How to diagnose the prediabetes?

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Diabetes is a chronic metabolic disease characterized by the presence of hyperglycemia that occurs due to defective insulin production and secretion by the pancreas, defective insulin action resulting from no response of the cells to insulin or both. High blood glucose leads to typical clinical symptoms : weight loss, polyuria, increased thirst, weakness (1).

Prediabetes is the term used to describe the condition with impaired fasting glucose (IFG), glucose concentrations higher than normal but below the established threshold for diabetes, or impaired glucose tolerance (IGT) recognized based on the results of a 2-hour oral glucose tolerance test (OGTT). People with prediabetes are at high-risk for developing diabetes and associated complications. It is estimated that each year 5-10% of individuals with prediabetes will develop T2 diabetes [8]. Occurrence of IFG and/or IGT is asociated with abdominal or visceral obesity, high serum triglycerides and/or low HDL-cholesterol andhypertension (1). In subjects with IGT lifestyle changes such as increase of physical activity, loosing weight (5-10%) and pharmacological therapy may prevent or delay the development of diabetes (2).

Diagnosis of prediabetes

World Health Organization (WHO) criteria for impaired fasting glucose differ from the American Diabetes Association (ADA) criteria, because the normal range of glucose is defined differently. ADA lowered the upper limit of normal to a fasting glucose under 100 mg/dL (5.6 mmol/L) as higher fasting plasma glucose (FPG) has been shown to increase complication rates significantly. WHO decided to keep FPG upper limit of normal at under 110 mg/dL (2).

Prediabetes is diagnosed when FPG is of 110 - 125 mg/dL (6.1 mmol/L - 6.9 mmol/L) according to WHO criteria or 100 - 125 mg/dL (5.6 mmol/L - 6.9 mmol/L) according to ADA criteria and/or when 2-hour glucose tolerance test after ingesting the standardized 75 g of glucose solution indicates glucose concentration of 140 -198 mg/dL (7.8 - 11.0 mmol/L) and/or when hemoglobin A1c (HbA1c) is between 5.7 - 6.4% (39-47 mmol/mol) (3).

According to ADA criteria published in 2010, the recommended order for prediabetes testing is as follows: HbA1c, FPG and/or OGTT (3). There is some controversy on whether HbA1c can be used as the only test and 2-hour post load glucose brings and added value. Moreover, HbA1c-defined prediabetes ranges are also a subject of debate, with some favouring 6.0- 6.4% (42- 47 mmol/mol) instead of 5.7-6.4% (4). FPG is recommended to be measured in venous plasma.

It should be mentioned that the analytical methods for glucose and HbA1c may affect the interpretation of results. It is important to note that both FPG and glucose tolerance test reflect distinct processes. Normal FPG reflects maintaining the adequate insulin secretion and control of hepatic glucose output whereas normal glucose tolerance indicates adequate secretion of insulin and insulin sensitivity in the target tissues. This explains why an individual with impaired fasting glucose may have IGT or even diabetes and individual with normal FPG may have IGT.

According to ADA and WHO, screening for prediabetes in the general population should add FPG for those with HbA1c of 6.0-6.5%. However there are some controversies concerning specific populations (Asian population) whether using only HbA1c and FPG without OGTT for detecting prediabetes, leads to false negative results (2). It seems clear that individuals with HbA1c of 6.0-6.5% are in the high-risk group and require lifestyle changes and management of risk factors that will be not changed based on the further information from OGTT. On the other hand, the estimated risk of mortality and CVD showed the strongest association with the results of OGTT than FPG or HbA1c (2).

OGTT, comparing to HbA1c, is more difficult to perform and time-consuming. HbA1c concentration may be affected by red blood cell survival time and renal function but has several advantages. Comparing to fasting glucose, HbA1c has a small intraindividual variability, good stability after blood collection and no need for fasting.

Recent data from the Centre for Disease Control showed that ~30% of adults in United States have prediabetes defined based on fasting plasma glucose (FPG 100-125 mg/dL) or glycated hemoglobin values (HbA1c 5.7- 6.4%). Without weight loss and increased physical activity 15-30% of Americans with prediabetes will progress to T2D within five years.

Prevalence of prediabetes in adults

In the study of Korean population the prevalence of diabetes and prediabetes was evaluated according to FPG alone or the two tests - FPG and HbA1c in combination (5). HbA1c in this study was measured with high performance liquid chromatography method. Using both tests a greater number of individuals with diabetes and prediabetes was detected. The prevalence of prediabetes was 19.3% (23.8% in men and 14.9% in women) when FPG only was used but increased up to 38.3% (41% in men and 35.7% in women) when HbA1c was added as the second test. It was concluded that adding HbA1c as complementary test to FPG allow to avoid underestimation of the diabetes and prediabetes prevalence.

From the practical point of view, screening with HbA1c is easier to perform however, it was suggested that fewer cases of prediabetes are detected than with OGTT. It may be understandable as both measurements reflect different physiological processes. In their study Vlaar et al (6) screened South Asian individuals aged 18-60 years performing OGTT and HbA1c measurements. Out of 353 cases meeting HbA1c prediabetes criteria only 62 met OGTT criteria (18%). In cases with prediabetes, defined on the basis of OGTT, the AUC (the area under the curve in ROC chracteristics) for HbA1c was 0.73 whereas in cases with diabetes it was

0.86. The optimal threshold for HbA1c for predicting prediabetes in this study was 5.8-6.3% (40-45 mmol/mol Hb). Individuals with prediabetes identified with HbA1c criteria had a high body mass index, hypertension and low insulin sensitivity. The authors conclude that each test identifies partially different group of subjects and that HbA1c only should not be used for detection of prediabetes.

