Prevention of Type 2 Diabetes

Insulin Resistance and β-Cell Function

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Type 2 diabetes is increasing worldwide in epidemic proportions. Its associated morbidity and mortality is imposing a major burden on the health care system. Based on a better understanding of the pathophysiology of glucose intolerance, clinical trials on the prevention of diabetes have been performed. It has now been demonstrated that diet and exercise, metformin, acarbose, and troglitazone can prevent or at least delay the development of diabetes in subjects with impaired glucose tolerance (IGT). It is now generally accepted that insulin resistance and β-cell dysfunction are major factors involved in the development of diabetes. The relative contribution of insulin resistance versus β-cell dysfunction on the pathogenesis of diabetes has aroused much debate. These two processes should be studied in relation to one another: their relationship is best described as hyperbolic in nature. When this relationship is taken into consideration, it becomes evident that subjects at risk of developing type 2 diabetes have β-cell dysfunction before they develop glucose intolerance. Insulin resistance may be mostly explained by the presence of obesity and accelerate the progression to diabetes in subjects with the propensity to β-cell failure. By the time hyperglycemia occurs, impairment in both insulin sensitivity and insulin secretion are present. There are still few data on insulin sensitivity and insulin secretion from the trials on the prevention of diabetes. The few data that we do have suggest that most interventions mostly have an effect on insulin resistance. By reducing insulin resistance, they protect and preserve the β-cell function. No intervention has yet shown any direct effect on β-cell function. *Diabetes* 53 (Suppl. 3):S34–S38, 2004

The prevalence of type 2 diabetes is increasing in epidemic proportions worldwide. It has been estimated that the diabetic population will double from 150 to 300 million in the next 25 years (1). Furthermore, the long-term complications associated with diabetes are major causes of morbidity and mortality, imposing a high financial burden on health care costs (2–4). Type 2 diabetes will certainly be one of the major diseases of the 21st century and should be recognized as a priority.

It is now well established that the development of type 2 diabetes results from the interaction between the genetic makeup of the individuals and their environment (5). The development of obesity seems to be an important factor in the development of insulin resistance (6,7). If this insulin resistance occurs in the presence of a genetically determined propensity to β-cell dysfunction, glucose intolerance can occur (5). Although there is still disagreement over the relative contribution in the alterations in insulin sensitivity versus β-cell function in the development of diabetes, it is becoming clear that reductions in both processes have already occurred by the time hyperglycemia develops (8).

The concept for the prevention of diabetes developed on the basis of a better understanding of the pathophysiology of glucose intolerance and stimulated by the ever-increasing burden of the disease. It has now been demonstrated that diabetes can be prevented, or at least delayed, by nonpharmacological interventions, such as lifestyle modification including diet and exercise (9–11), and by pharmacological intervention, including metformin (11), acarbose (12), and troglitazone (13) (Table 1).

The purpose of this article is to discuss the mechanism(s) involved in the prevention of type 2 diabetes by those different interventions. Is it through an effect on insulin resistance and/or insulin secretion or through some other mechanisms? In the first part, we will briefly review the pathophysiology of type 2 diabetes. In the second part, we will describe the major intervention trials on the prevention of type 2 diabetes and discuss the probable mechanism(s) involved in the prevention of diabetes.

THE PATHOPHYSIOLOGY OF TYPE 2 DIABETES

For a more detailed discussion on the pathogenesis of type 2 diabetes, we refer the readers to the recent review article by Kahn (14). For the purpose of our discussion, we will briefly discuss insulin resistance, insulin secretion, and their interactions in the development of type 2 diabetes.

Several longitudinal studies have clearly shown that insulin resistance is a major risk factor for the development of type 2 diabetes (15,16). In a prospective study of Pima Indians, Lillioja et al. (15) studied the relative roles of obesity, insulin resistance, and β-cell dysfunction in the development of type 2 diabetes in subjects with normal glucose tolerance (n = 151) or impaired glucose tolerance (IGT) (n = 49). All subjects had body composition assessment, oral and intravenous glucose tolerance tests, and a

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FSIVGTT, frequently sampled intravenous glucose tolerance test; IGT, impaired glucose tolerance.

