How to screen for diabetes risk in multi-ethnic populations: does one method fit all?

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Summary

The question as to how to screen diabetes risk in a multi-ethnic population is not easy to answer. There are a number of diagnostic procedures and risk score tools which may help identify people with increased risk. Some of the risk factors for diabetes have a clear ethnic component, thus the risk stratification is different in Caucasian, Asian and Latin American populations. However, we can expect that the pathophysiology for diabetes development consisting of insulin resistance and progressive beta-cell failure is very similar in its pathomechanistic background between ethnic groups, although the speed and progressive destruction may have ethnic and varying genetic components. In this environment, we have to find clinically applicable approaches to identify those with increased diabetes risk which have to be easy to understand, transparent and replicable for diabetes risk detection. The International Diabetes Federation recently started the PREDICT-2 study to develop a global diabetes risk score.

In this article, we discuss some of the strategies to identify diabetes risk and give some ideas about ethnic variation.

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Key words

risk score; diabetes risk; waist; type 2 diabetes; impaired glucose tolerence; risk stratification

Introduction

A European-wide project called IMAGE (Development and Implementation of a European Guideline and Training Standards for Diabetes prevention) developed recommendations for the detection for diabetes risk within the European population. As part of the project deliverables, the FINDRISC score was recommended as a screening tool, but also other screening questionnaires were listed for the detection of prevalent and incident diabetes. The IMAGE project was a European one, but within the scope of the project there was already a discussion that European diabetes risk scores are not equally applicable to all European Caucasian populations. Already, within Caucasian populations ethnic variation was seen, so we can expect a much higher relevance of ethnic variation to diabetes risk detection internationally.

Risk assessment in clinical practice

Because subjects with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) are at increased risk of developing type 2 diabetes mellitus (T2DM), they have been the focus of most previous prevention studies.[1–3] However, in long-term follow-up studies, only about half of those with IFG and/or IGT develop T2DM.[4] Moreover, many subjects with normal glucose tolerance (NGT) develop T2DM,[5] and, in longitudinal studies, ~40% of subjects who developed T2DM had NGT at baseline.[4] Thus, by solely relying on IFG and/or IGT to identify subjects at increased T2DM risk, many individuals who could have benefited from a prevention programme will have been left unidentified.

To overcome some of these limitations, several predictive models have been developed to identify subjects at increased risk for T2DM.[6–16] These models are based upon multivariate regression of risk factors for T2DM, i.e. age, gender, BMI, diabetes family history, fasting plasma glucose and lipid profile. Although HbA_{1c} reflects long-term glycaemic control, it has never been included in any of the multivariate predictive models. Recently, the American Diabetes Association (ADA) has changed the diagnostic criteria for diabetes (HbA_{1c} >6.5% [48mmol/mol]) and high risk individuals (HbA_{1c} 5.7–6.5% [39–48mmol/mol).[17]

Successful diabetes prevention programmes have included participants on the basis of having IGT,[18] which is diagnosed through an oral glucose tolerance test (OGTT), traditionally viewed as the gold standard method of identifying an impaired glucose response. IGT, unlike other forms of impaired glucose regulation (IGR), is primarily characterised by peripheral insulin resistance and therefore highly modifiable through lifestyle change, such as increased physical activity.[19] However, there are important practical limitations that have to be considered when performing an OGTT within a routine health care setting. For example, OGTTs represent a significant burden on health care resources and patient time, and are subject to a high level of

measurement error when conducted outside the rigorous standardised setting of a research environment.

In addition to issues around measurement, identifying those with IGR is also hampered by the sheer number of individuals meeting this risk factor within the population; for example, within some adult population groups prevalence rates can be as high as 50%.[20] Therefore, numbers with IGR in the population are likely to greatly exceed those that can be referred into prevention pathways considering the financial and infrastructure constraints inherent within primary care.

