Journal of Diabetes and Its Complications 28 (2014) 226–233

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Approaching Pre-diabetes ☆

Leigh Perreault [a,*], Kristine Færch [b]

[a] University of Colorado Anschutz Medical Center, Aurora, CO, USA
[b] Steno Diabetes Center, Gentofte, Denmark

ARTICLE INFO

Article history:
Received 12 September 2013
Received in revised form 18 October 2013
Accepted 19 October 2013
Available online 28 October 2013

Keywords:
Impaired fasting glucose
Impaired glucose tolerance

ABSTRACT

As the global epidemic of type 2 diabetes continues to rise, the time has come to revisit our approach to pre-diabetes. Recently, much ado has been made about screening, diagnosis, pathophysiology and clinical interventions in pre-diabetes, and all for good reason as the key to reversing the diabetes epidemic likely lies therein. The somewhat controversial term "pre-diabetes" represents collective dysglycemic states intermediate between normal glucose regulation (NGR) and diabetes. Not all people with pre-diabetes will develop diabetes, but the majority will. In fact, up to 70% of those with pre-diabetes may acquire the disease over their lifetime. Furthermore, even when overt diabetes is delayed or prevented, both micro- and macrovascular disease appears more prevalent in those with pre-diabetes compared to their normoglycemic peers. Hence, there is growing consensus that NGR should be the goal for people with pre-diabetes. Nevertheless, there is much to consider in that pursuit. Herein, we provide an update on the global burden of pre-diabetes, its underlying pathophysiology and discuss clinical considerations in these individuals at high risk of developing diabetes.

1. Diagnosis of pre-diabetes

Diagnostic criteria for "impaired glucose tolerance" (IGT; one subtype of pre-diabetes) were introduced by the National Diabetes Data Group in 1979, concurrent with the first ever proposed criteria for diabetes itself (Anon 1979). Interestingly, criteria for IGT have remained steadfast over the past three decades, whereas the introduction and refinement of criteria for impaired fasting glucose (IFG; a second subtype of pre-diabetes that can be seen in isolation or in combination with IGT) have been far more moveable (Anon 1997; Anon 2004). The latter observation stems from the explicit expectation that people with IFG would also have IGT, a notion repeatedly debunked over the past decade (de Vegt et al. 2001; Meigs, Muller, Nathan, Blake, & Andres 2003). IFG and IGT are indeed discreet pre-diabetic states (Table 1).

Unlike diagnostic criteria for diabetes that are based on their predictive value for retinopathy (Anon 1997), diagnostic thresholds for IFG and IGT are based on the likelihood of developing overt diabetes (de Vegt et al. 2001; Meigs et al. 2003; Engberg et al. 2009; Qiao, Lindstrom, Valle, & Tuomilehto 2003; Soderberg et al. 2004). However, discussion regarding the existing cut points is ongoing. Longitudinal data from a cohort of Israeli soldiers suggest that a fasting glucose above 87 mg/dl (~4.8 mmol/L) is associated with an increased risk of future diabetes (Tirosh et al. 2005). Further, misclassification is common given the day-to-day variability in the fasting (15%) and 2-h (46%) glucose concentrations (Mooy et al. 1996). Use of the 1-h glucose value (post-OGTT), fructosamine, 5-androhydroglucitol and others has also been proposed (Juraschek, Steffes, & Selvin 2012). With the standardization and widespread use of the HbA_{1c}, in 2010, the American Diabetes Association (ADA) advocated its use in the screening and diagnosis of pre-diabetes (e.g. 5.7%–6.4%) (Anon 2010). It should be noted, however, the HbA_{1c} does not discriminate between IFG and IGT. Furthermore, the World Health Organization (WHO) only supports the use of HbA_{1c} for diagnostic use if stringent quality assurance tests are in place, assays are standardized to criteria aligned to the international reference values, and no clinical conditions are present which preclude its accurate measurement (Organization 2011).

2. Global burden of pre-diabetes

The changes in diagnostic criteria over the past years make it difficult to estimate time trends in the global burden of pre-diabetes. However, by combining recent data from diverse sources, the burden of pre-diabetes can roughly be approximated. In 2011, the Centers for Disease Control (CDC) estimated that 79 million Americans – 35% of people over the age of 20 – had pre-diabetes. However, discordance in the diagnostic criteria for IFG and IGT, regional differences in surveillance and reporting for chronic diseases, and other cultural nuances pose challenges in estimating the global burden of pre-

☆ Conflicts of Interest. All authors disclose that there are no conflicts of interest to declare.

* Corresponding author at: University of Colorado Anschutz Medical Center, P.O. Box 6511, mailstop F8106, Aurora, CO, USA.
E-mail address: Leigh.perreault@ucdenver.edu (L. Perreault).

1056-8727/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jdiacomp.2013.10.008

Table 1
Diagnostic criteria for pre-diabetes.

	Fasting glucose concentration	2-h glucose concentration
Isolated IFG		
ADA/AACE	100–125 mg/dl (5.6–7.0 mmol/l)	<140 mg/dl (<7.8 mmo/l)
WHO/EASD	110–125 mg/dl (6.1–7.0 mmol/l)	<140 mg/dl (<7.8 mmo/l)
Isolated IGT		
ADA/AACE	<100 mg/dl (<5.6 mmol/l)	140–199 mg/dl (7.8–11.1 mmo/l)
WHO/EASD	<110 mg/dl (<6.1 mmol/l)	140–199 mg/dl (7.8–11.1 mmo/l)
Combined IFG and IGT		
ADA/AACE	100–125 mg/dl (5.6–7.0 mmol/l)	140–199 mg/dl (7.8–11.1 mmo/l)
WHO/EASD	110–125 mg/dl (6.1–7.0 mmol/l)	140–199 mg/dl (7.8–11.1 mmo/l)

