The epidemic of pre-diabetes: the medicine and the politics

This article is part of a series on overdiagnosis looking at the risks and harms to patients of expanding definitions of disease and increasing use of new diagnostic technologies

Aldous Huxley wrote that "Medical science has made such tremendous progress that there is hardly a healthy human left." Changes to the American Diabetes Association (ADA) guidance on the diagnosis of pre-diabetes in 2010 make this statement even more true.[1] If implemented globally the guidance could create a potential epidemic, with over half of Chinese adults,[2] for example, having pre-diabetes, a national burden of around 493 million people.

Pre-diabetes is an umbrella term and the most widely used phrase to describe a blood concentration of glucose or glycated haemoglobin (HbA_{1c}) that lies above normal but below that defined for diabetes. We explore the evidence and value of pre-diabetes as a category or diagnosis (box 1) and argue that current definitions risk unnecessary medicalisation and create unsustainable burdens for healthcare systems.

Impaired glucose tolerance was established in 1979,[3] and its definition has not been altered since. People with impaired glucose tolerance are at increased risk of developing diabetes, with 10 year incidence as high as 60% in some studies.[7] They are also at around 50% greater risk of coronary heart disease.[7-9] Several studies show lifestyle intervention can prevent, or perhaps delay, the onset of diabetes but the role of other interventions is less clear. There is also important debate about how well the new and expanded definitions of pre-diabetes are associated with future diabetes and arterial disease, and responses to interventions to modify risk.

Diagnostic change

Population measures of glycaemia are continuous, with no inflections to provide obvious cut-off points. Cut-offs for the diagnosis of diabetes are based on thresholds for risk of retinopathy.[3 5 10] Lesser degrees of hyperglycaemia increase the risk of developing diabetes and maybe arterial disease. But in both cases the risk is graded, making any choice of cut-off point purely arbitrary.

Between 1979 and 1997, the intermediate category was called impaired glucose tolerance. The standard test was measurement of plasma glucose two hours after a 75 g glucose load. The US National Diabetes Data Group defined diabetes as concentrations >11.1 mmol/l (200 mg/dL) and impaired glucose tolerance as 7.8-11.1 mmol/L (140-200 mg/dL),[3] and these definitions were ratified by the World Health Organization.

But glucose tolerance testing is laborious for the patient, who must fast, take the glucose load, and then have a blood test two hours later. It is also poorly reproducible—for example, a person with a test result of 8.0 mmol/L (just inside the definition for impaired tolerance) has a roughly 30% chance of a normal result on repeat testing.[7] After recommendations from an ADA expert committee in 1997[10] and WHO in 1999,[5] the criterion for diagnosis of diabetes was altered to a fasting plasma glucose concentration of ≥7.0 mmol/L (126 mg/dL), with the intermediate category termed impaired fasting glucose (6.1-6.9 mmol/L (110-125 mg/dL)).[5 10] This avoided the need for a glucose challenge test.

We should use available resources to change the food, education, health, and economic policies that have driven this epidemic

In 2003 an ADA expert committee recommended reducing the threshold for impaired fasting glucose from 6.1 mmol/L (110 mg/dL) to 5.6 mmol/L (100 mg/dL).[11] The committee said this expansion improved prediction of diabetes risk. But it may also have been influenced by concern that its 1997 fasting glucose criteria identified fewer people than the glucose tolerance test. WHO expressed concern at the public health implications of the change in threshold for impaired fasting glucose[4]; the expanded category would roughly double the prevalence of sub-diabetes and include people at lower risk of diabetes and cardiovascular disease, who were perhaps less likely to benefit from medical intervention.

More recently, the development of reference methods to standardise assays has allowed measurement of HbA_{1c} to enter as a third test to diagnose glucose intolerance.[6] In 2009, there was reasonable consensus on using HbA_{1c} >6.5% to diagnose diabetes,[1 6 12] although less around an intermediate category (box 1). But in 2010 the ADA reduced the threshold for this intermediate category from 6.0% to 5.7%,[1] a decision not endorsed by any other group.

There has also been little support for the ADA's proposal to label a category of pre-diabetes, into which is rolled all three definitions of sub-diabetes—impaired glucose tolerance, impaired fasting glucose, and borderline HbA_{1c} (box 2, see bmj.com).[4 6 12-14] This is partly because it has lowered the thresholds for impaired fasting glucose and HbA_{1c}, but it is also because the imperfect overlap between the three component definitions creates a large, poorly characterised, and heterogeneous category of glucose intolerance.