TABLE 1
Intervention studies on the prevention of type 2 diabetes

Studies (ref. no.)	No. of subjects	Interventions	Follow-up (years)	Relative risk reduction (%)
Lifestyle modifications				
Da Qing (1997) (9)	577	Diet and/or exercise	6.0	39
DPS (2001) (10)	522	Diet and exercise	3.2	58
DPP (2002) (11)	2,161	Diet and exercise	2.8	58
Drug interventions				
DPP (2002) (11)	2,151	Metformin	2.8	31
TRIPOD (2002) (13)	236	Troglitazone	2.5	50
STOP-NIDDM (2002) (12)	1429	Acarbose	3.3	36

hyperinsulinemic-euglycemic clamp study. The insulin resistance was the strongest single predictor for diabetes, with a 27% cumulative incidence of diabetes over 6 years (Fig. 1). The acute plasma insulin response alone was not a significant predictor for diabetes. However, the combination of insulin resistance and insulin response provided the strongest predictor with a 6-year cumulative incidence of diabetes of 39%. They concluded that insulin resistance was a major risk factor for the development of diabetes, with insulin secretion being an additional but weaker risk factor (15). Warram et al. (17) followed for 25 years 155 offspring of couples who both had type 2 diabetes. Subjects who developed diabetes had insulin resistance >10 years before they developed the disease. However, they found no evidence of an insulin secretion defect several years before the development of diabetes. In a few subjects, they noticed a gradual decline in insulin secretory capacity before the onset of diabetes. These observations argue in favor of insulin resistance as the primary defect in the development of diabetes. The major argument supporting insulin resistance as a primary genetic factor leading to diabetes is the observations that its appearance precedes detection of impaired β-cell function (17,18). However, Gerich (19) claims that the influence of obesity needs to be taken into consideration and that people at risk for diabetes are not insulin resistant relative to appropriate control, i.e., obese control! Moreover, although many obese subjects are insulin resistant, most of them do not progress to diabetes.

Vaag et al. (20) studied monozyzotic twins, one of whom already had diabetes and one of whom had either normal glucose tolerance or IGT. Those with normal glucose tolerance or IGT had decreased first-phase insulin release, while only those with IGT also had a significant reduction in insulin sensitivity compared with appropriate control (Fig. 2). This study provides evidence that impairment of β-cells can occur before insulin resistance is detectable. However, both seem to be present by the time hyperglycemia appears. Other reports have confirmed those observations in offspring of two parents with type 2 diabetes (17) or first-degree relatives of someone with type 2 diabetes (21,22). Taken together, these observations provide strong evidence that β-cell dysfunction is already present in normal glucose-tolerant individuals genetically predisposed to develop type 2 diabetes. It also suggests that insulin resistance can be attributed mostly to obesity and/or reduced physical fitness. This is suggested by a number of studies indicating that weight loss will reverse the insulin resistance (23–25) without normalizing the insulin secretory defect.

In interpretation of these observations, it is most often lost to the observers that insulin sensitivity is itself a determinant of the magnitude of the insulin response. Thus, insulin-resistant subjects have a greater insulin response to glucose, whereas insulin-sensitive subjects have a smaller insulin response (26). The relationship between insulin sensitivity and insulin secretion has been described as a hyperbolic relationship. The nature of this relationship implies that the product of insulin sensitivity and insulin response is a constant at a given degree of glucose tolerance (26) (Fig. 3). Therefore, when insulin sensitivity varies, a proportional and reciprocal alteration

