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 $\geq 25 \text{ kg/m}^2$ 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 $< 27 \text{ kg/m}^2$) subjects with IGM.

Objective: Assessment of IS and insulin resistance (IR) in L and obese (Ob; BMI $\geq 27 \text{ kg/m}^2$) 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 ($\Delta I/\Delta G$), and cumulative responses over 2 hours of OGTT (CRI/CRG), and IR by FIXFG, $\Delta IX\Delta G$, 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.

The American Diabetes Association (ADA) lowered body mass index (BMI) from $\geq 27 \text{ kg/m}^2$ to $\geq 25 \text{ kg/m}^2$ 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...
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/m²) and obese (BMI ≥ 27 kg/m²) 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 ± 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/m² and obese, BMI ≥ 27 kg/m². 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 × Glucose product (I×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.
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
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 (ΔI/G) were significantly greater than the rises in markers of insulin resistance (ΔIxG) in lean subjects with PreDM as well as DM2 (Table 4). In contrast, the rises in markers of insulin resistance...
resistance (ΔIxG) were significantly higher than the decline in indices of insulin secretion (ΔI/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/m²) 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 ≥ 27 kg/m²) 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/m² was documented to be significantly lower in comparison with the obese population in the United States as expressed by mean BMI > 27 kg/m² [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 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 (µU/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       | 1.08 ± 0.07     | 45 ± 6          |
| LDM2               | 6 ± 1           | 11.6 ± 2.3      | 0.52 ± 0.03     | 68 ± 8          |
| ObN                | 16 ± 3          | 5.1 ± 0.3       | 3.31 ± 0.20     | 81 ± 6          |
| ObPreDM            | 18 ± 4          | 6.6 ± 0.4       | 2.6 ± 0.18      | 120 ± 12        |
| ObDM2              | 22 ± 5          | 11.1 ± 2.8      | 1.9 ± 0.1       | 239 ± 32        |

*P < 0.01 vs LN.

| 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       | 2.59 ± 0.5      | 39 ± 4          |
| LDM2               | 8 ± 3           | 6.2 ± 0.9       | 1.31 ± 0.23     | 50 ± 7          |
| ObN                | 18 ± 3          | 2.4 ± 0.4       | 7.43 ± 0.71     | 44 ± 7          |
| ObPreDM            | 17 ± 3          | 3.8 ± 0.5       | 4.51 ± 0.36     | 66 ± 9          |
| ObDM2              | 13 ± 4          | 6.5 ± 0.8       | 2.17 ± 0.2      | 83 ± 1          |

*P < 0.01 vs LN.

bP < 0.01 vs LN for LPreDM and LDM2; vs ObN for ObPreDM and ObDM2.

cP < 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

| 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 ± 6ab    | 18.7 ± 1.4ab| 2.3 ± 0.3ab| 819 ± 57ab|
| LDM2      | 34 ± 5ab    | 30.5 ± 2.5ab| 1.2 ± 0.1ab| 1040 ± 62ab|
| ObN       | 89 ± 14ab   | 14.1 ± 1.1a | 6.2 ± 0.6ab| 1258 ± 71ab|
| ObPreDM   | 86 ± 10ab   | 19.8 ± 2.6ab| 4.5 ± 0.4ab| 1701 ± 87ab|
| ObDM2     | 72 ± 10ab   | 31.8 ± 3.1abc| 2.7 ± 0.4abc| 2293 ± 104abc|

αP < 0.05 vs LN.
βP < 0.01 for LPreDM and LDM2 vs LN and for ObPreDM and ObDM2 vs. ObN.
γP < 0.01 vs PreDM among both L and Ob groups.

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  | ΔI/ΔG  | ΔI x ΔG | CRI/CRG | CRI x CRG |
|-----------|--------|---------|---------|-----------|
| LPreDM    | 51 ± 6a| 26 ± 3  | 45 ± 7a | 17 ± 2    |
| LDM2      | 75 ± 8abc| 61 ± 6c | 71 ± 8abc| 47 ± 6bc  |
| ObPreDM   | 39 ± 5abc| 50 ± 8b | 27 ± 3a | 38 ± 5a   |
| ObDM2     | 52 ± 8abc| 88 ± 10bc| 57 ± 7abc| 82 ± 9bc  |

αP < 0.05 for ΔI/ΔG vs ΔI x ΔG and CRI/CRG vs CRI x CRG.
βP < 0.01 vs LPreDM.
γP < 0.01 for LDM2 vs LPreDM and ObDM2 vs ObPreDM.

