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COMMENTARY

What and when is diabetes? A devil's advocate perspective on contemporary controversies in diabetes criteria and classification

In a world of such incredible scientific progress in so many areas of human health, it may come as a shock to many, or at least a major surprise, that the question "What and when is diabetes?" is asked. This question raises a number of issues, and not just the more recent one of the relative utility of whether blood glucose or HbA1c is a better reflection of glucose tolerance status.

The joint issue of classification and criteria has serious implications not only for the management and prevention of diabetes, but also for biomedical research, particularly genomic studies where discrete categories need to be phenotypically "pure." This "purity" is almost impossible in type 2 diabetes mellitus (T2DM), where the actual determinants for cut-off points for diabetes, and indeed for impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), remain a subject of debate.[1] Traditionally, the threshold for the development of microvascular complications, like retinopathy, has been used as the marker for developing the diagnostic criteria for diabetes, but this may not be the best marker to target.

What is Diabetes? The issue of classification

In 1989, almost 30 years ago, one of us (PZ) raised issues arising as to the appropriate classification of diabetes.[2] It was argued that what we call T2DM is not a single or discrete entity, but part of a non-communicable disease (NCD) syndrome or risk factor complex. This argument was not new then and has continued with vigor uninterrupted until today, along with the argument regarding appropriate diagnostic criteria.[1–3]

Numerous attempts, particularly by World Health Organization (WHO) and the American Diabetes Association (ADA), have been made to get satisfactory answers on classification. These have been reviewed in detail elsewhere.[1]

Over the years, there have been several other attempts to reactivate debate[1] and, very recently, the international media ran a provocative headline "Diabetes is actually five separate diseases, research suggests."[4] That headline referred to a publication from Ahlqvist et al.[5] in which the authors stratified patients into five subgroups with differing disease progression and risk of diabetes complications. Ahlqvist et al.[5] suggested this innovative approach may eventually help tailor and target prompt treatment for the people with diabetes who would benefit most. Indeed, such an approach may also be useful for choosing subjects most likely to respond to different interventions for the prevention of T2DM. However neat a concept, given the heterogeneity of T2DM, the concept may be too simplistic.

The original attempts to classify diabetes were helped by the important observation of Himsworth in 1936,[6] who noted that there appeared to be two forms of diabetes, insulin sensitive and insulin insensitive. Some 15 years later, this was validated by Bornstein and Lawrence,[7] who, arguably, were the first to use a bioassay for insulin to describe the two discrete entities predicted by Himsworth, the conditions we now recognize as type 1 diabetes mellitus (T1DM) and T2DM. The main complexity, and that addressed in this Commentary, relates to T2DM (Himsworth's insulin-sensitive form), its classification, the much-debated diagnostic criteria and their appropriate use and value.

Over the subsequent six decades, there were been numerous attempts, particularly by the WHO and the National Diabetes Data Group (NDDG), to come to grips with a useful classification.[1] The classification should not only be of descriptive value, but also one that could be useful for individualizing treatment regimens given that T2DM is highly heterogeneous and there is an urgent need to provide a format that helps determine individual specific therapeutic needs.

Those attempts and the background discussion are detailed elsewhere,[1] but in 1965 the WHO held its first Expert Committee meeting on diabetes.[8] This was one of the first attempts to establish consensus on the classification of diabetes, but even so no global uniformity resulted. The contemporary classification of diabetes started with, and is still based largely on, that developed in 1979 by the NDDG[9] and the second WHO Expert Committee in 1980.[10] The first major revision of the 1980 WHO classification was published in 1999,[11] and this generated a new international classification and revised criteria.

Subsequently, there have been several attempts, including that by Ahlqvist et al.,[5] to provide a more contemporary classification more attuned to clinical needs rather than the current focus on T1DM and T2DM. Schwartz et al.[12] have recommended that there should be a re-evaluation of classification for informing both research programs and patient care. Their view was that the current classification presents challenges to the diagnosis and treatment of people with diabetes, due, in part, to the conflicting definitions of T1DM, T2DM, and the "newer" entity of latent autoimmune diabetes in adults (LADA), an entity that we first characterized.[13] In their view, available classifications lack a foundation that readily incorporates advances in the understanding of diabetes and its treatment.[12] Schwartz et al.[12] propose a novel approach and alternative classification based on a β-cell-centric classification that would avoid the inherent and unintended confusions of the current system. It is certain the overall issue for a globally acceptable, all-embracing classification is still some way from resolution!

When is Diabetes? The issue of diagnostic criteria

The diagnostic criteria for diabetes and associated states of glucose intolerance provides a similar dilemma.[1,3] We recently reviewed in more detail the various attempts to achieve consensus on criteria, particularly between the WHO and ADA.[1] The failures for international agreement have produced global confusion, with the use of different criteria making it impossibly difficult to compare data for both scientific and public health scenarios.

The report of the first WHO Expert Committee was one of the first attempts at international consensus.[8] The main diagnostic recommendation was a 2-h venous blood glucose of 130 mg/% (7.2 mmol/L) after a 50-g oral glucose load. The acceptance and effect of this decision was negligible and, despite a number of alternative diagnostic criteria being proposed in ensuing years, no semblance of uniformity existed until 1980.

