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International Diabetes Federation

Editorial

Back to the future—Do IGT and IFG have value as clinical entities?

1.   History

For many years levels of glycaemia intermediate between those considered normal and those labeled as diabetes, have been given different names. The first formal definition was proposed in 1965 by a WHO Expert Committee which recommended the term ''borderline'' diabetes [1]. In 1979 the US National Diabetes Data Group [2] defined a category, ratified in the 1980 WHO report [3], of Impaired Glucose Tolerance (IGT) based on the 2-h glucose values in an oral glucose tolerance test. This term was introduced, in part, to remove the stigma of the word ''diabetes'' from the other terms in use at the time to describe categories of high but not diabetic glucose levels, such as chemical, latent, borderline, subclinical or asymptomatic diabetes. IGT was defined as a state of increased risk of progression to diabetes and an independent cardiovascular risk factor. In 1997 the ADA Expert Committee [4] introduced the category of Impaired Fasting Glucose (IFG) to describe the zone between the upper limit of normal and the lower limit of the diabetic fasting blood glucose analogous to the zone described by IGT. Again this recommendation was adopted by WHO in 1999 [5]. In an attempt to aid public understanding of these related categories, the 1997 ADA committee suggested that IGT and IFG be collectively referred to as ''pre-diabetes''. Whereas previous committees had been keen to avoid labeling people with a ''diabetes'' related term for fear of the associated stigma, the proposal of the category ''pre-diabetes'' was deliberately chosen to suggest a high likelihood of future occurrence of disease and thus an urgent need for action. The proposal of more recent ADA groups to reduce the threshold for defining IFG [6], which would increase considerably the proportion of the population defined as having pre-diabetes, has stimulated interest in considering the utility of these categorical states [7].

2.   Rationale for IGT and IFG

IGT and IFG were conceived to define categories of glycaemia associated with an increased risk of developing diabetes. As such they have had pathophysiological, epidemiological and clinical uses. In the realm of understanding pathophysiology it is clear that the fasting glucose represents a different pathophysiological process to the 2-h glucose and that however diabetes is defined in the future, there will always be a value in studying these different processes alongside measures of insulin resistance and beta-cell function in order to understand disease mechanisms.

In an epidemiological framework, IGT, IFG and indeed ''pre-diabetes'' are standardized ways of describing the prevalence of non-diabetic hyperglycaemia in different populations at any one time or in the same population over time. Although there is no a priori reason why a category should be any better at defining the extent of the disease burden in a population than the mean and its standard deviation, it is certainly true that prevalence estimates are more immediately engaging for policy makers than measures describing a distribution.

As measures of future risk of diabetes, IGT and IFG certainly group people at higher risk. The annualized relative risk of a person with IGT progressing to diabetes is increased 6-fold compared with people with normal glucose tolerance [8]. This relative risk is even higher in people (12-fold) with both IFG and IGT. For IFG, the annualized relative risk of people with isolated IFG progressing to diabetes is 4.7-fold compared with people with normal glucose tolerance [8]. Categorizing people leads to an assumption that risk is similar throughout the range of values in the category and that there is no gradation of risk in those defined as normal. Both of these assumptions are incorrect [9]. A further assumption is that all of the cases of incident diabetes in the near future will come from the category of people with ''pre-diabetes'', whereas this is true for only about 60% [10].

Cardiovascular (CVD) risk is increased 1.7-fold with IGT and 1.2-fold with IFG [8]. However, the relationship between measures of glycaemia and CVD risk is linear across the range of non-diabetic hyperglycaemia, whether defined by fasting or 2-h glucose or by other measures such as HbA1c. There is no threshold at which the risk rises sufficiently to justify establishing a distinct category [7].

3.   Clinical value of IGT, IFG and "pre-diabetes"

One argument for "pre-diabetes" as a clinical category stems from diabetes prevention trials such as the Finnish and US diabetes prevention studies [11,12] which have used this category as an entry requirement. If one takes a view that these trials directly inform how diabetes prevention should be implemented in the real world, then the category "pre-diabetes" has logic. However, many commentators take the view that the results of these trials tell us that diabetes is preventable but that the implementation of prevention strategies needs to consider a wide range of other considerations.

A particular clinical concern with these categories is their lack of reproducibility. On re-testing individuals with IFG within 6 weeks, the proportion classified as IFG on the first test and on re-testing is approximately 50–60%, with the majority being reclassified as normal and less than 10% as having diabetes on repeat testing [8]. Similarly the proportion of people classified with IGT on the first test and on re-testing is 33–48%, with 39–46% being reclassified as normal and 6–13% as having diabetes on repeat testing [8]. Even over the medium term, the classification of "pre-diabetes" is really a misnomer since only a minority of people who have the condition will progress to diabetes over 5 years with a sizeable proportion reverting to normal without any intervention [13].

Another clinical limitation is that we do not currently tailor therapy to the specific metabolic abnormalities manifest by raised fasting or 2-h glucose. If this were the case, there would be a greater justification for their routine measurement. In the absence of such evidence, most clinicians find themselves in a situation in which the fasting and 2-h glucose levels are used to define pre-diabetic states, but that individuals are then monitored for progression without assessing 2-h glucose, which requires an oral glucose tolerance test, because of the time and effort required by patient and practitioner alike to undertake the test. If we were to use a measure of glucose to define risk of progression to diabetes and future risk of CVD, then it would be logical for this to be as practical as possible so that the same test could be used for diagnosis and monitoring of response to intervention.

4.   Implications of abandoning IGT/IFG

Recent guidelines published by WHO and IDF [7] and a recent review by the European Diabetes Epidemiology Group (EDEG), an EASD study group [14], have challenged the usefulness of these categories. EDEG recommended a review of the utility of categorical labels for non-diabetic hyperglycaemia suggesting that it may be timely to define risk in terms of glucose as a continuous variable. Similarly the WHO/IDF report recommended that consideration be given to replacing IGT and IFG by an overall risk assessment for the development of diabetes, cardiovascular disease, or both, which may include plasma glucose as a continuous variable.

There are already well developed options with which to replace IGT and IFG for risk assessment. For the purpose of predicting incident diabetes there are multifactorial risk scores, such as FINDRISC [15] which are being used in community-based prevention projects. Equally, for predicting CVD risk, global risk assessment tools are available and are widely used eg the Framingham equation [16].

5.   Conclusion

The continued use of categories of intermediate hyperglycaemia is coming under increasing scrutiny and is being increasingly questioned by a range of organizations. It is now approaching 30 years since the term IGT was introduced and over 10 years since IFG was proposed. Both appear to have reached their "use by date" for clinical purposes given their narrow risk assessment focus and the advent of more practical ways of more comprehensively assessing risk of both incident diabetes and CVD.

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