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)
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 patho-
physiology, 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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References and Notes

1. American Diabetes Association. Standard of medical care. Diabetes Care. 2017;1(Suppl):S1–S24.
2. Kabadi UM. Comparative efficacy between glimepiride and metformin in preventing progression of
pre-diabetes to type 2 diabetes. J Diabetes Mellitus. 2013;3:129–133.
3. Seltzer HS, Allen EW, Herron AL, Jr, Brennan MT. Insulin secretion in response to glycemic stimulus:
relation of delayed initial release to carbohydrate intolerance in mild diabetes mellitus. J Clin Invest.
1967;46(3):323–335.
4. Kabadi UM, Eisenstein AB. Glucose intolerance in hyperthyroidism: role of glucagon. J Clin Endocrinol
Metab. 1980;56(2):392–396.
5. Kabadi MU, Kabadi UM. Effects of glimepiride on insulin secretion and sensitivity in patients with
recently diagnosed type 2 diabetes mellitus. Clin Ther. 2004;26(1):63–69.
6. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DR, Turner RC. Homeostatic model
assessment. Diabetologia. 1985;28:412–419.
7. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing:
comparison with the euglycemic insulin clamp. Diabetes Care. 1999;22(9):1462–1470.
8. Kanauchi M, Yamano S, Kanauchi K, Saito Y. Homeostasis model assessment of insulin resistance,
quantitative insulin sensitivity check index, and oral glucose insulin sensitivity index in nonobese,
nondiabetic subjects with high-normal blood pressure. J Clin Endocrinol Metab. 2003;88(7):3444–3446.
9. Clarke N, Sivitz W, Kabadi U. Product of fasting plasma glucose and fasting plasma insulin: a simple
and reliable index of insulin sensitivity. Diabetes Res. 2005;39:25–31.
10. Berntorp K, Eriksson KF, Lindgård E. The importance of diabetes heredity in lean subjects on insulin
secretion, blood lipids and oxygen uptake in the pathogenesis of glucose intolerance. J Diabetes Mellitus.
1986;3:231–236.
11. Kelley DE, Mokan M, Mandarino LJ. Metabolic pathways of glucose in skeletal muscle of lean NIDDM
patients. Diabetes Care. 1993;16(8):1158–1166.
12. Pigon J, Giacca A, Ostenson CG, Lam L, Vranic M, Efendic S. Normal hepatic insulin sensitivity in lean,
mild noninsulin-dependent diabetic patients. J Clin Endocrinol Metab. 1996;81(10):3702–3708.
16. Kim J, Choi S, Kong B, Oh Y, Shinn S. Insulin secretion and sensitivity during oral glucose tolerance test in Korean lean elderly women. *J Korean Med Sci*. 2001; 16(5):592–597.

17. Amoah AG, Owusu SK, Schuster DP, Osei K. Pathogenic mechanism of type 2 diabetes in Ghanaians—the importance of beta cell secretion, insulin sensitivity and glucose effectiveness. *S Afr Med J*. 2002; 92(5):377–384.

18. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, DeFronzo RA; San Antonio Metabolism Study. Beta-cell dysfunction and glucose intolerance: results from the San Antonio Metabolism (SAM) Study. *Diabetologia*. 2004; 47(1):31–39.

19. Alvarsson M, Wajngot A, Cerasi E, Efendic S. K-value and low insulin secretion in a non-obese white population: predicted glucose tolerance after 25 years. *Diabetologia*. 2005; 48(11):2262–2268.

20. Elder DA, Prigeon RL, Wadwa RP, Dolan LM, D’Alessio DA. Beta-cell function, insulin sensitivity, and glucose tolerance in obese diabetic and nondiabetic adolescents and young adults. *J Clin Endocrinol Metab*. 2006; 91(1):185–191.

21. Tura A, Mari A, Winzer C, Kautzky-Willer A, Pacini G. Impaired beta-cell function in lean normo-tolerant former gestational diabetic women. *Eur J Clin Invest*. 2006; 36(1):22–28.

22. P B. The lean patient with type 2 diabetes: characteristics and therapy challenge. *Int J Clin Pract Suppl*. 2007; (133):76–81.

