Pre-Diabetes

By Ronald Steriti, ND, PhD

Pre-diabetes is an asymptomatic condition not associated with functional impairment, but is associated with future morbidity and mortality. (Bloomgarden 2008)

Screening adults for pre-diabetes and diabetes may save money. (Chatterjee, Narayan et al. 2010)

A recent study found that approximately 1 in 12 adults has a combination of pre-diabetes and risk factors that may justify consideration of metformin treatment for diabetes prevention. (Rhee, Herrick et al. 2010)

Three years after a major clinical trial demonstrated that interventions could greatly reduce progression from IFG/IGT to type 2 diabetes, the majority of the U.S. population with IFG/IGT was undiagnosed and untreated with interventions. (Karve and Hayward 2010)

It has been estimated that, by the year of 2025, the number of people with pre-diabetes will be 472 millions. Data from the World Health organization (WHO) and American Diabetes Association (ADA) estimated that around 27% of individuals with normal fasting glucose migrated to pre-diabetes and 8% to diabetes when submitted to oral glucose tolerance test (OGTT) and, more-over, 50% of subjects with dysglicemia develop diabetes. (Magalhaes, Cavalcanti et al. 2010)

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG)

IFG is a fasting glucose of 100 –125 mg/dl

IGT is a glucose 2-h post-load 75-g oral glucose of 140 –199 mg/dl

Impaired fasting glucose and impaired glucose tolerance (IGT) are associated with modest increases in the risk for cardiovascular disease. (Ford, Zhao et al. 2010)

Beta- and alpha-cell dysfunction are evident several years before diagnosis of impaired glucose tolerance, and islet dysfunction is manifested as impaired glucose sensitivity of the beta- and alpha-cells and reduced maximal insulin secretion. Subjects developing impaired glucose tolerance had lower insulin sensitivity than those maintaining normal glucose tolerance in the tests preceding diagnosis of IGT ($P < \text{or} = 0.05$). (Ahren 2009)

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are intermediate states in glucose metabolism that exist between normal glucose tolerance and overt diabetes. Insulin resistance and impaired beta-cell function, the primary defects observed in type 2 diabetes, both can be detected in subjects with IGT and IFG. While subjects with IGT have marked muscle insulin resistance with only mild hepatic insulin resistance, subjects with IFG have severe hepatic insulin resistance with normal or near-normal muscle insulin sensitivity. Both IFG and IGT are characterized by a reduction in early-phase insulin secretion, while subjects with IGT also have impaired late-phase insulin secretion. (Abdul-Ghani, Tripathy et al. 2006)

A stationary reduced insulin secretion followed by a decline in primarily hepatic insulin sensitivity characterizes the transition from normal glucose tolerance to isolated impaired fasting glycemia (i-IFG). In contrast, low whole-body insulin sensitivity with a secondary lack of beta-cell compensation is associated with the development of isolated impaired glucose tolerance (i-IGT). (Faerch, Vaag et al. 2009)

Glucose disposition index (GDI)

Glucose disposition index (GDI) is calculated as the product of first-phase insulin x insulin sensitivity. (Bacha, Gungor et al. 2009)

Obese youth with impaired glucose tolerance have significantly lower first-phase insulin and C-peptide levels and GDI ($P = 0.012$), whereas youth with type 2 diabetes have an additional defect in second-phase insulin. Fasting and 2-h glucose correlated with glucose disposition index ($r = -0.68$, $P < 0.001$ and $r = -0.73$, $P < 0.001$, respectively) and first-phase insulin but not with insulin sensitivity. (Bacha, Gungor et al. 2009)

Adolescents with NGT, pre-diabetes, and type 2 diabetes had similar body composition and abdominal fat distribution. R(d) was lower ($P = 0.009$) in adolescents with type 2 diabetes than in those with NGT. Compared with adolescents with NGT, first-phase insulin was lower in those with IFG, IGT, and IFG/IGT with further deterioration in those with type 2 diabetes ($P < 0.001$), and beta-cell function relative to insulin sensitivity (glucose disposition index [GDI]) was also lower in those with IFG, IGT, and IFG/IGT (40, 47, and 47%, respectively), with a further decrease (80%) in those with type 2 diabetes ($P < 0.001$). GDI was the major determinant of fasting and 2-h glucose levels. (Bacha, Lee et al. 2010)

One-Hour Oral Glucose Tolerance Test

The plasma glucose concentration at 1 h during the oral glucose tolerance test (OGTT) is a strong predictor of future risk for type 2 diabetes. A plasma glucose cutoff point of 155 mg/dl and the Adult Treatment Panel III criteria for the metabolic syndrome can be used to stratify non-diabetic subjects into

three risk groups: low, intermediate, and high risk. (Abdul-Ghani, Abdul-Ghani et al. 2008) (Abdul-Ghani, Lyssenko et al. 2009)