SUMMARY BOX

Clinical context—Attempts to tackle the increasing prevalence of diabetes have focused on identifying and treating people at risk of developing the disease

Diagnostic change—The definition of people at risk has expanded from impaired glucose tolerance to include people with raised fasting glucose or glycated haemoglobin (HbA_{1c}) concentrations and cut-off points have been lowered

Rationale for change—People in all the above categories have a raised diabetes risk, although prediction is poorer for fasting glucose and HbA_{1c} than for impaired glucose tolerance

Leap of faith—Treatment of people in newly defined categories will improve mortality and morbidity

Impact on prevalence—The expanded categories increase the prevalence of pre-diabetes by twofold to threefold

Evidence of overdiagnosis—New definitions result in over 50% of Chinese adults having pre-diabetes

Harms from overdiagnosis—A label of pre-diabetes bring problems with self image, insurance, and employment as well as the burdens and costs of healthcare and drug side effects

Limitations of evidence—No studies have examined the effect of lifestyle or drug interventions in newly added subcategories

Conclusion—Diabetes prevention requires changes to societies and therefore a concerted global public health approach. Diagnoses and thresholds for clinical application may unrealistically burden societies in exchange for limited value

Effect of ADA criteria on prevalence

A recent study in 98 658 Chinese adults[2] found a prevalence of impaired glucose tolerance of 8.3%, but over three times as many people (27.2%) satisfied the expanded ADA criteria for impaired fasting glucose and even more (35.4%) met the glycated haemoglobin criteria. Furthermore, the imperfect overlap of the populations that the tests identify provided a total population of 50.1% with ADA defined pre-diabetes.[2] These numbers represent 493.4 million Chinese adults.

The convenience of measuring glycated haemoglobin is likely to influence diagnostic patterns. Glucose tolerance testing is uncommon and testing fasting glucose is inconvenient. Glycated haemoglobin can be measured regardless of time of day, making the process of screening and case finding simpler. But this will result in the highest prevalence of pre-diabetes.

Overdiagnosis and underdiagnosis

Using the oral glucose tolerance test, fasting glucose, and HbA_{1c} to diagnose glucose intolerance is harder and more error prone than diagnosing diabetes. This is because intolerance is created between two cut-off points (rather than one for diabetes) for measures that have substantial biological and assay variability.

Another challenge is that even were the three tests to diagnose a similar prevalence of the population as being glucose intolerant, they do not identify the same people.[7 13] For example, the prevalence of borderline HbA_{1c} concentrations in non-Hispanic black people is twice as high as in non-Hispanic white people, while the converse is true for impaired glucose tolerance. People of black African heritage also have higher concentrations of glycated haemoglobin and other markers of glycaemia than other ethnic groups.[17 18] Care is therefore needed when thresholds for glucose intolerance derived from one population are applied to other demographic groups.

Furthermore, glucose tolerance by all criteria deteriorates with ageing[13] so prevention of diabetes may represent little more than delaying its eventual development. Because impaired glucose tolerance, fasting glucose concentrations, and HbA_{1c} reflect different metabolic phenomena, any relation with complications such as arterial disease may also differ.

Box 1 | Definitions of "sub-diabetes" (impaired glucose metabolism)

Impaired glucose tolerance[1-4]
Plasma glucose concentration 7.8-11.1 mmol/L (140-200 mg/dL) two hours after 75 g glucose load

Impaired fasting glucose
WHO: fasting plasma glucose 6.1-6.9 mmol/L (110-125 mg/dL)[4 5]
American Diabetes Association: 5.6-6.9 mmol/L (100-125 mg/dL)[1]

Pre-diabetes
International Expert Committee (2009):
"The categorical clinical states pre-diabetes, IFG, and IGT fail to capture the continuum of risk and will be phased out of use as A_{1c} measurements replace glucose measurements"
Intervention for HbA_{1c} ≥6.0% (and maybe below this level if patient demonstrably at high risk[6]
American Diabetes Association (2010): HbA_{1c} 5.7%-6.4%[1]

Questions over value of pre-diabetes

The logic of creating a diagnostic category of pre-diabetes is that it can provide benefit by precisely identifying those who will develop diabetes, allowing for effective interventions targeting both the disease and its complications. However, the evidence does not necessarily support this logic.

Is a test of glycaemia necessary for prediction?