Given the two important considerations of measurement and prevalence, it is obvious that pragmatic strategies are needed to identify and prioritise those with the highest risk of T2DM within routine primary care for referral into prevention programmes. There is now emerging international consensus (based on screening approaches used in practice in the US, Germany, Australia, Finland and other countries) that a targeted, staged approach is the most effective way of meeting this demand.[21–23] For the adult population, this commonly involves using a validated risk score in the first stage to identify those with the highest risk of progressing to T2DM and then using a single blood test to confirm classification of IGR and/or rule out T2DM.[16] This approach has also been endorsed by the UK National Institute for Health and Clinical Excellence who recommended that a stepped strategy involving risk scores followed by fasting glucose (5.7–6.9mmol/L) or HbA_{1c} (6.0–6.4% [42–46mmol/mol]) testing should be used in the identification of IGR within the general adult population.[24] Using a large dataset of over 8000 adult individuals screened for T2DM through the Leicester arm of the ADDITION study,[25] 10–15% of the adult population within a multi-ethnic primary care based population would typically meet these stepped criteria for IGR depending on the risk score and biochemical measure used [unreported observation].

Risk scores

The Finnish Diabetes Risk Score (FINDRISC) questionnaire, which has been developed and validated in Finland, is a practical screening tool to estimate diabetes risk and the probability of asymptomatic T2DM in adults.[15] Several risk assessment tools have been developed for a variety of different settings.[16] The FINDRISC questionnaire is the most widely used risk tool internationally.[15] It uses weighted scores from eight easily accessible risk characteristics to calculate an overall risk profile. It can be used as a method of identifying those with prevalent T2DM or IGR or those with a high risk of developing T2DM in the future. FINDRISC has been shown to have good sensitivity (~0.8) and specificity (~0.8) at predicting the 10-year absolute risk of T2DM in a European population.[15]

It is widely recognised that risk scores need to be tailored to the population in which they are to be used, as differing population characteristics and distribution of risk factors can affect the weighting assigned to each variable within the risk score.[23] Therefore, risk scores that are based on, or similar to, FINDRISC have been developed and validated across different populations, including Germany, Denmark, and the UK.[11,26–29]

FINDRISC is currently evaluated in a large number of studies worldwide indicating differences in its performance and diabetes prediction, but it reveals the most commonly used risk score whereas in some populations modified FINDRISC scores perform better.

The results of a recent study indicate that the FINDRISC also can be applied to detect insulin resistance in a population at high risk of T2DM and predict future impairment of glucose tolerance.[12] FINDRISC is typically used as a method of self-assessing diabetes risk. However, given the need to incorporate risk identification strategies within routine care, risk scores utilising commonly collected and coded variables have been developed for use within primary care. This allows automated platforms to be used on patient databases to quickly and easily rank individuals for diabetes risk. The UK has led this approach internationally where three different practice-based risk scores, of varying utility, have been developed.[30–32] For example, the Leicester Diabetes Risk Score has been modified for use within general practice through the development of a software package that automatically ranks diabetes risk using commonly-coded patient level variables.[29,32]

As well as forming part of a stepped strategy for assessing diabetes risk, self-assessment risk scores can be valuable in their own right in helping promote a wider agenda around the importance of assessing and monitoring diabetes risk within the general population. For example, the British-based charity, Diabetes UK, hosts an online diabetes risk assessment tool that has been extensively used and promoted alongside a wider public health agenda aimed at the prevention of chronic disease (www.diabetes.org.uk/riskscore) leading to increased awareness of personal disease susceptibility. In addition, given their pragmatic nature, risk scores can be used as the primary method of detecting diabetes risk where resources are scarce and the opportunity for blood testing is limited. However, it is important that risk scores are developed or modified and then validated for the population in which they are used.[33]

Risk scores in different ethnic clienteles

There will be a variation in the applicability of risk scores based on patient-reported risk factors between different ethnic clienteles. This makes sense, because we know that the speed of development of T2DM varies between different populations and ethnic subgroups. On the one hand, we can expect that the pathomechanism of T2DM development is very similar and based on the development of insulin resistance and secretory defects in general. On the other hand, there are clear ethnic differences with the genetic background defining a higher susceptibility to develop insulin resistance or also early insulin secretory failure. Furthermore, there are a number of diabetes risk-influencing factors like visceral obesity which also have an ethnic genetic component and, in some populations, a strong environmental component.

