Minimizing Cardiovascular Complications by Early Diagnosis of Diabetes

a report by

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Excess cardiovascular disease (CVD) with diabetes has been recognized for some time. Among diabetic individuals, CVD accounts for >50% of all deaths, and stroke accounts for an additional 15%.[1] Diabetic women are at particularly high risk of CVD; diabetes eliminates the well described female advantage for coronary disease mortality.[2] This is alarming since the prevalence of type 2 diabetes is increasing, particularly in children.[3]

The Connection

In his 1988 Banting lecture, Reaven noted that resistance to insulin was common among patients with coronary artery disease.[4] Some of these patients were frankly diabetic, but others had mildly impaired glucose tolerance and some had normal glucose tolerance. He also identified other CVD risk factors that were associated with resistance: hypertension, elevated triglycerides, and low high-density lipoprotein (HDL) cholesterol. He named this cluster 'syndrome X.' He attributed the co-existence of CVD risk factors and diabetes to elevated free fatty acids. The latter are increased with increasing visceral adiposity and lead to excessive triglyceride production by the liver, increased glucose output by the liver, and increased resistance to insulin in muscle cells. The rising insulin level will usually balance the resistance by increasing insulin production. In some, due to genetics, lipid or glucose toxicity, or 'overproduction,' insulin production fails to maintain strides with the resistance

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leading to various degrees of glucose intolerance. The UK Prospective Diabetes Study[5] of several thousand type 2 diabetic patients gave evidence that at the time of diagnosis of diabetes, half of beta-cell function was gone. Thereafter, over the next 10–15 years, the function would continue to decline, leading to the failure of the oral antiglycemic medications and the need for insulin treatment. The implication, then, is early treatment of glucose intolerance and the associated CVD risk factors will lead to reduction in CVD events.

Diagnosing Diabetes

Diabetes is diagnosed only by plasma glucose *(see Table 1)*. If fasting glucose is greater than 125mg/dl on two consecutive occasions or if the second hour plasma glucose following a 75g glucose oral drink is greater than 199mg/dl on two consecutive occasions then the diagnosis of diabetes is secured.[6] As mentioned above, glucose intolerance is a continuum—it is recognized that between 'normal glucose' and diabetes there exists a pre-diabetes condition. There are two forms of pre-diabetes: impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). IFG is diagnosed when the fasting plasma glucose is 100–125mg/dl on two consecutive periods and IGT is diagnosed when the second hour following a 75g oral glucose drink is 140–199mg/dl on two consecutive periods. It is important to properly diagnose these conditions. A person with pre-diabetes suffers an 11% chance/year of developing diabetes.[7] Owing to the clustering of other CVD risk factors, such diagnosed patients have a greater risk of developing CVD. Owing to the genetic nature of glucose intolerance, family members of patients with pre-diabetes are also at increased risk for the same.

Reversing the Course

It is not only appropriate to delay or prevent diabetes in those diagnosed as pre-diabetic, but also to reduce the CVD risk factors associated with the pre-diabetic state.[8] The Diabetes Prevention Program (DPP)[9] was a large, multicenter, placebo-controlled comparison of diet and increased activity, metformin, and troglitazone. The troglitazone treatment arm was discontinued during the first year of the study due to a death related to idiosyncratic hepatitis. Patients treated with a low-calorie, low-fat diet and 150 minutes of exercise a week to achieve a targeted weight loss of 7% of bodyweight were observed to have a reduced risk of developing diabetes of 58% compared with the control group. However, the subjects were recruited for the study only after rigorous screenings and successfully passing tests of compliance. In addition, the lifestyle modification consisted of individualized and group multiple sessions by nutritionist, exercise therapist, and other therapists. In summary, it was reassuring to see the effectiveness of such therapy, but the possibility of widespread clinical application of this approach is limited. The study was not designed to evaluate the CVD outcomes, but blood pressure in the diet/activity group was significantly less than that in the control group.

