

How Does Pioglitazone Prevent Progression of Impaired Glucose Tolerance to Diabetes?

Saul M. Genuth

It is now common knowledge that we are in the midst of a worldwide epidemic of type 2 diabetes (T2D). This disease occurs disproportionately in African Americans, Hispanic Americans, and other minorities. T2D is a major cause of cardiovascular disease morbidity and mortality, and these unfavorable outcomes are greatly increased in the presence of T2D (1–4). Impaired glucose tolerance (IGT) is itself a risk factor for cardiovascular disease (5). Obesity and IGT are each major risk factors for T2D, with yearly incidence of T2D in individuals with IGT ranging from 3.9 to 8.7% in various American populations, with an average of 5.7% (6), and averaging 6.5% in a meta-analysis of global studies (7). Both insulin resistance and diminished β -cell function (insulin secretion) are crucial pathogenetic factors in the progression from IGT to T2D, with the proportional impact of these defects varying in different reports and populations (8). The rate of progression can be reduced by lifestyle modification leading to weight loss (9) and the use of metformin (9), the thiazolidinedione drugs pioglitazone (PIO) (10) and rosiglitazone (11), α -glucosidase inhibitors (12), sulfonylureas (13), and insulin (14). Selection of therapeutic agents could be enhanced by matching their dominant actions on insulin resistance and/or β -cell dysfunction to the relative dominance of these abnormalities in specific individuals or populations with IGT.

For the above reasons, the study by DeFronzo et al. (15) in this issue is of particular interest. In the Actos Now for the prevention of diabetes (ACT NOW) study (10), which included 602 high-risk IGT patients, PIO reduced the progression to T2D over 2.4 years from an annual incidence of 7.6% in the placebo (PLAC) group by 72% (95% CI 51–84%); 48% of the PIO group reverted to normal glucose tolerance (NGT) compared with 28% in the PLAC group ($P < 0.001$). In the current report, 441 (73%) of these subjects had oral glucose tolerance tests at baseline and at study completion, with sampling of plasma glucose, insulin, and C-peptide. The protocol permitted calculation of insulin sensitivity by the Matsuda Index (16) as well as insulin secretion rate using plasma insulin and deconvolution of plasma C-peptide (17). Insulin sensitivity increased 92% in the PIO group compared with 17% in the PLAC group ($P = 0.002$), whereas insulin secretion rate increased 33% in the PLAC group compared with 11% in the PIO group ($P < 0.001$). The

Disposition Index (insulin secretion rate/insulin resistance) increased 66% with PIO compared with 12% with PLAC ($P < 0.001$). The focus of DeFronzo et al., however, was on the relative changes from baseline of these derived parameters of glucose metabolism. Subjects were grouped into three categories according to their follow-up oral glucose tolerance tests: progression to T2D ($N = 15$ PIO and 45 PLAC), no change in IGT status, and reversion to NGT. In subjects who reverted to NGT, insulin sensitivity was increased 96% with PIO compared with PLAC, whereas insulin sensitivity changed little in those who progressed to T2D in either group. Insulin secretion in response to glucose declined with PIO and PLAC in those who progressed to T2D. Of importance, the Disposition Index fell slightly and similarly in both these groups.

In an analytical tour de force, a plot of incidence of T2D in the combined PIO and PLAC groups was negatively associated with octiles of the decrease in the natural logarithm of the Disposition Index with an extraordinary correlation coefficient of 0.99. The use of the somewhat unusual octiles reflected a curvilinear association between the variables. While this exceedingly strong association was driven by an outlier value at the lowest octile of the Disposition Index that corresponded to the highest incidence of diabetes, the remaining 7 points yielded a visually convincing but much more shallow curvilinear association. IGT subjects who experienced a $>80\%$ improvement in the Disposition Index had an approximate 2% incidence of diabetes whereas the incidence was 14% in those whose Disposition Index declined 60–80%.

Better final glucose tolerance status (NGT $>$ IGT $>$ T2D) was categorically associated with increase in insulin sensitivity (odds ratio [OR] = 0.61), insulin secretion (OR = 0.61), and Disposition Index (OR = 0.26). In multivariate analyses of factors associated with end of study outcome, NGT and IGT data were combined and compared with T2D. In the PIO group, the combined favorable outcome was associated with a 21% increase in insulin secretion rate, and a 70% increase in insulin secretion in response to glucose. There was a 109% increase in insulin sensitivity comparing only the group who reverted from IGT to NGT to the group that did not.