What does this mean for the use of risk scores in different ethnic populations? Until today, it was not possible to develop one global risk score for diabetes risk that would be applicable to a wide variety of ethnic populations. The PREDICT-2 study began at the 2012 World Congress for the Prevention of Diabetes and its Complications (WCPD) in Dresden with the first workshop to try to evaluate the feasibility of developing one global diabetes risk score. The idea was to take the evidence and scientific information from more than 50 existing risk scores worldwide and to re-analyse the data from all the studies in a combined database to finally develop a global diabetes risk score.

A second workshop was performed at the 2012 WCPD in Madrid to discuss further steps. The conclusion was to focus on a prospective procedure and to define patient criteria and study procedures that can be performed prospectively and which would support the development of a global risk score. The current situation is summarised in previous work which shows a constantly increasing number of risk scores to detect diabetes risk worldwide.

Do we need a global diabetes risk score?

A global risk score which is applicable to a number of populations and ethnic groups by a large number of researchers and scientific as well as patient organisations would have a high potential to reach visibility and a number of stakeholders worldwide. This visibility then can foster the implementation and use of risk scores in clinical practice as well as implementation into medical guidelines. The global scope of the risk score at the end is a tool to enhance the implementation of prevention programmes. However, if those programmes are in place and local risk tools are successfully implemented, there is no reason for replacing them with a global score, because the aim of the global risk score is already met. Another secondary advantage of a global risk score would be to make scientific analysis regarding diabetes risk development more comparable between populations, which may foster the understanding of diabetes risk pathophysiology with its ethnic variation.

The PREDICT-2 project, now ongoing, aims to develop a globally applicable risk score. The risk prediction tools for identifying people at high risk of developing type 2 diabetes (PREDICT-2) project is an initiative of the IDF.[34] The project aims to establish and validate a methodology for adapting diabetes risk prediction scores for populations with locally available demographic data. This will allow countries without longitudinal data to develop their own country-specific diabetes prediction score based on a set of instructions from PREDICT-2 and local diabetes risk factor variables that are easily obtainable within their countries.

Blood tests

Although a range and combination of blood tests for adults have been proposed for classifying diabetes risk, including 2-hour or 1-hour post-challenge values, in reality fasting blood glucose or HbA_{1c} are the only values that are likely to fit the criteria of being pragmatic, clinically relevant and valid. This is consistent with recent recommendations from the UK.[24] Fasting glucose is well recognised as a method of assessing T2DM risk; ranges of 5.5–6.9mmol/L or 6.0–6.9mmol/L have been proposed as high risk categories by the ADA and WHO respectively.

The use of HbA_{1c} is more controversial and less well defined. A consensus approach by WHO recently included the use of HbA_{1c} >6.5% (48mmol/mol) as a diagnostic threshold for T2DM. However, there is no clear consensus on how or whether HbA_{1c} should be used to classify diabetes risk below this level. The ADA tentatively suggested that HbA1c 5.7–6.4% (39–46mmol/mol) indicates a high risk of T2DM, whereas an international expert committee suggested a range of 6.0–6.4% (42–46mmol/mol).[17,35] Prospective data from the UK support the use of 6.0–6.4% as those in this group were found to have a risk of future T2DM that was twice that of those in the range of 5.5–5.9% (37–41mmol/mol). However, other data from Germany suggest 5.7% (39mmol/mol) is likely to have the best sensitivity and specificity at detecting future diabetes risk.[36] Further, the optimal HbA_{1c} cut point for identifying subjects at increased diabetes risk is 5.65% (38mmol/mol)[36,37] and not 6.0% as originally suggested by the ADA expert committee.[17] If an HbA_{1c} of >6% was used to identify subjects at increased risk for future T2DM, only

about a third of subjects who developed T2DM would have been identified. Thus, use of an HbA_{1c} cut point of 5.65% would identify many additional high-risk individuals who could benefit from an intervention programme.[33,36,38,39]