The other study aimed to identify the optimal threshold of HbA1c and to evaluate the predictive performance of HbA1c in diagnosing prediabetes, detected previously with OGTT, in a middle-aged and elderly Han Chinese population from northwest China (7). HbA1c with the threshold of 6.1% showed to be an effective and convenient test for identifying prediabetes in this population.

Recently, the report from England was presented on the prevalence of prediabetes in individuals 16 -75 years in the period from 2003 to 2011 (8). The data are worrisome as the prevalence of prediabetes, defined as HbA1c value between 5.7- 6.4%, increased markedly in this period, from 11.6% to 35.3%. Moreover, within these eight years 50.6% of overweight individuals over 40 years developed prediabetes. These findings were not affected by the methodological issues as the HbA1c measuring devices were calibrated (8).

Morris et al (4) published a meta-analysis of 70 prospective observational studies in which participants had prediabetes at baseline defined by different criteria : ADA-defined IFG (100 -125 mg/dL or 5.6-6.9 mmol/l), WHO-defined IFG (110 – 125 mg/dL or 6.1-6.9 mmol/l), IGT (140-198 mg/dL or 7.8-11.0 mmol/l) or elevated HbA1c (6.0 -6.4% or 42-47 mmol/mol). It was found that HbA1c 6.0-6.4% identify prediabetes most similarly to ADA-defined IFG but with nonsignificantly lower rate than IFG combined with IGT. Clearly, the definition of prediabetes effects the incidence rates and it seems that HbA1c 6.0-6.4% identify individuals at a lower diabetes risk.

Another study from England on community based population compared diagnostic accuracy of HbA1c in screening for impaired fasting glucose with standard criteria 5.6-6.9 mmol/l (100-125 mg/dL) (9). Defining prediabetes at a lower HbA1c threshold of

39 mmol/mol (5.7%) instead of 47 mmol/mol (6.4%) increases its sensitivity in diagnosing IFG that allows to detect 40% more prediabetics.

Very recent report performed on adults without known diabetes from the National Health and Nutrition Examination Survey (NHANES) assessed ROC curves of HbA1c pertaining to the diagnosis of prediabetes by FPG and/or 2-hr OGTT (10). When patients were diagnosed using both FPG and OGTT the false-negative rate for HbA1c in identifying prediabetes was 64.9% but decreased markedly (9.2%) when HbA1c was combined with FPG for diagnosis.

In the above presented studies the performance of hemoglobin A1c, advocated for the diagnosis of diabetes and prediabetes, has been assessed in corroboration with FPG or with the combination of FPG and 2-hr OGTT glucose values. It appears that regarding recent American Diabetes Association and joint European Society of Cardiology and European Association for the Study of Diabetes guidelines, it is important to point out that HbA1c below 5.7% do not reliably exclude the presence of prediabetes. The above presented data support the idea for greater use of oral glucose tolerance tests in combination with FPG for diagnosis of dysglycemia.

Prediabetes in children and adolescents

The prevalence of prediabetes have increased also among overweight and obese youth that has implications for long-term health. Haemer et al reviewed the available literature on current screening programs, diagnosis, and treatment of prediabetes at 25 childhood obesity hospital treatment centers (11). They found that current prediabetes diagnostic criteria are derived from adult-based studies and are not modified in respect to the lower age group. There is however, some evidence on beneficial effects of preventing programs in children which result in a high proportion of obese with prediabetes returning to normoglycemia without pharmacotherapy.

Li et al investigated Chinese adolescents (11-16 years of age) without known diabetes and evalu-

ated the performance of HbA1c in detecting prediabetes as well its association with cardiometabolic risk (12). Prediabetes was diagnosed according to ADA criteria with HbA1c, FPG and OGTT in all individuals with HbA1c within 5.7-6.4%. ROC curve for HbA1c to identify prediabetes diagnosed by OGTT had an AUC of 0.53 only. These findings indicate a weak agreement between HbA1c and FPG or OGTT in detecting prediabetes.

Future perspectives

Secreted frizzled-related protein 4 (SFRP4), a recently discovered adipocytokine, has been described as a potential biomarker of early pancreatic β-cells dysfunction (13). Expression of SFRP4 mRNA and secretion of this protein from visceral adipose tissue is increased in obesity and correlates with insulin resistance. A significant inverse correlation of SFRP4 expression in human pancreatic islets with insulin secretion and positive relationship with glycated hemoglobin level was observed. A novel purpose for SFRP4 investigation as a biomarker of the pancreatic islet dysfunction was indicated. SFRP4 is elevated in the serum several years before clinical diagnosis of diabetes has been made and its presence increases the risk of diabetes up to five times. Therefore, SFRP4 might be used as an early risk predictor of prediabetes/diabetes, especially in apparently healthy individuals. The above mentioned cytokine should meet general requirements for biomarkers prior to its application in routine clinical practice. The assay should be standardized (preferably adapted for automatic analyzers) with proven analytical performance. Clinical performance and evaluation of clinical efectiveness is necessary in order to confirm the diagnostic goal and prognostic value in assessing risk of prediabetes/T2D. Another important aspect is a cost-effectiveness analysis which compares the change in costs and in health effects of introducing new test. Despite the promising results on the contribution of SFRP 4 in the pathogenesis of T2D, more detailed large population-based studies are needed to evaluate its diagnostic and clinical utility.

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