In assessing all of these impressive results, several points should be considered. The authors strongly assert that the overall conclusions indicate that improvement in β -cell function, i.e., the Disposition Index, is the dominant factor associated with final glucose tolerance status, and that the beneficial effect of PIO on reduced progression to T2D or increased reversion to NGT is largely attributable to the thiazolidinedione effect on this factor (OR = 0.26). This conclusion is consistent with most previous reports showing that insulin resistance is a factor in the earlier stages of IGT (8,18) whereas deteriorating insulin secretion in response to glucose is a later determinant of worsening glucose tolerance and severity of T2D (19). Hence,

From the School of Medicine, Case Western Reserve University, Cleveland, Ohio.

Corresponding author: Saul M. Genuth, smg15@case.edu.

DOI: 10.2337/db13-1175

© 2013 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

See accompanying original article, p. 3920.

the decrease in conversion rate of IGT to T2D reflects less deterioration of β -cell function in the PIO group. However, the Disposition Index incorporates both of these functional parameters of glucose metabolism, and increases in both insulin sensitivity and insulin secretion were individually associated with the final impact of PIO therapy.

This should not be surprising. Although the temporal sequence of insulin resistance and diminished β -cell responsiveness cited above is widely accepted and appears logical, this does not mean that they are independent events. Several animal models support a homeostatic relationship between insulin sensitivity and insulin secretion (Fig. 1). Decreased sensitivity to insulin elicits production, especially by the liver, of betatrophin, a molecule that stimulates proliferation of β -cells, expansion of β -cell mass, and improvement in glucose tolerance in experimental animals (20). Moreover, insulin resistance—specifically at the level of the β -cell—impairs first phase insulin secretion in response to glucose (21).

Thus, there are two ways to interpret PIO's effects on the Disposition Index and its individual components (Fig. 1). The most straightforward is that PIO is a thiazolidinedione and has positive actions on both insulin sensitivity in its target tissues as well as on β -cell function (22). Plasma glucose homeostasis is thereby maintained at an acceptable level because PIO only rarely causes hypoglycemia. A second speculative construct is to posit a brain regulating center with overall control of total body insulin action (Fig. 1). When there is need for more total body insulin action on all its target tissues, in addition to its effects on glucose metabolism, this center would simultaneously increase insulin sensitivity and insulin secretion. Of course, there would be need for a negative feedback plasma/intracellular glucose brake on the output of such neurons

to prevent hypoglycemia. PIO has been shown to affect glucose metabolism in brain cells (23). The possibility that the ultimate seat of T2D could lie in the brain has also been suggested before (24), given the importance of insulin in regulating energy expenditure and storage through central as well as peripheral effects. PIO could presumably act by stimulating the output of such putative neurons. These two alternative mechanisms of PIO action, peripheral and central, need not be mutually exclusive.

These speculative ruminations aside, the main importance of the observations by DeFronzo et al. may be to encourage further development of T2D treatments that have ameliorative effects on glucose dysmetabolism, but less severe and less frequent adverse effects on the risks of congestive heart failure (25), fractures (26), and possibly bladder cancer (27). Their observations on the natural history of progression or reversion of IGT could also be applied to modification or development of other therapeutic agents. From bedside to bench and back to bedside should be a productive therapeutic path to follow.

ACKNOWLEDGMENTS

No potential conflicts of interest relevant to this article were reported.

REFERENCES

- Laakso M. Hyperglycemia and cardiovascular disease in type 2 diabetes. *Diabetes* 1999;48:937–942
- Wilson PW. Diabetes mellitus and coronary heart disease. *Endocrinol Metab Clin North Am* 2001;30:857–881
- Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;16:434–444
- Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Ann Intern Med* 2004;141:413–420
- Ford ES, Zhao G, Li C. Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. *J Am Coll Cardiol* 2010;55:1310–1317
- Edelstein SL, Knowler WC, Bain RP, et al. Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. *Diabetes* 1997;46:701–710
- Gerstein HC, Santaguida P, Raina P, et al. Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. *Diabetes Res Clin Pract* 2007;78:305–312
- Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia* 2003;46:3–19
- Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403
- DeFronzo RA, Tripathy D, Schwenke DC, et al.; ACT NOW Study. Pioglitazone for diabetes prevention in impaired glucose tolerance. *N Engl J Med* 2011;364:1104–1115
- Gerstein HC, Yusuf S, Bosch J, et al.; DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006;368:1096–1105
- Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002;359:2072–2077
- Eriksson JG, Lehtovirta M, Ehrnström B, Salmela S, Groop L. Long-term beneficial effects of glipizide treatment on glucose tolerance in subjects with impaired glucose tolerance. *J Intern Med* 2006;259:553–560
- Bolli GB, Consoli A, Giaccari A. Early insulin treatment in type 2 diabetes: ORIGINAL sin or ORIGINAL choice as ORIGINAL treatment? An open debate on the ORIGIN study results. *Nutr Metab Cardiovasc Dis* 2012;22:1007–1012

