Editorial

Controversies and Current Approaches in the Diagnosis of Prediabetes and Diabetes Mellitus

Chapter 1. Overview


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The International Diabetes Federation (IDF) estimates that 8.3% of the world's population or 387 million individuals have diabetes with 592 million, or 1 in 10, expected to develop diabetes by 2035 [1,2]. By the year 2050, it is estimated that 1 in 3 will have diabetes in conjunction with an ageing population [1, 2]. In addition, 316 million are considered at high-risk for developing diabetes with an expectation that this will increase to 500 million within a generation [1, 2]. The economic impact of this epidemic is monumental as one US dollar in 9 is spent on diabetes reaching $612 billion in 2014 [1, 2]. Diabetes accounts for over 5 million deaths annually and 500 billion US dollars in health-related expenditures [1, 2].

Forty per cent of adults face a life time risk of diabetes representing a substantial increase from 20% in the late 1980s [3]. Delaying the diagnosis can result in at least one complication by the time an individual has been diagnosed. These statistics are particularly disturbing as more than 70% of cases, approximating 150 million cases by the year 2035 [1, 2], can be delayed or prevented by adopting a healthier lifestyle. Furthermore, up to 11% of total healthcare expenditure in every country could be saved by addressing risk factors for type 2 diabetes [1, 2]. Once progression to diabetes occurs, many are unaware of their status with "gaps" demonstrated in risk factor control [4]. From 2007-2012, approximately 7.9 million individuals in the US with diabetes were unaware of their diagnosis although 85% had access to a care provider [4]. The preponderance had HbA1c levels below therapeutic targets although above the diagnostic threshold ($\geq$ 6.5%) with inadequate risk factor control and suboptimal use of blood pressure and lipid-lowering medications. The latter is fundamental as poor risk factor control exposes individuals to diabetes complications [4]. Furthermore, in the US from 2011-2012 among those with new onset diabetes between 18-64 years having private insurance, participation in diabetes self-management education and training was very low (6.8%) within 1 year after diagnosis [5]. The importance of this resides in that education is associated with increased use of primary and preventive services and less frequent need for acute hospitalization [5].

Thus, with the considerable benefits inherent in the prevention of diabetes, why does this remain so difficult to achieve? Fineberg [6] describes the paradox of prevention which is "celebrated in principle" but "resisted in practice." Among the obstacles he describes, "success of prevention is invisible, lacks drama, often requires persistent behavior change, and may be long delayed…Prevention of disease will succeed over time insofar as it can be embedded in a culture of health." Elliot Joslin acknowledged in 1921 [7] that "real headway against the ravages of a disease begins with its prevention rather than with its treatment…" Furthermore, the healthcare community has traditionally been schooled in addressing established conditions rather than in prevention so curricula therefore need to include greater emphasis on public health, increased professional training and practice towards prevention and integrated screening and prevention within the healthcare delivery system [8, 9]. What complicates this process considerably is the heterogeneity in defining and diagnosing glucose disorders-the subject of this monograph. Accurately defining prediabetes is challenging as glucose and HbA1c are relatively insensitive for diagnosing subtle metabolic conditions and may identify different populations [10-13]. Categorical definitions applied to a continuous process may therefore considerably underestimate those at risk for progression to diabetes [14]; the overwhelming number of individuals at risk is therefore undiagnosed.

Differences in the definitions of prediabetes and diabetes by the ADA and WHO pertaining to glucose and HbA1c parameters have recently been reviewed [15]. Defining glucose disorders is nevertheless imprecise whether HbA1c or glucose criteria are utilized [16]. Individuals with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) have relatively little overlap and demonstrate distinctive underlying biological mechanisms and pathophysiological abnormalities based on fasting glucose, 2-hour glucose or HbA1c levels [16, 17]. Those with an increase in both fasting and 2-hour post-load glucose levels do not represent a mixture of each phenotype but rather a distinctive entity [18]. Individuals with both IFG and IGT experience the steepest rise in the development of diabetes [18]. The importance of early identification of those at risk goes beyond the potential for developing diabetes *per se* as individuals with elevated fasting and 2-hour glucose concentrations also have a higher risk of cardiovascular disease [18] warranting intervention with aggressive modifications in lifestyle [19].