Diagnostic criteria for states of glucose intolerance (diabetes and IGT) began with, and are still based largely on, those developed in 1979 by the NDDG[9] and WHO in 1980.[10] Preceded by an ADA attempt,[14] a major revision of the 1980 WHO criteria occurred in 1999.[11] The fasting plasma glucose (FPG) threshold for diabetes was lowered from 7.8 to 7.0 mmol/L. In addition, impaired fasting glucose (IFG), a new category of abnormal glucose metabolism with an FPG of 6.1–6.9 mmol/L, was introduced. Furthermore, the ADA report,[14] but not the WHO report,[11] recommended that FPG rather than the oral glucose tolerance test (OGTT) be used as the diagnostic test of choice for both clinical and epidemiologic purposes.

This latter recommendation, albeit seemingly a practical decision, was misguided and pivotal in initiating considerable confusion. Indeed, it resulted in many countries, researchers, and the WHO STEPS program using FPG as the standard procedure for diagnosing diabetes despite FPG underestimating diabetes prevalence by as much as 30%.[1] To add to the confusion, in 2003 the ADA Expert Committee had recommended that the threshold for IFG be lowered from 6.1 to 5.6 mmol/L.[15] This proposal was rejected by a joint WHO and International Diabetes Federation consultation, and they retained 6.1 mmol/L as the IFG threshold.[16]

Just to further confuse the issue of diabetes diagnosis, the suggested use of HbA1c emerged as a more practical means to diagnose diabetes and other forms of glucose intolerance.[17] However, it is clear from several studies that correlation between HbA1c and the OGTT diagnosis of diabetes is not necessarily synchronous.[1] It is still uncertain which test is better, glucose or HbA1c, but the latter is more convenient, showing less day-to-day variation and not requiring fasting. An International Expert Committee convened by the ADA in 2009 had recommended the use of HbA1c for diagnosis, with the criterion of HbA1c ≥6.5% as diagnostic of diabetes,[18] and 2 years later the WHO followed.[11] There are a number of qualifications and HbA1c use requires stringent quality assurance tests,[17] and there may be differences between different ethnic groups. However, in 2010, the ADA recommended that people with HbA1c of 5.7%–6.4% were also at increased risk of diabetes and should be considered as "prediabetes."[19] The effect of this decision was to generate yet another round of controversy. For example, the UK introduced HbA1c 6.0%–6.4% as the risk category in its national screening program but, with a lack of evidence to support the ADA decision, the WHO did not follow.[17]

Consequently, there is now a range of criteria and methods to diagnose diabetes, including FPG ≥7.0 mmol/L, the 75-g OGTT, 2-h plasma glucose ≥11.1 mmol/L, and HbA1c ≥6.5%. Therefore, it should not come as a surprise to anyone that these various tests do not all identify the same individuals as having diabetes.[19] In addition, these different criteria result in large variations in the estimated prevalence of undiagnosed diabetes. Cowie et al.[20] also showed in a US population that the prevalence of previously undiagnosed diabetes mellitus was 2.5% by FPG, 4.9% by 2-h plasma glucose,

and 1.6% by HbA1c. Only 1.2% of subjects met all three criteria.[20]

What and when is prediabetes?

If the diagnosis of diabetes represents a formidable task, the situation surrounding "prediabetes" provides even greater challenges.[1] Using the ADA definition,[1] if one or more of FPG, 2-h plasma glucose or HbA1c are measured, there are at least 18 possible combinations that can designate a person as "prediabetes"! In contrast, the WHO criteria for intermediate hyperglycemia are a 2-h plasma glucose after a 75-g OGTT of 7.8–11.0 mmol/L (IGT) or FPG 6.1–6.9 mmol/L with 2-h plasma glucose <7.8 mmol/L (IFG).[18] The result is that the ADA definition diagnoses much larger numbers of people with prediabetes. So, although the criteria for diabetes are testing, those for people at elevated risk of developing T2DM who are designated as having "intermediate hyperglycemia" by the WHO[17] or "prediabetes" by the ADA[19] are even more confusing.

As mentioned earlier, the ADA determined that people with HbA1c levels ≥5.7%–6.5% should be considered as a high-risk category (prediabetes). The WHO, having rejected this suggestion, retained FPG and 2-h plasma glucose as the only criteria for intermediate hyperglycemia. The WHO criteria for intermediate hyperglycemia has only three possible combinations: IFG, IGT, or IGT and IFG.[17] The extent to which these many combinations overlap is unclear, but emerging evidence now suggests that the phenotype and possibly the cause of hyperglycemia in people with isolated IFG differs from that in people with IGT.[21] This raises questions for designing interventions for prevention of T2DM in people at high risk of T2DM, especially those with isolated IFG. Prevention of diabetes in these subjects may be less effective (S. Thirunavukkarasu et al. unpublised observation, 2018).

Just like the situation for diabetes, the disparities in the interpretation of criteria for prediabetes clearly cause difficulty in comparisons of prevalence between different countries and in defining who may best benefit from intervention.

Conclusions

It is obvious from the above discussions that despite major advances in the genetics, pathophysiology, and treatment of diabetes, there are still major problems related to classification and diagnosis. Careful longitudinal studies relating both glycemia and HbA1c to outcomes are still needed so that those with highest risk can be identified. Similarly, more in-depth studies are needed to improve current classification, which inevitably affects treatment and even basic research strategies.

There are some other practical issues regarding the diagnosis of diabetes that have been described in more detail elsewhere,[1] including the correct conditions and method for measurement of plasma glucose and the different methodologies for measuring HbA1c and the limitations of its use.[17]

Reliable data on the burden posed by major types of diabetes mellitus are needed for many reasons beyond just raising and maintaining awareness of diabetes. These include meeting national and local needs for planning purposes to identify current and future healthcare priorities, to estimate direct and indirect economic and societal costs of the disease, and to allocate appropriate healthcare resources and expenditures for health care delivery.

Disclosure

None declared.

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