Physical inactivity

Epidemiological, experimental and randomised controlled clinical studies have all consistently demonstrated that levels of physical activity are centrally involved in the regulation of glucose homeostasis, independent of other factors, including adiposity, in nearly all ethnic groups.[18,40–42] However, the role of physical inactivity in helping identify diabetes risk is less clear and more problematic for several reasons.

First, physical inactivity is an almost universal condition: it has consistently been shown that 50–80% of the population in both developed and developing countries fail to meet the minimum recommendations for health.[43–45] Indeed, when physical activity levels are objectively measured, rather than by subjective self-report, as much as 95% of the population are considered inactive.[45,46] Therefore, commonly used definitions of physical inactivity do not provide a clear mechanism for stratifying diabetes risk. Second, methods that rely on individuals self-reporting their activity levels are highly inaccurate and unreliable.

However, it is important that physical inactivity, as with other lifestyle variables, is considered for individual assessments of diabetes risk.[33] Changing eating habits can be effective in diabetes prevention but most effective seems to be to 'walk the diabetes away': 10 000 steps and more a day prevent diabetes sustainably but, more importantly, 1000 steps additional to the normal daily amount (even if much less than 10 000) are as effective as 1000mg of metformin.[47]

Waist circumference

Waist circumference is a powerful indicator of metabolic dysfunction as it represents a surrogate indication of the accumulation of visceral fat.[48,49] There is a strong risk association between an increase in visceral fat mass and risk of developing T2DM.[50]

From a public health point of view, waist circumference presents a clinically valuable measure because of accessibility,[51] as neither laboratory investigation nor invasive procedure are needed.

On the other hand, waist circumference has a clear ethnic bias. Most of the recommendations regarding waist circumference are based on Caucasian populations. In Asian populations, the waist circumference has a different relevance. Central obesity based on waist circumference is defined as ≥94cm for Europid men and ≥80cm for Europid women. For Asian populations, this is ≥90cm for men and ≥80cm for women. This is also applicable for those of South and Central American origin. The IDF recognises the increasing evidence that visceral adiposity is common to the metabolic syndrome, but also to diabetes mellitus and that this implies a clear aetiological link. Waist circumference is now a necessary requirement for the metabolic syndrome definition. The background for this is the strong evidence linking waist circumference with cardiovascular disease, other metabolic syndrome components and diabetes.

Cost-effectiveness/cost-benefit associated with risk screening

There is controversy about the cost-effectiveness of screening for diabetes risk.[52,53] Some expert groups argue that diabetes prevention is cost-effective and therefore the screening, which is the first step for prevention, also has to be cost-effective. There are others who argue that the screening alone does not provide any cost-benefit because it consumes a large amount of resources and may lead to the identification of more diabetes patients which entails for some of them a significant loss of money.

A recent unpublished paper has analysed the cost-effectiveness of diabetes screening in six European countries and found interesting results [manuscript in preparation]. The degree of effectiveness depends very much on health care structures, payment policies and the availability and cost of interventions afterwards.

Summarising the recent evidence shows that screening alone has probably no beneficial effect on preventing diabetes itself. The effectiveness as well as cost-benefit from diabetes risk screening depends completely on the transition of the people screened into inclusion in an intervention programme.[47]

We should act to ensure screening and intervention are always a combined package. Screening alone may have negative cost-effects and will stigmatise the people at risk but, in combination with the intervention, it will facilitate and boost cost-effectiveness from the individual, medical, payer and public health points of view.