Genetics plays a role in determining the underlying etiology of prediabetes [18] with the transcription factor 7–like 2 gene (TCF7L2) having a particularly important role in the pathogenesis of type 2 diabetes [20]. Common variants in TCF7L2 were associated with an increased risk of diabetes among those with IGT in the Diabetes Prevention Program. The risk-conferring genotypes in TCF7L2 was associated with impaired β-cell function but not with insulin resistance [21].

Determining the optimal method to identify individuals at high-risk for developing diabetes is challenging as no single modality is likely to be uniformly applicable. Recent approaches to addressing this issue have recently been reviewed including the evaluation of biomarkers such as adiponectin and interleukin-1-receptor antagonist (IL-1Ra) as well as metabolomics which quantify small molecules (*e.g.*, amino acids, glycine, lysophosphatidylcholine, α-hydroxybutyrate, linoleoyl-

glycerophosphocholine) [19]. Fructosamine and glycated albumin levels above the 95th percentile have been shown to be related to a higher risk of incident diabetes and were predictive of retinopathy and CKD [19]. Whether these approaches will be clinically useful in determining those at risk remains requires further exploration.

HbA1c as a diagnostic tool identifies those with a mixture of abnormalities found when applying glucose criteria [17]. The latter, furthermore, can be affected by a variety of clinical circumstances which need to be taken into consideration [11-13, 22]. In addition, HbA1c and the OGTT do not relate uniformly across all ethnic groups in those with normal, intermediate glucose tolerance or with diabetes [23]. For example, in the US, African Americans have higher HbA1c than both Mexican Americans and non-Hispanic Whites [13].

Another approach for diagnosing dysglycemic conditions is through the application of a ''personalized'' glucose or HbA1c and insulin profile. Those demonstrating deterioration in glucose metabolism on an individual basis but not on a population level would encourage early intervention [22]. Consistent with previous observations, the 1-hour post-load glucose level during the OGTT was recently shown to be continuously associated with increasing HbA1 concentrations and therefore could serve as an early marker for abnormalities in glucose tolerance potentially identify at-risk individuals well before the traditional 2-hour glucose value [24-27]. To avoid relying on laboratory testing as a first-line approach to identifying those at high-risk, screening tools have been developed based on known risk factors for diabetes. Established tools developed in one population, though, need to be calibrated to assess specific diabetes risk in other ethnic groups. The latter can be applied for purposes of public screening and glucose testing can be incorporated subsequently to definitively stratify those at risk [28].

Eradicating diabetes will require increased attention to prevention on a worldwide basis. Indeed, global initiatives in this effort have been the subject of a recent text [29]. Government, food and agriculture stakeholders, in conjunction with public health authorities, community and medical institutions, play a vital and integrative role in thwarting the "diabesity" epidemic. This monograph, authored by established experts and global thought leaders in their respective fields, highlights the controversies, challenges and approaches for addressing the problems outlined.

The current issue of CDR includes seven comprehensive chapters authored by international experts in their respective fields. In Chapter 2, "**Definition of Prediabetes and Diabetes Mellitus,**" Buysschaert and colleagues examine the historical background as well as current diagnosis of glucose disorders and their inherent controversies. The diagnosis of diabetes is based on validated plasma glucose criteria and/or HbA1c concentrations. Prediabetes is considered as a main risk factor for the development of diabetes as well as of cardiovascular disease. Diagnostic criteria of the latter have changed over time and vary according to the ADA and WHO. Further long-term research examining clinically relevant outcome parameters based on different diagnostic criteria is needed in order to harmonize current definitions. Nevertheless, identification of prediabetes, on the basis of published criteria, permits early intervention in order to delay progression to complications.

In Chapter 3, "**HbA1c, Fructosamine, and Glycated Albumin in the Detection of Dysglycemic Conditions,"** Ribeiro and colleagues discuss fructosamine and glycated albumin as alternative markers of glycemia which can provide additional information to HbA1c or serve as reliable measures when HbA1c is not dependable. Whereas HbA1c assesses exposure to glucose for a three months period, glycated albumin and fructosamine represent a shorter duration of exposure which may be useful to monitor more rapid metabolic changes such as emanating from diabetes treatment. The use of these markers for diagnosing prediabetes and diabetes, evaluating glucose variability and risk prediction are considered as well. Glycated albumin may also contribute to glucose intolerance and may also lead to the potentiation of atherogenesis exacerbating cardiovascular risk.