The Kraft Criteria

The Kraft Criteria for diagnosing insulin resistance uses a 4-hour glucose-insulin tolerance test (GITT). (Kraft 1975)

Pattern I Normal	Normal fasting insulin between 0-10, peaks at ½ or 1 hour 2^{nd} hour is less than 50, 3^{rd} hour is less than 2^{nd} hour 2^{nd} hour plus 3^{rd} hour is less than 60 Subsequent hours at fasting range (0-10)
Pattern II Peak at ½ to 1 hour with delayed return to normal	Normal fasting insulin between 0-10, peaks at ½ or 1 hour 2^{nd} plus 3^{rd} hour is 60-100; Borderline for insulin resistance 2^{nd} plus 3^{rd} hour > 100; Considered insulin resistance
Pattern III-A Diagnostic for insulin resistance	Normal fasting insulin between 0-10 Insulin peaks at 2^{nd} hour
Pattern III-B Positive for insulin resistance	Normal fasting insulin greater than 10 Insulin peaks at 3^{rd} hour
Pattern IV Positive for insulin resistance	Fasting insulin greater than 10
Pattern V Insulinopenic Pattern	Low Insulin Response: All values < 30 If glucose values are elevated; Considered to be 'juvenile' pattern of Diabetes This is in effect insulin deficiency, probably because of dead or near dead islet cells If normal or borderline glucose tolerance; may be due to low carbohydrate diet

Hemoglobin A1C

An International Expert Committee (IEC) and the American Diabetes Association (ADA) proposed diagnostic criteria for diabetes and pre-diabetes based on A1C levels.

A1C >/= 6.5% for diabetes

6.0-6.4% (IEC) or 5.7-6.4% (ADA) for high risk/pre-diabetes

The proposed criteria missed 70% of individuals with diabetes, 71-84% with dysglycemia, and 82-94% with pre-diabetes. The proposed A1C diagnostic criteria are insensitive and racially discrepant for screening, missing most Americans with undiagnosed diabetes and pre-diabetes. (Olson, Rhee et al. 2010)

The Insulin Resistance Atherosclerosis Study (IRAS) compared A1C between 5.7 and 6.4% with fasting (FPG) and 2-h plasma glucose as a marker for identifying pre-diabetes, insulin sensitivity and secretion, and cardiovascular risk factors. IFG and IGT identified 69.1 and 59.5% of all individuals at increased risk of diabetes, respectively. A1C 5.7-6.4% detected 23.6% of all at-risk individuals, although more African Americans (31.4%) and Hispanics (35.2%) than non-Hispanic whites (9.9%). (Lorenzo, Wagenknecht et al. 2010)

Data from the National Health and Nutrition Examination Survey 1999-2006 (n = 7,029) were analyzed to determine the percentage and number of U.S. adults without diabetes classified as having pre-diabetes by the elevated A1C (5.7-6.4%) and by the impaired fasting glucose (IFG) (fasting glucose 100-125 mg/dl) criterion separately. The prevalence of pre-diabetes among U.S. adults was 12.6% by the A1C criterion and 28.2% by the fasting glucose criterion. Only 7.7% of U.S. adults, reflecting 61 and 27% of those with pre-diabetes by A1C and fasting glucose, respectively, had pre-diabetes according to both definitions. A1C used alone would reclassify 37.6 million Americans with IFG to not having pre-diabetes and 8.9 million without IFG to having pre-diabetes (46.5 million reclassified). Using IFG as the reference standard, pre-diabetes by the A1C criterion has 27% sensitivity, 93% specificity, 61% positive predictive value, and 77% negative predictive value. (Mann, Carson et al. 2010)

Pancreatic Beta-Cell Area

Beta cell dysfunction is considered an important early defect in diabetes type 2 and it is present since the pre-diabetes phase. (Magalhaes, Cavalcanti et al. 2010)

Glucose control is closely related to pancreatic beta-cell area in humans. A C-peptide-to-glucose ratio after oral glucose ingestion appears to better predict beta-cell area than fasting measures. Beta-Cell area was related to

fasting glucose concentrations in an inverse linear fashion (r = -0.53, P = 0.0014) and to 120-min post-challenge glycemia in an inverse exponential fashion (r = -0.89). beta-Cell area was best predicted by a C-peptide-to-glucose ratio determined 15 min after the glucose drink (r = 0.72, P < 0.0001). However, a fasting C-peptide-to-glucose ratio already yielded a reasonably close correlation (r = 0.63, P < 0.0001). (Meier, Menge et al. 2009)

