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**Opinion**

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# Hyperglycaemia, Pre-Diabetes and Diabetes: Can we Choose who to 'Fast-Track' into Diabetes Prevention?



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## Abstract

Global numbers of overweight and obesity have been increasing steadily for the past few decades, driving a rapid parallel increase in type 2 diabetes (T2D) morbidity and associated mortality. Hindered by our inability to clearly define the characteristics and therefore the assessment biomarkers for 'pre-diabetes', there remains significant difficulty in identifying those most at risk, essential in order to prioritize public health initiatives for those who would most benefit from 'fast-track' prevention. Implementation of a population-wide approach to T2D prevention is likely to be prohibitively expensive and unsuccessful, so more focused strategies are required. 'Pre-diabetes' is defined by any/all of 4 biomarker methods, comprising impaired fasting glucose (IFG), impaired glucose tolerance (IGT), IFG plus IGT, and mildly raised glycated haemoglobin (HbA1c). Each definition defines quite different sub-cohorts of the population, hence quite different risk profile, and may lead to both 'missed' and 'false positive' pre-diabetics. This problem must be resolved before we are able to make substantial strides and reliably choose who is most at risk and would most benefit from 'fast-track' into diabetes lifestyle and/or pharmaceutical prevention.

**Keywords:** HbA1c; glycated haemoglobin; Dysglycaemia; Pre-diabetes; Obesity; Type 2 diabetes; Prevention

**Abbreviations:** ADA: American Diabetes Association; T2D: Type 2 Diabetes; IFG: Impaired Fasting Glucose; IGT: Impaired Glucose Tolerance; WHO: World Health Organisation

## Opinion

Despite considerable global efforts the number of people diagnosed each year with type 2 diabetes (T2D) continues to increase, hindered by our inability to both clearly define and to identify those most at risk, and therefore in turn to prioritise public health initiatives for those who could most benefit from 'fast-track' prevention. T2D is a disease with its origins in poor diet and lifestyle with excess weight gain and adiposity as the primary cause, and hence prevention of weight gain and/or weight loss is a central tenet to any prevention program. Global numbers of overweight and obesity have been increasing steadily for the past few decades [1-3], with little sign of slowing, despite significant global efforts to halt the increase, with the World Health Organisation (WHO) estimating that almost 2 billion adults have a body mass index (BMI) of 25kg/m<sup>2</sup> or above [4]. In parallel T2D is becoming increasingly common [5]. In 1994 approximately 100 million people globally were reported with T2D, which increased to 382 million in 2013, and now with a projected increase

to 592 million over the next 20 years [6]. Those who have high levels of central adiposity are at particular risk of T2D, with abdominal obesity strongly associated with important changes in body composition including lipid infiltration into critical organs such as pancreas and liver [7]. WHO also estimates that up to 80% of heart disease, stroke and T2D could be prevented by eliminating risk factors resulting from an unhealthy lifestyle [8], resulting in significant improvement both to the individual and national health care systems. In the US alone the medical consequences of obesity have been estimated to be in excess of US \$150billion each year [9].

Key to prevention is the identification of those who are most at risk and who are most likely to benefit from intervention. Certainly some success has been achieved by several large international programs investigating lifestyle and pharmaceutical (metformin) approaches for T2D prevention [10-13], yet the inexorable climb in patient numbers highlights the urgent continued problem. There is a strong fiscal argument

against implementation of a population-wide approach, likely to be prohibitively expensive in many countries. Asia is an example of recent 'nutrition transition' to Westernized lifestyle, where T2D is a rapidly growing problem for many countries. China alone comprises a population of 1 billion, where up to 10% of adults are living with T2D and a further 30% estimated to be overweight and at risk of later disease [14]. An alternate and likely more successful strategy is to identify these individuals who are at greatest risk of later development of T2D, commonly termed as those with 'pre-diabetes', and focus resources into prevention for these sub-cohorts of the wider population. A major problem with this strategy however is how to identify those who truly are high-risk, and who left untreated will develop T2D in the following years.

The term 'pre-diabetes' has been used since the 1950s [15], and today is defined using a (wide) variety of criteria set by several different international bodies [16-18]. In short, pre-diabetes may be identified in 4 main ways. Firstly, through raised fasting plasma glucose (isolated impaired fasting glucose, IFG), indicative of individuals who primarily have hepatic insulin resistance hence raised glucose concentrations resulting from increased gluconeogenesis and hepatic glucose output even in the fasting state; secondly through impaired glucose tolerance (isolated IGT) identified during a standardised 2 hour oral glucose tolerance test (OGTT), indicative of individuals who have insulin resistance at the site of skeletal muscle and hence poor insulin-mediated glucose disposal following consumption of a meal; thirdly those with both IFG and IGT; and fourthly those individuals who are identified with raised levels of glycated haemoglobin (HbA1c), more recently proposed by the American Diabetes Association (ADA) [17] as an indicator of prolonged raised glucose levels resulting from long-term exposure to both basal and post-meal hyperglycaemia, and potentially representative of the combination of adverse pathologies that underly IFG and IGT. However, HbA1c clearly identifies a different pool of individuals as pre-diabetic compared to those identified using glucose cut offs, in addition to effects of gender and ethnicity, possibly a result of differences in glycation and/or red cell survival.

Depending on the definition chosen, these tests identify very different populations with quite different aetiology of pre-diabetes [19] and it may be expected that they will have very different risks of converting to full blown T2D. Indeed Barry and colleagues (2017) have recently shown by meta-analysis that as these different tests for pre-diabetes define vastly different populations, significant misclassification does occur [20]. This results in two opposing outcomes where large numbers of individuals are either (i) 'missed' pre-diabetics who fail to be correctly identified as high risk and so not fast tracked for intervention, or (ii) 'false' pre-diabetics likely to take up lifestyle or pharmaceutical treatment unnecessarily. Clearly this problem must be resolved before we are able to make substantial strides and reliably choose who to 'fast-track' into diabetes prevention.

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