American Diabetes Association (ADA) Anon 2013.
American Association of Clinical Endocrinologists (AACE).
World Health Organization (WHO).
European Association for the Study of Diabetes (EASD) Ryden et al. 2007.

diabetes. To this point, the literature is currently devoid of any estimate of global prevalence of IFG. In 2012, the International Diabetes Federation estimated the worldwide prevalence of IGT at 280 million — a number expected to increase to 400 million by 2030, with the greatest absolute increases in Africa and the Western Pacific region (Fig. 1) (Federation 2012). Data from the National Health and Nutrition Examination Survey (NHANES) would contend that the prevalence of IFG is twice that of IGT (Cowie et al. 2009) (using ADA criteria), suggesting that the worldwide prevalence of pre-diabetes (IFG and/or IGT) may currently approach 840 million. Such estimations hold staggering implications for global human morbidity and mortality related to diabetes and highlight the huge need for screening and prevention of pre-diabetes.

3. Screening for pre-diabetes

A significant proportion of people with diabetes and pre-diabetes remain undiagnosed. According to ADA, adults above 45 years without additional risk factors or adults of any age who are overweight (BMI > 25 kg/m^2) and have additionally one other risk factor should receive a screening test for diabetes or pre-diabetes (Anon 2013). The screening test should be HbA_{1c}, fasting glucose or 2-h glucose, and repeated at least at 3-year intervals; once yearly in those diagnosed with pre-diabetes (Anon 2013). The European Society of Cardiology and the European Association for the Study of Diabetes (EASD) stated in 2007 that step-wise screening for type 2 diabetes using a non-invasive risk score (Heikes, Eddy, Arondekar, & Schlessinger 2008) as first step and then an OGTT for those with high score values, is more efficient than performing invasive testing in all people (Ryden et al. 2007). However, the efficiency of a step-wise screening strategy may be counter-balanced by the observation that many high-risk individuals fail to complete the first step of the screening program unless they are in contact with a doctor for other reasons (Christensen, Sandbaek, Lauritzen, & Borch-Johnsen 2004). Therefore, *opportunistic*, step-wise screening for diabetes and pre-diabetes may be the most cost-effective approach for identifying individuals at risk (Dalsgaard et al. 2010).

4. Risk for overt type 2 diabetes

Screening for and diagnosis of pre-diabetes are advocated as pre-diabetes represents a high-risk state for the development of overt type 2 diabetes. A recent meta-analysis showed that the yearly progression rate to diabetes in individuals with pre-diabetes is 3.5%–7.0% (vs. 2%/year in their normoglycemic counterparts (Engberg et al. 2009), with highest rates in those with combined IFG and IGT and the lowest in those with IFG by ADA (vs. WHO) definition (Morris et al. 2013) (Fig. 2). Increasing HbA_{1c} is also associated with increased risk of diabetes with yearly incidence rates approximating 5% for those with an HbA_{1c} of 5.7%–6.0% and up to 10% for those with an HbA_{1c} of 6.1%–6.4% (Zhang et al. 2010). Adding non-glycemic risk factors (obesity, hypertension, and family history of diabetes) to the diagnosis of pre-diabetes markedly increases risk for diabetes, approaching 30% per year (Rasmussen, Glumer, Sandbaek, Lauritzen, & Borch-Johnsen 2007). The latter observation underscores the significant interaction in these risk factors in the pathogenesis of diabetes.

5. Preventing or delaying diabetes

With the global surge in the prevalence of type 2 diabetes, focus on its prevention has intensified. Clinical trials for diabetes prevention around the globe have universally enrolled participants with untreated pre-diabetes due to their high risk for acquiring overt diabetes (Buchanan et al. 2002; Chiasson et al. 2002; Eriksson & Lindgarde 1991; Gerstein et al. 2006; Knowler et al. 2002; Torgerson, Hauptman, Boldrin, & Sjostrom 2004; Tuomilehto et al. 2001). Approaches for the prevention of diabetes have included intensive lifestyle modification or drug therapy (Fig. 3), as well as occasional combination drug therapy, as was the case in the CANOE trial (Zinman et al. 2010). Lifestyle interventions have utilized a low fat (<30% calories from fat; <10% from saturated fat) hypocaloric diet and moderate intensity exercise ~150 min per week for the purpose of 5%–7% weight reduction. With the exception of the NAVIGATOR Trial, collective results demonstrate that diabetes incidence can be reduced by 25%–75% over 2.4–6 years in a wide range of ethnic groups.

Despite the various strategies employed, only intensive lifestyle modification has been universally advocated (whereas metformin can be considered) for the treatment of pre-diabetes (Nathan et al. 2007). The rationale for this decision has included the questionable risk/benefit ratio, cost effectiveness and reduction in complications, such as cardiovascular disease, in people with pre-diabetes using medications for glucose lowering or weight reduction. Nevertheless, any intervention appears to lose its effectiveness over the long-term (Knowler et al. 2009). Waning benefit post-intervention has been attributed to lack of long-term adherence to lifestyle changes or drug therapy. An alternate explanation, however, may be that lack of progression to diabetes rather than the restoration of NGR has been the goal in all trials performed so far.

6. Reversing pre-diabetes

In clinical trials to date, interventions were deemed successful if diabetes was prevented or delayed, yet many participants remained with pre-diabetes. Arguably, prevention of diabetes and its complications lies in the restoration of NGR rather than in the maintenance of pre-diabetes. This was confirmed by a recent post-hoc analysis from the Diabetes Prevention Program Outcomes Study (DPPOS) (Perreault et al. 2012). This analysis demonstrated a 56% lower risk of diabetes 10 years from randomization among those who were able to achieve NGR during DPP vs. those who remained with pre-