A recent paper reviewed 94 risk prediction models for diabetes, less than half of which included a measure of glycaemia.[19] There was almost complete overlap of the discrimination and calibration characteristics of those with and without such measures.

Does diagnosis of pre-diabetes guarantee future diabetes?

The term pre-diabetes implies inevitable progression and risks stigmatisation. Yet a meta-analysis of the progression rates of pre-diabetes defined according to different glycaemic measures found that even with the best predictor, impaired glucose tolerance, more than half of people identified will be free of diabetes 10 years later.[20] The same meta-analysis suggests that around two thirds of people with impaired fasting glucose will not have diabetes after 10 years. To date, studies have suggested that rates of progression in people with borderline glycated haemoglobin are similar to those with impaired fasting glucose,[21-23] but none has assessed the new lower ADA glycated haemoglobin threshold.

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Does lifestyle intervention prevent diabetes and its complications?

There have been three major trials of diabetes prevention with intensive lifestyle counselling—in China (n=577),[24] Finland (n=522),[25] and the US (the Diabetes Prevention Program, n=3234).[26] All were in people with impaired glucose tolerance and a mean age around 50 years. Each 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 impaired glucose tolerance for three years.[27-29] But the rates of diabetes during follow-up after the trials imply that the lifestyle interventions delayed the onset of diabetes by around two to four years, rather than prevented it altogether.[28 29]

The Chinese study had three intervention groups: healthy diet, exercise, or both. It reported that the combination of diet and exercise intervention reduced the 20 year incidence of severe diabetic retinopathy from 16.2% to 9.2%.[30] The 23 year cardiovascular and all cause mortality was reduced by 20% to 12% and by 38% to 28% respectively, these differences being seen only in women.[31] These findings seem surprising for interventions that delayed diabetes onset by only 3.6 years.[29] The Finnish study found no effect on cardiovascular risk,[32] and this was confirmed in a meta-analysis.[33] There are no data on the effect

Evidence on value of various definitions of sub-diabetes

	Diabetes			Arterial disease			Retinal disease
	Predicts	Effect of lifestyle interventions	Effect of drugs	Predicts	Effect of lifestyle interventions	Effect of drugs	Predicts
Impaired glucose tolerance (7.8-11.1 mmol/L)*	+++	+++ (delays) + (prevents)	+++ (disguises) + (prevents)			?	+
Impaired fasting glucose (6.1-6.9 mmol/L)	++	?	(+)†	+	?	?	?
Expanded impaired fasting glucose (5.6-6.9 mmol/L)	+	?	?	+	?	?	?
Borderline HbA_{1c} (6.0-6.4%)	++	?	?	+	?	?	?
Expanded borderline HbA_{1c} (5.7-6.4%)	+	?	?	+	?	?	?

*Two hours after 75 g glucose load.
† The DREAM Study included 14% of subjects with impaired fasting glucose in whom rosiglitazone showed comparable effects to those with impaired glucose tolerance at the end of the intervention,[37] although this group was not reported separately after drug washout.[45]

of similar interventions among people labelled as pre-diabetic using impaired fasting glucose or HbA_{1c}.

The interventions in these studies were based on individual attention and advice. Rolling out intensive lifestyle interventions like these to populations with pre-diabetes (comprising an estimated 86 million people in the US[34] or 493 million in China[2]) would be challenging.

What about drugs?

The concept of pharmacological prevention is attractive for both the busy clinician and the drug industry. The Diabetes Prevention Program included a randomised controlled trial of metformin and troglitazone in people with impaired glucose tolerance. The troglitazone arm was discontinued because of toxicity. Metformin reduced the 2.8 year incidence of diabetes by 31% compared with placebo,[26] but the final oral glucose tolerance test was done while participants were still taking metformin—the first line treatment for type 2 diabetes. Most of this effect remained after 1-2 weeks of drug washout.[36] Longer follow-up showed that metformin did not prevent diabetes but delayed diabetes by around two years, even though over half these people were taking metformin during the follow-up.[28]

Two studies of thiazolidinediones have also been published, both in people with impaired glucose tolerance. The three year DREAM trial[37] of rosiglitazone studied 5269 people with impaired glucose tolerance or with impaired fasting glucose by WHO criteria (box 1) and the ACT NOW trial[38] of pioglitazone followed 602 people with impaired glucose tolerance for around 2.4 years. In both trials, the incidence of diabetes was reduced (relative risk reduction 62% in DREAM and 72% in ACT NOW). However, testing was done without drug washout, raising the question of whether diabetes had been prevented or merely disguised by treatment.