23. Suraamornkul S, Kwancharoen R, Ovartlarnporn M, Rawdaree P, Bajaj M. Insulin clamp-derived measurements of insulin sensitivity and insulin secretion in lean and obese Asian type 2 diabetic patients. *Metab Syndr Relat Disord*. 2010; 8(2):113–118.

24. Morimoto A, Tatsumi Y, Deura K, Mizuno S, Ohno Y, Miyamatsu N, Watanabe S. Impact of impaired insulin secretion and insulin resistance on the incidence of type 2 diabetes mellitus in a Japanese population: the Sakub study. *Diabetologia*. 2013; 56(8):1671–1679.

25. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V; Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia*. 2006; 49(2):289–297.

26. Nanditha A, Snehalatha C, Ram J, Selvam S, Vijaya L, Shetty SA, Arun R, Ramachandran A. Impact of lifestyle intervention in primary prevention of Type 2 diabetes did not differ by baseline age and BMI among Asian-Indian people with impaired glucose tolerance. *Diabet Med*. 2016; 33(12):1700–1704.

27. Weber MB, Ranjani H, Stainmez LR, Anjana RM, Ali MK, Narayan KM, Mohan V. The stepwise approach to diabetes prevention: results from the D-CLIP Randomized Controlled Trial. *Diabetes Care*. 2016; 39(10):1760–1767.

28. de Mello VD, Lindström J, Eriksson J, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Sundvall J, Laakso M, Tuomilehto J, Uusitupa M. Insulin secretion and its determinants in the progression of impaired glucose tolerance to type 2 diabetes in impaired glucose-tolerant individuals: the Finnish Diabetes Prevention Study. *Diabetes Care*. 2012; 35(2):211–217.

29. Lindström J, Peltonen M, Eriksson JG, Ilanne-Parikka P, Aurola S, Keinänen-Kiukaanniemi S, Uusitupa M, Tuomilehto J; Finnish Diabetes Prevention Study (DPS). Improved lifestyle and decreased diabetes risk over 13 years: long-term follow-up of the randomised Finnish Diabetes Prevention Study (DPS). *Diabetologia*. 2013; 56(2):284–293.

30. Wylie-Rosett J, Herman WH, Goldberg RB. Lifestyle intervention to prevent diabetes: intensive and cost effective. *Curr Opin Lipidol*. 2006; 17(1):37–44.

31. Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q, Li H, Li H, Jiang Y, An Y, Shuai Y, Zhang B, Zhang J, Thompson TJ, Gerzof RB, Roglic G, Hu Y, Bennett PH. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet*. 2008; 371(9623):1783–1789.

32. Li G, Zhang P, Wang J, An Y, Gong Q, Gregg EW, Yang W, Zhang B, Shuai Y, Hong J, Engelgau MM, Li H, Roglic G, Hu Y, Bennett PH. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. *Lancet Diabetes Endocrinol*. 2014; 2(6):474–480.

33. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002; 346(6):393–403.

34. O’Brien MJ, Whitaker RC, Yu D, Ackermann RT. The comparative efficacy of lifestyle intervention and metformin by educational attainment in the Diabetes Prevention Program. *Prev Med*. 2015; 77:125–130.

35. Ramachandran A, Snehalatha C, Mary S, Selvam S, Kumar CK, Seeli AC, Shetty SA. Pioglitazone does not enhance the effectiveness of lifestyle modification in preventing conversion of impaired glucose
tolerance to diabetes in Asian Indians: results of the Indian Diabetes Prevention Programme-2 (IDPP-2). *Diabetologia*. 2009;52(6):1019–1026.

36. Binnert C, Seematter G, Tappy L, Giusti V. Effect of metformin on insulin sensitivity and insulin secretion in female obese patients with normal glucose tolerance. *Diabetes Metab*. 2003;29(2 Pt 1): 125–132.

37. Vuković M, Lapečević M, Kalezić N, Gvozdenović BS. [The effect of metformin on fasting and postprandial insulin secretion in obese patients with diabetes mellitus type 2]. *Srps Arh Celok Lek*. 2007; 135(7-8):447–452.

38. Lamontagne J, Pepin E, Peyot ML, Joly E, Ruderman NB, Poitout V, Madiraju SR, Nolan CJ, Prentki M. Pioglitazone acutely reduces insulin secretion and causes metabolic deceleration of the pancreatic beta-cell at submaximal glucose concentrations. *Endocrinology*. 2009;150(8):3465–3474.