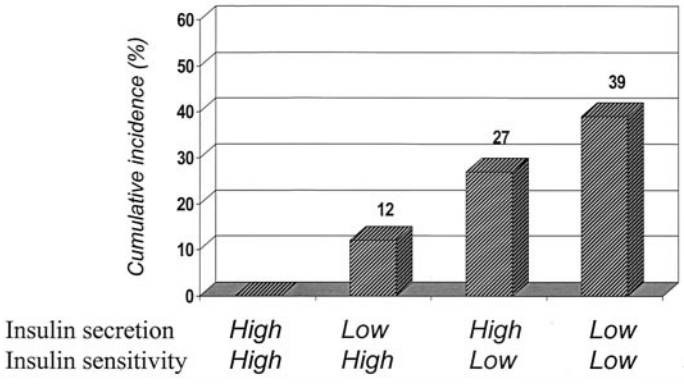

FIG. 1. Six-year cumulative incidence of diabetes according to insulin sensitivity and insulin secretion. Adapted from Lillioja et al. (15).

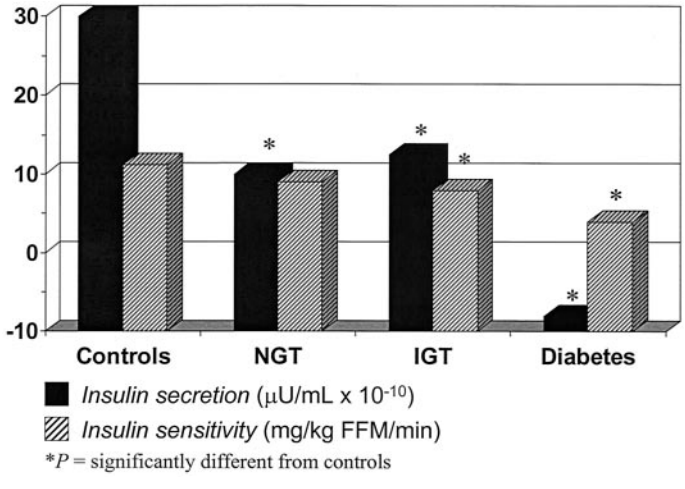

FIG. 2. Insulin secretion and insulin sensitivity in monozygotic twins with normal glucose tolerance, impaired glucose tolerance, or diabetes. Adapted from Vaag et al. (20).

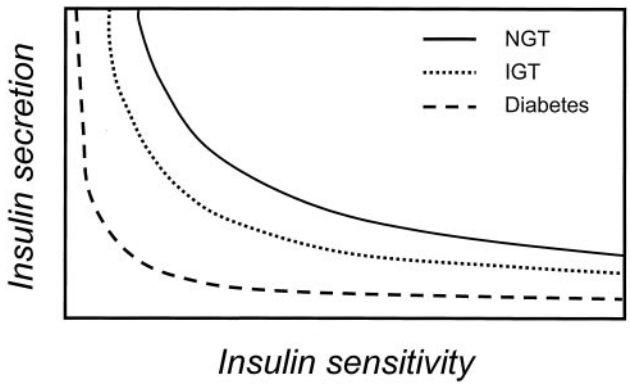

FIG. 3. Schematic representation of hyperbolic relationship between insulin sensitivity and insulin secretion in subjects with different glucose tolerance. NGT, normal glucose tolerance. Adapted from Kahn et al. (26).

in insulin output has to occur for glucose tolerance to remain constant. As such, the product of insulin sensitivity and insulin response provides a better measurement of β-cell function rather than the insulin or C-peptide response examined in isolation. When this relationship between insulin sensitivity and insulin secretion is taken into consideration, it becomes evident that subjects who are at high risk of developing type 2 diabetes have demonstrated β-cell dysfunction at a time when they still have normal glucose tolerance. The first-degree relatives of patients with diabetes (27–29) and subjects with IGT (30,31) can all be shown to have β-cell dysfunction that is reduced relative to the degree of insulin sensitivity. These cross-sectional data are also supported by a longitudinal study in Pima Indians who had normal glucose tolerance at baseline (32). Those who developed diabetes had a 78% decline in insulin secretion and a 14% decrease in insulin sensitivity (Fig. 4). On the other hand, those who did not develop diabetes also had an 11% decrease in insulin sensitivity, but the change was associated with a 30% increase in insulin secretion. In this latter group, the relationship between insulin sensitivity and insulin release was maintained. Close examination of these responses therefore show the presence of impaired β-cell function in subjects at risk of developing diabetes, even when these subjects still have normal glucose tolerance. This is further supported by a recent study from Ferrannini et al. (33), who demonstrated a defect in glucose sensitivity and insulin release in IGT subjects that predominated over insulin resistance.

