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Pre-diabetes: Is this a clinical problem with pharmaceutical solutions?

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Prevalence of prediabetes is increasing significantly and poses a challenge to both developed and developing nations alike.[1] The vast majority of people with prediabetes are unaware of the condition and they are at very high risk of developing diabetes.[2] According to the IDA, approximately one-fifth of all adults with diabetes in the world live in the South-East Asia region.[3] It has been also forecasted that people with diabetes in the region will increase to 120.9 million by 2030, or 10.2% of the adult population. It was also pointed out that there were 23.8 million people with impaired glucose tolerance (IGT) in 2011, and this will increase to 38.6 million by 2030.[3] The number of people with diabetes in India, Bangladesh and Sri Lanka make up 99% of the total for the region (IDF).[3] It has been predicted that there will be about 471 million people with prediabetes globally by 2035.[4] There are 86 million, or more than 1/3rd of the population, in the USA[5] and an estimated 77.2 million people in India[6] who are suffering from pre -diabetes. The condition is associated with enhanced risk of developing micro- and macrovascular complications, which are more common in people with prediabetes than individuals at normal blood glucose levels.[2,8-13] Most studies demonstrated that 5% to 10% of people with prediabetes progress to diabetes each year[14,15] and with the same proportion converting back to normoglycemia.[15]

The treatment diabetes imposes a substantial burden on the economy of a country. People with diabetes have medical costs that are 2.3 times more than patients without diabetes.[16] Dramatic rise in costs for those with prediabetes and undiagnosed diabetes is also 'alarming'. The national cost associated with prediabetes in the USA is $44 billion (2012 estimate) and $510 annually per person (medical costs only).[5] The annual cost of diabetes in Bangladesh is US$314/person and total estimated annual cost to treat diabetes is US$1.5 billion, which is a large burden for a developing country like Bangladesh.[17] Increased costs associated with prediabetes and undiagnosed diabetes highlight the growing importance of prevention and early intervention and treatment.

There are more controversies than consensus in defining prediabetes among different authorities. The American Diabetes Association (ADA)[18] in 1997 and World Health Organization (WHO)[19] in 1999 defined the criterion for diagnosis of diabetes to a fasting plasma glucose concentration of ≥7.0 mmol/L (126 mg/dL), and impaired fasting glucose (IFG) [6.1-6.9 mmol/L (110-125 mg/dL)]. However, ADA in 2003 recommended reducing the threshold for IFG from 6.1mmol/L (110mg/dL) to 5.6mmol/L (100 mg/dL) to improve the prediction of diabetes risk.[20] This was not endorsed by the WHO or any other authorities.[21] Concerns were expressed that this new IFG level would roughly double the prevalence of sub-diabetes.[22] The expanded IFG level would include people at lower risk of diabetes and cardiovascular disease who may perhaps be less likely to benefit from medical interventions.[22]

Prediabetes can also be diagnosed by glycosylated hemoglobin A1C (HbA1c). There was reasonable consensus on using HbA1c >6.5% (48 mmol/mol) to diagnose diabetes[23-25] and less around pre-diabetes.[22] The International Expert Committee[25] and the National Institute for Health and Clinical Excellence[26] (UK-based) supported using 6.0–6.4% (42-46 mmol/mol) for prediabetes range and recommended intervention if HbA1c ≥6.0% and may be below this level for patients who are at increased risk. In 2010, the ADA reduced the threshold for prediabetes from 6.0% to 5.7%,[23] a decision not supported by WHO or other agencies.[22] These changes caused a lot of havoc! For example, if this guideline is used, over half of all Chinese adults would have prediabetes i.e. approximately 493 million people – and this should be considered an epidemic situation![22]

Several clinical trials have shown that intensive lifestyle interventions and the use of pharmacological agents can significantly reduce the incidence of overt DM in individuals with prediabetes. Three major trials of diabetes prevention with intensive lifestyle counselling conducted in China,[27] Finland[28] and America[29] reported a 40%-60% relative risk reduction in the incidence of diabetes, with one case of diabetes being 'averted' by treating around seven people with IGT for three years.[22] Several oral agents including metformin, thiazolidinedione's (TZDs), acarbose and insulin have been evaluated for the prevention of DM in patients with prediabetes; however, these studies have only had modest success and reported various side-effects and toxicity.[30]

So the question is: should we screen and diagnose prediabetes? The criterion recommended by the ADA overestimated number of the prediabetes. Approximately, there are 3.2 million people in the UK suffering from T2DM, but approximately 16 million people would fall into the ADA's prediabetes category.[22] The ADA category of prediabetes includes millions of people who are at a much lower risk of

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progressing to diabetes, for whom any benefit from treatment is currently unknown.[22] Prof John Yudkin, of UCL said: 'Pre-diabetes is an artificial category with virtually zero clinical relevance. There is no proven benefit of giving diabetes treatment drugs to people in this category before they develop diabetes, particularly since many of them would not go on to develop diabetes anyway'.[22]

Should we treat the prediabetic patients with medication? Do we have enough resources to treat these so called 'patients'? Will this distract us from managing and treating the huge number of diabetic patients? Moreover, there is no evidence that earlier intervention based on the ADA's criteria can lead to either improved health or a reduced risk of death. The treatments to reduce blood sugar in prediabetes patients only delayed the onset of T2DM by a few years, and until now there is no evidence of long-term health benefits.[30]Even from improving health, the drugs can cause more side-effects and even death! Professor Yudkin and Professor Montori argued the situation by highlighting the findings of the DREAM study:[31] '14 in 100 people were prevented (or postponed) from developing diabetes by taking rosiglitazone for 3 years. This means that 86 in 100 healthy people who weren't going to develop diabetes in three years were put on a drug that causes heart failure and fractures and has been under suspicion of increasing cardiovascular risk'.[22] Troglitazone and Rosiglitazone have been withdrawn from the market or advised to be used cautiously due their toxicity or adverse effects. They also mentioned that labeling people with moderately high blood sugar as prediabetic is a drastically premature measure with no medical value and huge financial, social and emotional costs.[22] Moreover, a range of newer and more expensive drugs are being explored (such as DPP-4 inhibitors and GLP-1 receptor agonists) as treatments for pre-diabetes which will incur more costs[30] and will divert resources from priority health issues. It was emphasized that we should not consider prediabetes as a 'clinical problem with pharmaceutical solutions'.[32] Rather, money and efforts should focus on improving priority public health issues. Healthy diet and physical activity should be considered as the best options to prevent and to tackle prediabetes and diabetes. To harmonize current definitions of prediabetes, further long-term clinical research is required by considering clinically relevant outcome parameters based on different diagnostic criteria.[33]

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