Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Role of various indices derived from an oral glucose tolerance test in the prediction of conversion from prediabetes to type 2 diabetes

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ARTICLE INFO

Article history:
Received 22 May 2014
Received in revised form
16 July 2014
Accepted 23 August 2014
Available online 3 September 2014

Keywords:
β-Cell function
Insulin resistance
Oral glucose tolerance test
Prediabetes
Type 2 diabetes

ABSTRACT

Aims: The clinical implications of prediabetes for development of type 2 diabetes may differ for Asian ethnicity. We investigated various indices derived from a 2-h oral glucose tolerance test (OGTT) in people with prediabetes to predict their future risk of diabetes.
Methods: We recruited 406 consecutive subjects with prediabetes from 2005 to 2006 and followed them up every 3–6 months for up to 9 years. Prediabetes was defined as isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), combined glucose intolerance (CGI), or isolated elevated HbA1c (5.7–6.4%, 39–46 mmol/mol) without IFG or IGT. The rate of diabetes conversion was compared between prediabetes categories. The association of glycemic indices with development of diabetes was also investigated.
Results: Eighty-one patients were diagnosed with diabetes during the 9-year follow-up (median 46.0 months). The rate of diabetes conversion was higher in subjects with CGI (31.9%), or isolated IGT (18.5%) than in those with isolated IFG (15.2%) or isolated elevated HbA1c (10.9%). Surrogate markers reflecting β-cell dysfunction were more closely associated with diabetes conversion than insulin resistance indices. Subjects with a 30-min postload glucose ≥165 mg/dL and a 30-min C-peptide <5 ng/mL had 8.83 times greater risk (95% confidence interval 2.98–26.16) of developing diabetes than other prediabetic subjects.
Conclusions: In Asians, at least Koreans, β-cell dysfunction seems to be the major determinant for diabetes conversion. A combination of high glucose and low C-peptide levels at 30 min after OGTT may be a good predictor for diabetes conversion in this population.

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http://dx.doi.org/10.1016/j.diabres.2014.08.014
0168-8227/

1. Introduction

The prevalence of prediabetes is increasing, and 35% of adults aged 20 years or older and 50% of people aged 65 years or older in the United States are estimated to have prediabetes [1]. This will lead to a future increase in type 2 diabetes. Prediabetes status is defined as intermediate hyperglycemia that shares the main pathophysiology of diabetes: impaired insulin secretion and increased insulin resistance [2]. The definition of prediabetes has been revised over time [3]. In the 2010 American Diabetes Association (ADA) guidelines, a hemoglobin A_{1C} (HbA1c) of 5.7–6.4% (39–46 mmol/mol) has been included in a category of markers of increased risk of diabetes that also includes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) [4]. Several epidemiologic studies have shown that IFG and IGT describe distinct populations of hyperglycemia [5,6]. IFG reflects hepatic insulin resistance [7,8], while IGT reflects relatively high muscle insulin resistance [9]. Both IFG and IGT share impaired early-phase insulin secretion, while IGT also shows a reduction in late-phase insulin secretion [10]. Thus, individuals with prediabetes defined by distinct diagnostic criteria might be a heterogeneous group with different pathophysiology and prognosis.

In this situation, a more detailed assessment for predicting development of diabetes in people with prediabetes is needed. Older age and a family history of diabetes are well-known risk factors for this, but biochemical measures, such as lipids, uric acid, or liver enzymes, have failed to demonstrate predictive value for diabetes [11–13]. Fasting insulin concentration was also not notably useful for the prediction of diabetes [14]. However, measures derived from the oral glucose tolerance test (OGTT), including 1-h glucose or the insulin secretion/insulin resistance index showed strong predictive power for diabetes [15]. A recent study has shown that the patterns of insulin concentration during an OGTT strongly predict the development of diabetes [16]. Thus, the OGTT could provide more accurate information about the risk of diabetes, especially in people with prediabetes who have impaired glucose metabolism [16,17]. More specifically, plasma insulin and C-peptide concentrations after glucose loading are more likely to reflect β-cell dysfunction and insulin resistance than are fasting samples. Further, the combination of insulin and glucose levels at a specific time point during the OGTT might be a good predictor of future diabetes. However, to the best of our knowledge, no previous studies have assessed the predictive value of this combination.