Table 1: Criteria for the Diagnosis of Diabetes and Pre-diabetes[6]

Variable	Diabetes Diagnosed	Pre-diabetes Diagnosed
Fasting plasma glucose (mg/dl)	>125	>99–125
Two hours after 75g oral glucose drink (mg/dl)	>199	>139–199

In the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM),[10] acarbose, a blocker of disaccharide digestion, not only reduced the incidence of diabetes, but also demonstrated a reduced rate of increase in carotid intima-media thickness compared with placebo. In the same study, acarbose treatment was associated with a 49% reduction in composite CVD events. However, the studies have not been confirmed. In addition, acarbose is taken before each meal and has gastrointestinal side effects that limit its widespread use. As mentioned above, in the DPP study[9] metformin 850mg twice a day was one of the treatment arms. There was a 31% reduction in the development of diabetes compared with the control group. Unfortunately, this was a lesser reduction than the lifestyle-modification arm and was associated with a drop-out rate of 17% due to gastrointestinal side effects. After discontinuing metformin for an average of 11 days, the percentage reduction in those developing diabetes fell to 24.9%. Clearly, in some patients metformin was reducing the incidence of diabetes by treating, not delaying, the development of diabetes. Lastly, the blood pressure response to metformin was not different from placebo.

The thiazolidinediones (TZDs) that are currently marketed include rosiglitazone and pioglitazone. These are antihyperglycemics that bind to the peroxisome-proliferator-activated receptor (PPAR-γ) in the nucleus of the cell. They sensitize muscle, fat, and the liver to insulin, thereby reducing insulin levels. In addition, they lower blood pressure, increase HDL cholesterol, decrease triglycerides (predominately pioglitazone), reduce micro-albuminuria, and decrease inflammation. With these actions, they would seem ideal for the delay of the development of diabetes and reduction of CVD. The Troglitazone in Prevention of Diabetes (TRIPOD)[11] study evaluated the ability of this TZD to reduce the incidence of diabetes in a group of Mexican-American women with a previous history of gestational diabetes (a high-risk group). At 400mg per day, troglitazone reduced the incidence of diabetes by around 58% by the fifth year compared with placebo. Interestingly, those that were destined to not develop diabetes with this TZD were those whose insulin levels fell upon treatment. This would suggest that the earlier the treatment is initiated, the better. Contrary to the experience with metformin, once the TZD was discontinued there was no immediate increase in the incidence of diabetes. This study has been confirmed with pioglitazone, in the Pioglitazone in Prevention of Diabetes (PIPOD) study,[12] and has shown that the beta-cell preservation may be a class effect of the TZDs. These studies did not address cardiovascular risk factors or CVD events. The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM)[13] study evaluated the reduction in development of diabetes in subjects with pre-diabetes. Confirming the class effect of TZDs, the incidence of diabetes was again reduced to around 60%. Although there were more CVD events in the rosiglitazone-treated group compared with placebo, it was not significant due to the small number of subjects. Especially interesting is the TZD effect on CVD surrogate markers. Carotid intima-media thickening appears to be a effect of TZDs—at least troglitazone and pioglitazone.[11,12] For CVD events, the Prospective Pioglitazone Clinical Trial In Macro Vascular Events (PROACTIVE) study[15] evaluated the effects of the addition of pioglitazone 45mg per day to existing therapy for glucose, lipids, and blood pressure in subjects with type 2 diabetes and demonstrated vascular disease. Although the primary composite outcome of secondary events was lower but not significantly different from the control group, the secondary outcome established before the study was conducted was significant. The latter outcome revealed that all-cause mortality, nonfatal myocardial infarction (excluding silent myocardial infection), and stroke were reduced by 16% (p=0.027).

Dampening the enthusiasm for TZDs, however, are the costs and the side effects. Weight gain and edema can be troublesome. In the DREAM and PROACTIVE studies, the incidence of congestive heart failure was increased in the treated groups. Although the overall incidence of new heart failure was low, in the PROACTIVE study incidence of new heart failure was increased by 44%. It should be noted that the mortality rate in those with heart failure was not higher than in the control group.

Conclusion

Diabetes is commonly associated with CVD. Early detection of diabetes is important to identify those patients at risk for the progression to diabetes and the development of CVD. Treatment of the risk factors, such as hypertension and dyslipidemia, is paramount. Diet and increased activity is still the recognized mainstay for the treatment of the pre-diabetic patient. Although TZDs are tantalizing to consider in treating pre-diabetes, the cost and side effects deter the thoughtful clinician. ∎

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