39. Vardarli I, Arndt E, Deacon CF, Holst JJ, Nauck MA. Effects of sitagliptin and metformin treatment on incretin hormone and insulin secretory responses to oral and “isoglycemic” intravenous glucose. *Diabetes*. 2014;63(2):663–674.

40. Widén EI, Eriksson JG, Groop LC. Metformin normalizes nonoxidative glucose metabolism in insulin-resistant normoglycemic first-degree relatives of patients with NIDDM. *Diabetes*. 1992;41(3):354–358.

41. Iannello S, Camuto M, Cavaleri A, Milazzo P, Pisanò MG, Bellomia D, Belfiore F. Effects of short-term metformin treatment on insulin sensitivity of blood glucose and free fatty acids. *Diabetes Obes Metab*. 2004;6(1):8–15.

42. Malin SK, Gerber R, Chipkin SR, Braun B. Independent and combined effects of exercise training and metformin on insulin sensitivity in individuals with prediabetes. *Diabetes Care*. 2012;35(1):131–136.

43. Krysiak R, Okopien B. Haemostatic effects of metformin in simvastatin-treated volunteers with impaired fasting glucose. *Basic Clin Pharmacol Toxicol*. 2012;111(6):380–384.

44. Snehalatha C, Mary S, Selvam S, Sathish Kumar CK, Shetty SB, Nanditha A, Ramachandran A. Changes in insulin secretion and insulin sensitivity in relation to the glycemic outcomes in subjects with impaired glucose tolerance in the Indian Diabetes Prevention Programme-1 (IDPP-1). *Diabetes Care*. 2009;32(10):1796–1801.

45. Nanditha A, Ram J, Snehalatha C, Selvam S, Priscilla S, Shetty AS, Arun R, Godeland IF, Johnston DG, Ramachandran A. Early improvement predicts reduced risk of incident diabetes and improved cardiovascular risk in prediabetic Asian Indian men participating in a 2-year lifestyle intervention program. *Diabetes Care*. 2014;37(11):3009–3015.

46. Gujral UP, Mohan V, Pradeepa R, Deepa M, Anjana RM, Mehta NK, Gregg EW, Narayan K. Ethnic variations in diabetes and prediabetes prevalence and the roles of insulin resistance and β-cell function: the CARRS and NHANES studies. *J Clin Transl Endocrinol*. 2016;4:19–27.

47. Sonnenberg GE, Garg DC, Weidler DJ, Dixon RM, Jaber LA, Bowen AJ, DeChamley GS, Mullican WS, Stonesifer LD. Short-term comparison of once- versus twice-daily administration of glimepiride in patients with non-insulin-dependent diabetes mellitus. *Ann Pharmacother*. 1997;31(6):671–676.

48. Korytkowski M, Thomas A, Reid I, Tedesco MB, Gooding WE, Gerich J. Glimepiride improves both first and second phases of insulin secretion in type 2 diabetes. *Diabetes Care*. 2002;25(9):1607–1611.

49. Singh J, Umnikrishnan AG, Agrawal NK, Singh SK, Agrawal JK. Immunoreactive insulin response to a single dose of glimepiride in lean type 2 diabetic subjects. *J Assoc Physicians India*. 2002;50:1232–1235.

50. Sato J, Ohsawa I, Oshida Y, Sato Y, Sakamoto N. Effects of glimepiride on in vivo insulin action in normal and diabetic rats. *Diabetes Res Clin Pract*. 1993;22(1):3–9.

51. Muller G, Satoh Y, Geisen K. Extrapancreatic effects of sulfonylureas—a comparison between glimepiride and conventional sulfonylureas. *Diabetes Res Clin Pract*. 1995;28(Suppl):S115–S137 (Review).

52. Raptis SA, Hatzigelaki E, Dimitriadis G, Draeger KE, Pfeiffer C, Raptis AE. Comparative effects of glimepiride and glibenclamide on blood glucose, C-peptide and insulin concentrations in the fasting and postprandial state in normal man. *Exp Clin Endocrinol Diabetes*. 1998;107(6):350–355.

53. Kabadi UM, Kabadi M. Comparative efficacy of glimepiride and/or metformin with insulin in type 2 diabetes. *Diabetes Res Clin Pract*. 2006;72(3):265–270.