A recent study investigated whether beta-cell function index from the OGTT reflects pancreatic beta-cell area in Korean patients. The beta-cell area of the pancreas was 1.07 +/- 0.33% in the normal glucose tolerance group, 1.71 +/- 0.85% in the pre-diabetes group (impaired glucose tolerance and impaired fasting glucose), and 1.08 +/- 0.57% in the diabetes group. The beta-cell area of the pre-diabetes group was significantly higher than that of the diabetes group. Pancreatic beta-cell area showed a significant correlation with a homeostasis model assessment of beta-cell function (r=0.358, P=0.016), disposition index (r=0.336, P=0.024), fasting glucose (r=-0.359, P=0.015), and the C-peptide/glucose 30 min ratio (r=0.319, P=0.035). (Kim, Kim et al. 2011)

Women

The Western New York Study found that women who progressed from normoglycemia to pre-diabetes have greater endothelial dysfunction than men as well as more hypertension and a greater degree of fibrinolysis/thrombosis. (Donahue, Rejman et al. 2007)

Alcohol

High alcohol consumption increases the risk of abnormal glucose regulation in men. In women the associations are more complex: decreased risk with low or medium intake and increased risk with high alcohol intake. (Cullmann, Hilding et al. 2011)

Rheumatic Disease

A retrospective study found increased incidence of pre-diabetes mellitus at a department of rheumatology. The study examined the levels of hemoglobin A1c (HbA1c) in a total of 498 patients with rheumatic diseases between April 2007 and March 2008 at the Department of Rheumatology in Nagasaki University Hospital. Of the 498 patients, 409 (82.1%) had HbA1c levels higher than 5.6% (National Glycohemoglobin Standardization Program; NGSP) and were recommended for health guidance with a focus on metabolic syndrome. Serum HbA1c levels higher than 6.0%, a possible indicator of DM, were seen in 227 patients (45.6%). Serum HbA1c levels higher than 6.5%, which constitute a high risk for DM, were found in 115 patients (23.1%). (Origuchi, Yamaguchi et al. 2011)

Smoking

The Western New York Health Study found that cigarette smoking is associated with conversion from normoglycemia to impaired fasting glucose. The odds ratio of incident IFG among former and current smokers (vs. never) was 1.68 (95% confidence interval: 0.99-2.80) and 2.35 (95% confidence interval: 1.17-4.72) (p trend=0.008), respectively. (Rafalson, Donahue et al. 2009)

Glucose Intolerance In Pregnancy

A recent study found that any degree of abnormal glucose homeostasis in pregnancy independently predicts an increased risk of glucose intolerance postpartum. (Retnakaran, Qi et al. 2008)

Cataract

An older study found that IFG, a pre-diabetic condition, may be a risk factor for the development of cortical cataract. They found a 2-fold higher 5-year incidence of cortical cataract in participants with IFG, multivariate adjusted odds ratio (OR) 2.2, 95% confidence interval (CI) 1.1-4.1. (Saxena, Mitchell et al. 2004)

Vascular Disease

In pre-diabetes, microvascular dysfunction correlates with plasma insulin levels and not blood glucose. Here we discuss the concept that insulin, at levels found in pre-diabetes, contributes to microvascular disease in skeletal muscle by inhibiting the release of the vasodilator, adenosine triphosphate (ATP), from erythrocytes. (Sprague and Ellsworth 2010)

Arterial Stiffness

Increased arterial stiffness was found in healthy subjects with high-normal glucose levels and in subjects with pre-diabetes. An increase in FPG, even within the normal range, was associated with aggravated arterial stiffness. (Shin, Lee et al. 2011)

Ferritin

Elevated serum ferritin concentrations were found in prediabetic subjects. The IFG group had higher serum ferritin concentrations (85.5+/-6.6 microg/L vs. 49.4+/-3.7 microg/L, p=0.001). A positive correlation was found between fasting plasma glucose and serum ferritin (r=0.29, p=0.001). Using multiple regression analysis, we found an association between serum ferritin and blood pressure (0.15, p=0.01), FPG (0.29, p=0.001), triglyceride (0.08, p=0.01) and cholesterol (0.07, p=0.03). The odds ratio for the association of IFG in male subjects with a high serum ferritin level was 8.3

(95% CI: 1.2-11.9, p=0.01) and for females was 3.06 (95% CI: 0.58-15, p=0.1). (Sharifi, Nasab et al. 2008)

Red Cell Count

A recent study demonstrated that diabetes precursor states are associated with an increased red cell count, which can be explained, in part, by an increased HbA1c. (Simmons 2010)

Magnesium

Another recent study found that hypomagnesaemia is associated with diabetes, but not pre-diabetes, obesity or the metabolic syndrome. (Simmons, Joshi et al. 2010)

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