	45 ± 7^{a}	17 ± 2
LDM2	75 ± 8^{abc}	61 ± 6^{bc}	71 ± 8^{abc}	47 ± 6^{bc}
ObPreDM	39 ± 5^{ab}	50 ± 8^{b}	27 ± 3^{a}	38 ± 5^{b}
ObDM2	52 ± 8^{abc}	88 ± 10^{bc}	57 ± 7^{abc}	82 ± 9^{bc}

$^{a}P < 0.05$ for ΔI/ΔG vs ΔI x ΔG and CRI/CRG vs CRI x CRG.
$^{b}P < 0.01$ vs LPreDM.
$^{c}P < 0.01$ for LDM2 vs LPreDM and ObDM2 vs ObPreDM.

subjects with both PreDM and DM2 may not be appropriate. Moreover, lowering BMI for diagnosis of obesity and the treatment based on obesity in lean American population with PreDM and DM2 may not be appropriate as well. Rather, the treatment based on pathophysiology, *e.g.*, the decline in insulin secretion, administration of an insulin secretagogue may be more appropriate and beneficial as reported in the study showing better efficacy of glimepiride in delaying progression from PreDM to DM2 in lean subjects as compared with metformin in an obese population [2].

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