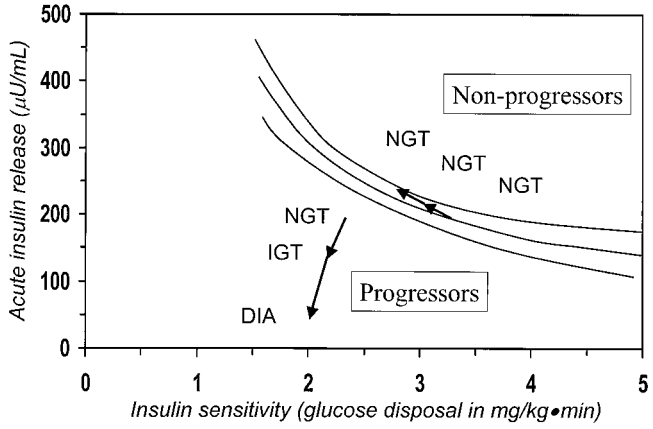

FIG. 4. Changes in β-cell function and in insulin sensitivity at low insulin concentration with the development of glucose intolerance. Adapted from Weyer et al. (32).

In summary, insulin resistance seems to be explained mostly by the presence of obesity. In fact, weight reduction is associated with a normalization of insulin sensitivity. On the other hand, β-cell dysfunction is present years before glucose intolerance appears, and no intervention has yet been able to correct this abnormality. This would support the concept that β-cell failure is the primary defect leading to the development of diabetes. Insulin resistance, acquired though obesity, and decreased physical activity will further accelerate the progression to diabetes. This would explain the epidemic explosion of diabetes in a world getting fatter and more sedentary.

THE PREVENTION OF DIABETES: AN EFFECT ON INSULIN SENSITIVITY AND/OR INSULIN SECRETION?

The major intervention trials on the prevention of diabetes are relatively recent, and analysis of the data is ongoing (Table 1). For that reason, we still do not have published data on insulin sensitivity and insulin secretion for those studies.

A number of observational studies suggested that weight loss and physical activity could reduce the risk of developing diabetes (34–36). Three prospective intervention studies have now confirmed the efficacy of lifestyle modification, including diet and exercise (9–11), in reducing the risk of type 2 diabetes in a high-risk population with IGT. The Da Qing Study (37) was the first to show in 577 subjects with IGT that diet and/or exercise could lower the risk of diabetes by 39% over 6 years. Using homeostasis model assessment (HOMA), the authors have looked at the effect of insulin resistance and β-cell dysfunction on the incidence of diabetes in a subgroup of patients ($n = 284$) in the four treatment groups (38). Both insulin resistance and impaired insulin secretion at baseline were significantly associated with the development of diabetes at follow up ($P < 0.05$, $P < 0.01$). When the subgroup was split in two, according to insulin resistance and insulin secretion, those who were less insulin resistant responded better to lifestyle modification. Those who had greater insulin secretion, however, did not respond significantly better to the intervention. The missing analysis is whether intervention per se had any effect on insulin resistance and insulin secretion. Other studies would support an effect of diet and exercise on insulin resistance (23–25). An effect of lifestyle modification on insulin secretion, however, is unlikely (24).