In this longitudinal study, we followed subjects with prediabetes for up to 9 years for the development of diabetes. We compared the ability to predict conversion to diabetes between different definitions of prediabetes, and assessed various parameters related to glycemic regulation derived from the glucose and insulin concentrations detected in a three-point OGTT (0, 30, and 120 min). Finally, we suggest a diabetes risk-prediction model using a combination of glycemic and insulin-related parameters.

2. Subjects, materials and methods

The study population included pre-screened individuals with prediabetes who visited the diabetes clinic at Seoul National University Bundang Hospital (SNUBH), a tertiary referral hospital, in 2005 and 2006 for evaluation of their glycemic control. They were referred to the diabetes clinic after they were diagnosed with prediabetes at their health check-up or primary clinic. Subjects who took oral hypoglycemic agents or insulin were excluded from this study. We consecutively enrolled 418 participants with prediabetes based on the results of a 75-g OGTT. After excluding 12 who were lost to follow-up within 1 year after enrollment, 406 participants were included with a follow-up rate of 97.1%. The median follow-up duration was 46.0 (3.0–107.8) months. Among 406 participants with prediabetes, 141 subjects agreed to measure all the values of plasma C-peptide, insulin, and glucose at fasting, 30 min, and 2 h. Predictive model for type 2 diabetes using 30-min plasma glucose and 30-min C-peptide was based on this data. This study was approved by the institutional review board of SNUBH. Written informed consent was obtained from every participant.

2.1. Definition of prediabetes and diabetes

Prediabetes was defined according to the ADA 2010 criteria [4]. Isolated IFG was defined as fasting plasma glucose (FPG) levels of 100–125 mg/dL and a 2-h postprandial glucose (2-h PG) <140 mg/dL, and isolated IGT as 2-h PG 140–199 mg/dL and FPG <100 mg/dL. Subjects with IFG and IGT were defined as combined glucose intolerance (CGI). Subjects with HbA1c of 5.7–6.4% (39–46 mmol/mol) and neither IFG nor IGT were also included in this study as a category of isolated elevated HbA1c prediabetes. Diabetes mellitus was diagnosed when the FPG was ≥126 mg/dL, or the 2-h PG was ≥200 mg/dL or HbA1c was ≥6.5% (48 mmol/mol).

2.2. Measurement of anthropometric and biochemical parameters

Height and body weight were measured by standard methods. BMI was calculated as body weight divided by height squared (kg/m^2). Blood pressure measurements were made after subjects had remained seated for 10 min. Measurements were made twice, with a 5-min rest period in between, and the mean value of the measurements was used. Smoking status was divided into three categories: current smokers, ex-smokers, and never smokers. Alcohol intake was assessed by frequency and quantity of beer, spirit, sake, and wine intake during the previous 12 months, and was categorized into non-, light (<1/wk), moderate (≤3/wk), and heavy (>3/wk) drinkers. Physical activity was classified into four categories: no, light (1/wk), moderate (2–3/wk), and heavy (≥4/wk) exercise episodes. One episode of exercise was defined as exercising for at least 30 min.

Plasma glucose levels were measured with a Hitachi 747 chemistry analyzer (Hitachi, Tokyo, Japan). HbA1c was measured with a Bio-Rad variant II Turbo HPLC analyzer (Bio-Rad, Hercules, CA, USA) in the National Glycohemoglobin Standardization Program (NGSP) level II certified laboratory at SNUBH. Plasma C-peptide and insulin concentrations were measured by radioimmunoassay (Linco, St. Louis, MO, USA). The fasting plasma concentration of total cholesterol, triglycerides, and high-density lipoprotein (HDL) and low-density