Harms and risks of overdiagnosis

But even if drugs can delay diabetes in some or all types of pre-diabetes, should people receive these drugs in order to slow the incidence of diabetes? The concept, perhaps combined with epidemic levels of pre-diabetes in "emerging markets," is exciting the pharmaceutical industry. A search on the ClinicalTrials.gov registry using the search terms "pre-diabetes" and "drugs" shows 422 such trials (21 April 2014). However, there is a hazard in creating a pre-disease associated with a disease such as type 2 diabetes, which is itself little more than a risk factor. The biochemical diagnosis of type 2 diabetes is based on a surrogate endpoint.[39] The downsides of being diagnosed with diabetes include the need for medical care and treatment, with its costs and risks, challenges with insurance and employment, anxiety about future complications, and self image. Pre-diabetes could be defined as a risk factor for developing a risk factor. With this label comes much of the same baggage as for diabetes, without evidence of long term benefit (box 3, see bmj.com).

Individual or population approach?

Only a year before the ADA produced its latest guidelines, it partnered the European and international diabetes associations to appoint an expert committee.[6] The committee recommended abandoning the term pre-diabetes and suggested an HbA_{1c} level of ≥6.0% as a threshold for preventive interventions. Nevertheless it is the ADA's 2010 criteria, and the label of pre-diabetes, that dominate the scientific literature, despite the reservations of many organisations, including WHO (box 2, see bmj.com). The marked contrast in approach may represent the dominance of a medical model over a public health approach, predicating individual lifestyle advice and perhaps drugs, to prevent or delay increasing glycaemia. This "glucocentric" approach[41] is perhaps influenced by the dominance in committees of clinical endocrinologists, rather than by any ties to industry, as has been suggested for other conditions.[42]

The implementation of the new ADA criteria for pre-diabetes[1] is unfeasible. Providing everyone identified by these criteria with personalised lifestyle advice, with or without metformin or other medication, will place unmanageable demand on health services. This strategy also risks distracting attention from those who actually have diabetes and are at higher risk, and in arguably greater need of personalised medical attention.

The dramatic increase in the numbers of people developing diabetes is a global public health problem and needs population and ecological strategies to tackle it. Interventions to improve diet and increase physical activity are less likely to succeed when they seem to be aimed at just a subset of the population which is being encouraged to swim against the tide—although when, as in China, over 50% of adults have pre-diabetes the tide may be turning.

Population strategies to "prevent diabetes" and to treat diabetes are identical. The dividing line is, in this sense, largely irrelevant: pre-diabetes represents little more than a downward shift of the criteria for diagnosing a single disease, so embracing people who may or may not develop the condition.

Fortuitously, first line "treatment" for pre-diabetes by whatever definition is lifestyle advice. And because the risk factors overlap with those of other non-communicable diseases, the question is why focus attention on a specific group of people with a diagnosis of pre-diabetes while ignoring the remainder of the healthy population who would benefit from the same advice. For countries with a high prevalence, such as China, the case for a whole population public health approach is compelling. The real question is whether it is "worth" having the category of pre-diabetes at all.

The effect of preventive interventions needs exploring at both public health and individual level. Biochemical measures are of greater importance to physicians than to patients, whose main concerns are the long term complications of the condition, and these outcomes must be the prime considerations when designing future studies. Because the effect of glucose lowering on such outcomes may take decades to become apparent, modelling approaches may be needed. Until then, the recommendations of the 2009 International Expert Committee regarding the continuum of risk[6] should be accepted and the term pre-diabetes put in cold storage.

We need a shift in perspective. It is critically important to slow the epidemic of obesity and diabetes. Rather than turning healthy people into patients with pre-diabetes, we should use available resources to change the food, education, health, and economic policies that have driven this epidemic.

WHAT TO DISCUSS WITH PATIENTS

A diagnosis of pre-diabetes does not mean that you will develop diabetes. In fact, of 100 people like you, fewer than 50 are likely to develop diabetes in the next 10 years

There are ways of reducing your risk of developing diabetes that involve changing your diet and being active. These can result from efforts you make as well as changes in your environment (food supply, workplace conditions, education, and other social determinants of health)

There are drugs to delay diabetes, but these are the same drugs you will need if you do develop diabetes, and the value of starting them before you have developed diabetes is unknown

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