Performing your own OGTT

The OGTT is the gold standard in diabetes risk screening. In a recent paper, a new test was presented allowing people to perform their own OGTT at home.[54] This is a very interesting approach, because it may enable people at risk, but also those with diabetes, to perform this test independently from a medical setting and only use the medical setting for the interpretation of the data. The test is technically very well developed. The patient has a plastic strip and is guided through every step of the procedure (starting the test, measuring the first glucose, drinking

glucose, measuring the 2-hour glucose, finishing the test). The test strip for measuring capillary glucose is included. After the test the patient breaks the tip of the plastic strip and sends this to the physician. The strip incudes a small chip incorporating all relevant data for quality assurance and the calibration of plasma glucose values.

The initial study performed to test acceptance and quality showed that 78% of subjects, who were completely untrained, were able to perform the test accurately. The study was performed in a controlled environment and showed very good acceptance values, but still too large a variation in glucose values, especially in the high value range.

It would be interesting to know, comparing the self-administered OGTT with the FINDRISC questionnaire, which of the tests enables a higher degree of motivation to change lifestyle after a positive test. The FINDRISC is limited in its ability to motivate people to change, but the self-administered OGTT may have a higher potential because patients perform the test themselves and this already shows a greater degree of engagement and may lead to a higher motivation to change lifestyle. This kind of a self-administered OGTT, therefore, is a highly attractive tool for screening.[54] We have to wait until prices are known and what technology is necessary for the physician (chip reader) to get a feeling about the test's feasibility.

Emerging risk factors

In nearly all populations worldwide, physical inactivity is becoming increasingly prevalent and this is often due to occupational sedentary time.[55] Decreasing occupational sedentary time can be a significant health policy aspect for diabetes prevention.[56] Environmental risk factors vary greatly and it is often argued that urbanisation is leading to obesity and diabetes. Studies from Africa show that, over a mid-term period, urbanisation has had the contrary effect, because in an urban environment people have a higher degree of availability of food and more healthy food available.[57] Over a period of two to five years this leads to a more healthy lifestyle but this then collapses and the energy-dense food overtakes the health benefit and the prevalence of obesity, metabolic syndrome and diabetes increases.

Epigenetic changes are newly discussed risk factors. Very recent studies have shown that circulating microRNA presents a characteristic profile if people develop diabetes.[58] The hypothesis could be that, for example, the liver becomes insulin resistant through fatty liver disease or toxic substances. The insulin-resistant liver cells then secrete microRNA particles which induce, in fat cells and muscle cells, insulin resistance without having the environmental and behavioural triggers for it. Much research is currently ongoing to identify microRNA profiles and their association with diabetes, and in the future we will probably receive a number of surprises from the emerging risk factors and their relevance for diabetes development.

Conclusion

The risk factors themselves are the same in nearly all ethnic environments and the ethnic variation only influences the speed of progression of disease accumulation.

It is important to know what increases diabetes risk. Visceral obesity seems to be the strongest pathophysiological factor for diabetes risk. Eating behaviour and, maybe even more relevant, physical inactivity are the risk factors that drive the progression of diabetes risk. There are ethnic variations in the susceptibility to accumulate visceral fat, but also to the degree to which physical activity may influence the accumulation of risk factors. It is relevant to know about these differences, because an Asian may have a higher risk than a Caucasian with the same waist circumference, and this is of high importance for an individual patient.

The main challenge is not that we start to develop very sophisticated ethnic-adjusted different tools for diabetes risk detection, rather that we start to do something towards reducing diabetes risk in our environment and population. The use of any risk score, the use of waist circumference as unique parameters, or the establishment of national screening campaigns and prevention management programmes – including early health checks – are the relevant challenge. Effecting standardised health checks at population level will have a relevant impact in identifying people at risk of diabetes, and hopefully the knowledge gained will translate into individualised and personalised prevention programmes.

It is important to be aware of ethnic variations in terms of risk factors. That said, the public health policy to make diabetes management a political priority and to develop standardised risk detection and prevention management programmes is the task for the upcoming years.

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