In the Finnish Diabetes Prevention Study (DPS) (10), lifestyle modification in subjects ($n = 522$) with IGT resulted in a 58% reduction in the risk of diabetes. The frequent sampling intravenous glucose tolerance test (FSIVGTT) was done at baseline and repeated at 4 years. At 4 years, the insulin sensitivity tended to be higher in the intervention group ($P = 0.067$) (39). There was a strong correlation between weight change and change in insulin sensitivity. In fact, those who lost weight in the control group were also protected against diabetes. Although no improvement was observed in insulin secretion in the intervention group, it declined significantly in the control

TABLE 2
Average annual incidence rates of diabetes in tertiles of the troglitazone group defined by changes in insulin sensitivity or by changes in IVGTT insulin between baseline and 3 months on trial

	Tertile 1	Tertile 2	Tertile 3	*P*
Change in S_I				
Median	−0.09	0.99	2.28	
Range	−2.13 to 0.44	0.54 to 1.41	1.43 to 7.67	
Annual diabetes incidence (%)	9.8	1.1*	4.8†	0.04
Change in IVGTT insulin area				
Median	−40	−1,813	−5,315	
Range	4,487 to −1180	−1,238 to −3,053	−3,160 to −193,64	
Annual diabetes incidence (%)	7.2	7.8	0.9‡	0.05

Data are from 108 women randomized to troglitazone who had IVGTTs at baseline and 3 months on trial. *P* values among subgroups by log-rank test. *$P < 0.01$, †$P < 0.05$, and ‡$P < 0.001$ vs. diabetes incidence in placebo group (log-rank test). Adapted from Buchanan et al. (42).

group. They concluded that weight change resulted in a significant improvement in insulin sensitivity, which was associated with a reduction in the incidence of diabetes. Insulin secretion, on the other hand, remained constant in those who were able to lose weight (39).

At present, no data on insulin sensitivity and insulin secretion in relation to lifestyle modification have been published for the Diabetes Prevention Program (40,41); it is very likely that observations similar to those of the DPS will be seen. In addition, no data for the metformin treatment group have yet been published.

The effects of troglitazone on insulin sensitivity and insulin secretion were tested at baseline and 12 weeks in the TRIPOD study using the FSIVGTT (42). In this study, 266 Hispanic women with a history of gestational diabetes were randomized to placebo or troglitazone 400 mg o.d. Treatment with troglitazone reduced the risk of diabetes by 50% over 30 months. Insulin sensitivity improved significantly at 12 weeks in the troglitazone treatment group (2.60 ± 1.67 to 3.76 ± 2.27; $P < 0.0001$). On the other hand, troglitazone did not have a significant effect on acute insulin release ($P = 0.10$). To examine the relationship between early changes in insulin sensitivity and subsequent protection from diabetes, the troglitazone group was divided into tertiles defined by changes in insulin sensitivity or by changes in insulin area under the curve in response to intravenous glucose. Based on insulin sensitivity, the incidence of diabetes was significantly reduced in the second tertile as well as the third tertile (Table 2). Based on insulin secretion, however, the incidence of diabetes was not reduced in the second tertile, but only in the third tertile. Furthermore, those who did not have an improvement in insulin sensitivity were not protected from diabetes. They concluded that the effect of the drug on the incidence of diabetes was due primarily to an effect on insulin sensitivity. This effect resulted in a protective and preservative effect on the pancreatic β-cell function.

We are currently analyzing the effect of acarbose on insulin sensitivity and β-cell function in the STOP- NIDDM Trial. These data have not yet been published.

CONCLUSION

Based on observational studies as well as on prospective intervention trials, it is suggested that the prevention of diabetes is due to a primary effect on insulin sensitivity rather than on insulin secretion. However, such a decrease in insulin resistance offers a protective effect on the β-cell and, therefore, has a preservative effect on the β-cell function. Furthermore, all interventions on the prevention of diabetes so far could not show any effect on β-cell function. At best, it can preserve the insulin secretion capacity by decreasing the stress on the β-cells. This would support the concept that the major genetic defect in the development of diabetes is related to β-cell dysfunction.

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