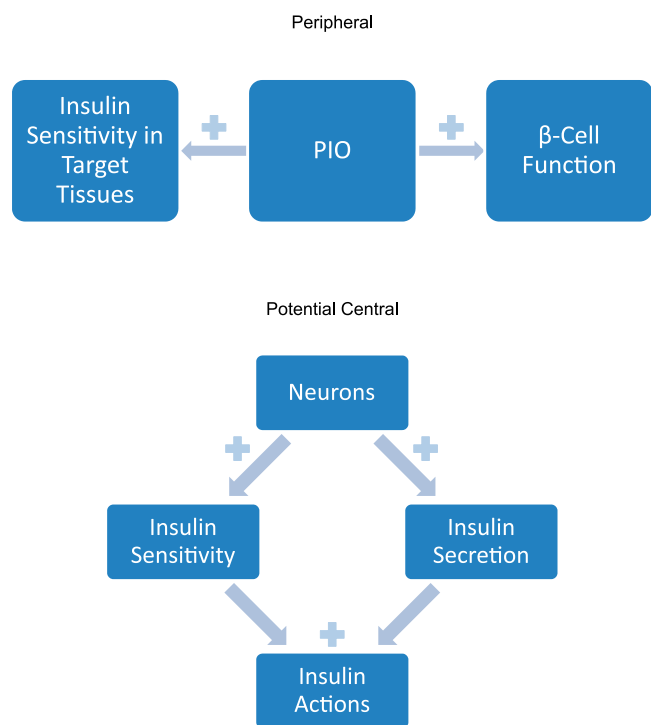


FIG. 1. Established and speculative beneficial effects of PIO.

15. DeFronzo RA, Tripathy D, Schwenke DC, et al.; for the ACT NOW Study. Prevention of diabetes with pioglitazone in ACT NOW: physiologic correlates. *Diabetes* 2013;62:3920–3926
16. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 1999;22:1462–1470
17. Van Cauter E, Mestrez F, Sturis J, Polonsky KS. Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance. *Diabetes* 1992;41:368–377
18. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 1999;104:787–794
19. Turner RC, Cull CA, Frighi V, Holman RR; UK Prospective Diabetes Study (UKPDS) Group. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *JAMA* 1999;281:2005–2012
20. Yi P, Park JS, Melton DA. Betatrophin: a hormone that controls pancreatic β cell proliferation. *Cell* 2013;153:747–758
21. Kulkarni RN, Brüning JC, Winnay JN, Postic C, Magnuson MA, Kahn CR. Tissue-specific knockout of the insulin receptor in pancreatic beta cells creates an insulin secretory defect similar to that in type 2 diabetes. *Cell* 1999;96:329–339
22. Yki-Jarvinen H. Drug therapythiazolidinediones *N Engl J Med* 2004;351:1106–1118
23. Dello Russo C, Gavriluk V, Weinberg G, et al. Peroxisome proliferator-activated receptor gamma thiazolidinedione agonists increase glucose metabolism in astrocytes. *J Biol Chem* 2003;278:5828–5836
24. Porte D Jr, Seeley RJ, Woods SC, Baskin DG, Figlewicz DP, Schwartz MW. Obesity, diabetes and the central nervous system. *Diabetologia* 1998;41:863–881
25. Erdmann E, Charbonnel B, Wilcox RG, et al.; PROactive investigators. Pioglitazone use and heart failure in patients with type 2 diabetes and pre-existing cardiovascular disease: data from the PROactive study (PROactive 08). *Diabetes Care* 2007;30:2773–2778
26. Dormandy J, Bhattacharya M, van Troostenburg de Bruyn AR; PROactive investigators. Safety and tolerability of pioglitazone in high-risk patients with type 2 diabetes: an overview of data from PROactive. *Drug Saf* 2009;32:187–202
27. Lewis JD, Ferrara A, Peng T, et al. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. *Diabetes Care* 2011;34:916–922