In Chapter 4, "**DNA Methylation and MicroRNA-Based Biomarkers for Risk of Type 2 Diabetes**," O'Connell and Markunas describe various biological markers that may provide additional approaches in the early identification of glucose abnormalities. Genetic and environmental factors are both influential in the progression to type 2 diabetes. There are more than 65 genetic loci implicated in the susceptibility to type 2 diabetes which explain about 10% of the risk. The latter signifies that genetic models do not have the penetrance to be useful in population screening tools, or that they are only predictive when present along with other factors. Prediction models using genetic information do not perform substantially better than those based on routine clinical measures. The search for new biomarkers must integrate new, independent factors beyond the static genome that are influenced by environmental conditions. Modulation of gene expression by epigenetic modifications and the action of microRNAs are being recognized as critical processes affecting the risk for type 2 diabetes. Unlike the genome, these factors are responsive to environmental conditions including diet and exercise, which are well established in their relationship to diabetes prediction. Future genetically based biomarkers will likely leverage a combination of these types of biomarkers to provide enhanced prediction.

In Chapter 5, "**Heterogeneity of Prediabetes and Type 2 Diabetes: Implications for Prediction, Prevention and Treatment Responsiveness,"** Faerch and colleagues describe the distinctive phenotypic forms of prediabetes, their evolution to diabetes and treatment responses related to diagnostic criteria. Pathophysiological mechanisms resulting in type 2diabetes differ depending on whether the diagnosis is based on fasting plasma glucose, the 2-hour post-OGTT glucose level or HbA1c. Furthermore, the authors discuss whether markers of diabetes risk including the 30 minute and 1-hour post-OGTT glucose levels provide additional information to established diagnostic criteria. Predicted response to lifestyle or pharmacological interventions is predicated on genetic and physiological characteristics including glucose levels, insulin resistance and insulin secretory capacity. Understanding the underlying pathophysiology associated with either fasting or postprandial glucose regulation should assist in optimizing treatment strategies.

In Chapter 6, "**Population Approaches for Detecting Glucose Disorders**," Lee and Colagiuri describe diagnosing glucose disorders from a population perspective. Although diabetes and related complications can be prevented through early detection, lifestyle intervention and/or treatment, universal screening for diabetes has not been adopted. There are, instead, recommendations for a multi-step screening approach, which includes identifying people at risk through non-invasive methods such as a risk assessment tool followed by blood testing. Most screening initiatives have limitations such as low follow-up rate with primary care providers, abnormal screening results not being communicated to primary care providers, failure to provide appropriate follow-up, time and cost barriers and low acceptance of the oral glucose tolerance test. If these limitations can be addressed, diabetes screening initiatives have the potential to detect undiagnosed diabetes in most populations.

In Chapter 7, "**Ethnicity Considerations in Diagnosing Glucose Disorders,"** Hare and Shaw review the impact of ethnicity on burden of disease, diagnostic criteria for diabetes and the identification of people at risk of developing diabetes. Ethnicity is an important concept to consider when evaluating the definition and diagnosis of diabetes, as well as when screening for individuals at high-risk of diabetes. Having three different diagnostic measures for diabetes can create confusion due to significant discordance in the populations identified. However, there is no convincing evidence to date to suggest that any one of the criteria is inappropriate or inaccurate for a particular ethnic group. Each has advantages and disadvantages that must be weighed within the local setting. Further consideration should be given to the potential limitations of high-risk individual diabetes prevention strategies compared to population-based interventions in ethnic groups where a large proportion of the population is likely to be identified as high-risk.

Finally, in Chapter 8, **"Individualized Approaches for Detecting Prediabetes and Diabetes,"** Roth and Dankner examine the role of a personalized approach to diagnosing glucose disorders. The detection of those at risk for developing type 2 diabetes is particularly suited to a personalized approach since the essence of its diagnosis is the identification of individuals who may benefit from early intervention. Individual trajectories of progression to diabetes suggest the possibility of establishing personalized profiles based on serial measurements. Demographic, clinical, genetic, and environmental factors also need to be considered.

I am indebted to all the outstanding authors, highly regarded international experts in their individual fields, for taking from their valuable time and for their collaboration in contributing to this authoritative monograph. I am grateful as well to Bentham Science Publishers for recognizing the importance of this topic as a theme for the current issue. It is hoped that the monograph will stimulate further thought and research in confronting this enormous global public health crisis.

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