Prediabetes and Cardiovascular Disease

Pathophysiology and Interventions for Prevention and Risk Reduction

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KEYWORDS

• Impaired fasting glucose • Impaired glucose tolerance • Prediabetes complications • Cardiovascular disease • Macrovascular

KEY POINTS

- Prediabetes carries an increased risk in cardiovascular disease.
- Significant physiologic, metabolic, and biochemical features are dysregulated in prediabetes.
- Extensive randomized, controlled trials have demonstrated that lifestyle modification can decrease the rate of progression from prediabetes to diabetes.
- Early detection and intervention is vitally important for the prevention of prediabetes progression to diabetes.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the major causes of premature morbidity and mortality worldwide with the World Health Organization reporting that 1 in 10 adults worldwide had T2DM in 2014.[1] In the United States, 1 of every 5 health care dollars is spent on diabetes-related health care.[2] Diabetes mellitus also imposes a huge drain in developing countries on national health budgets comprising on average at least 5% of their total health expenditures on diabetes in 2010.[3] Of these, macrovascular complications are the greatest contributor to the direct and indirect costs of diabetes.[4] The

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development of T2DM is punctuated by an interlude of prediabetes, itself a toxic state that is associated with the development of macrovascular complications.

DIAGNOSIS AND THE BURDEN OF PREDIABETES

The prelude to diabetes is prediabetes in what can be described as a continuum from normoglycemia through worsening dysglycemia. Prediabetes is defined specifically as impaired glucose tolerance (IGT) and/or impaired fasting glucose.[5] According to the American Diabetes Association, IGT is defined as a 2-hour plasma glucose value in the 75-g oral glucose tolerance test (OGTT) of 140 to 199 mg/dL (7.8 to 11.0 mmol/L).[6] Impaired fasting glucose is defined as a fasting plasma glucose of 100 to 125 mg/dL (5.6 to 6.9 mmol/L).[6] Finally prediabetes can also be defined as a hemoglobin A1c (HbA1c) of 5.7% to 6.4% (39–46 mmol/mol).[6,7] It bears stressing that the American Diabetes Association criteria stipulate normal glucose tolerance (NGT) as a fasting glucose level less of than 100 mg/dL and a 2-hour postload OGTT plasma glucose level of less than 140 mg/dL. With regard to using HbA1c as a diagnosis of prediabetes, it must be stressed that there are many well characterized "pitfalls" such as anemia, chronic kidney disease, and other systemic illness and hematologic disorders that disrupt the reliability of HbA1c as an integrated measure of mean plasma glucose.[8–12] In particular, racial and ethnic differences in the relationship between blood glucose values and HbA1c call for caution when using HbA1c levels for the diagnosis of prediabetes.[8–14] It is always prudent to confirm diagnosis with actual blood glucose measurement before instituting therapeutic measures.[8] Estimates by the Centers for Disease Control and Prevention in the United States indicated that there were approximately 29 million adults with diabetes and 86 million with prediabetes in 2014.[15,16] Worldwide, there are more than 400 million people with prediabetes and projections indicate that more than 470 million people will have prediabetes by 2030.[17] In addition, many studies from across the globe have pointed out that the risk of many comorbidities are the same in diabetes and prediabetes and affect all age groups.[18–23]

PATHOPHYSIOLOGIC DEFECTS IN PREDIABETES

The known pathophysiologic defects that underlie T2DM are being increasingly recognized in the prediabetic state.[24–28] The natural progression of dysglycemia involves increasing insulin resistance and loss of pancreatic beta-cell function.[29] Significant defects in insulin action and secretion are consistently demonstrable in the prediabetic state of IGT.[30–32] Several cross-sectional studies and a few longitudinal studies have carefully documented the various defects leading to prediabetes and T2DM.[33–35]

FINDINGS FROM LONGITUDINAL ASSESSMENT OF INSULIN ACTION AND SECRETION

A landmark longitudinal study that tracked high-risk subjects from the stage of NGT to prediabetes reported that the transition to prediabetes was associated with an increase in body weight, increase in insulin resistance, and a decrease in endogenous insulin secretion (beta-cell dysfunction).[29] The study further demonstrated that progression from prediabetes to T2DM was accompanied by a worsening of weight gain, insulin resistance, and beta-cell dysfunction.[29] Thus, the salient finding from the longitudinal observation was that insulin resistance and beta-cell failure coevolve simultaneously rather than sequentially, as was previously believed. Individuals who maintained NGT status, despite weight gain and associated insulin resistance, were those who mounted a robust endogenous insulin secretory response.[29] Thus, if