Diabetes 1

Prediabetes: a high-risk state for diabetes development

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Prediabetes (intermediate hyperglycaemia) is a high-risk state for diabetes that is defined by glycaemic variables that are higher than normal, but lower than diabetes thresholds. 5–10% of people per year with prediabetes will progress to diabetes, with the same proportion converting back to normoglycaemia. Prevalence of prediabetes is increasing worldwide and experts have projected that more than 470 million people will have prediabetes by 2030. Prediabetes is associated with the simultaneous presence of insulin resistance and β-cell dysfunction—abnormalities that start before glucose changes are detectable. Observational evidence shows associations between prediabetes and early forms of nephropathy, chronic kidney disease, small fibre neuropathy, diabetic retinopathy, and increased risk of macrovascular disease. Multifactorial risk scores using non-invasive measures and blood-based metabolic traits, in addition to glycaemic values, could optimise estimation of diabetes risk. For prediabetic individuals, lifestyle modification is the cornerstone of diabetes prevention, with evidence of a 40–70% relative-risk reduction. Accumulating data also show potential benefits from pharmacotherapy.

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This is the first in a Series of three papers about diabetes

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Introduction

Prediabetes, typically defined as blood glucose concentrations higher than normal, but lower than diabetes thresholds, is a high-risk state for diabetes development. Diagnostic criteria for prediabetes have changed over time and vary depending on the institution of origin (table 1).

According to WHO, people are at high risk of developing diabetes if they have one of two distinct states: impaired fasting glucose (IFG), defined as a fasting plasma glucose (FPG) concentration of ≥6·1 and <7·0 mmol/L, without impaired glucose tolerance (IGT); and IGT, defined as an FPG concentration of <7·0 mmol/L and a 2 h postload plasma glucose concentration of ≥7·8 and <11·1 mmol/L, measured during a 75 g oral glucose tolerance test (OGTT).[1] The American Diabetes Association (ADA) applies the same thresholds for IGT, but uses a lower cutoff value for IFG (FPG 5·6–6·9 mmol/L), and has introduced glycated haemoglobin A_{1c} (HbA_{1c}) 5·7–6·4% as a new category for high diabetes risk.[2]

The term prediabetes has been criticised because many people with prediabetes do not progress to diabetes, and it might imply that no intervention is necessary because no disease is present. Furthermore, diabetes risk does not necessarily differ between people with prediabetes and those with a combination of other diabetes risk factors. Indeed, WHO use the term intermediate hyperglycaemia and an International Expert Committee convened by the ADA prefers the "high-risk state of developing diabetes" to prediabetes.[1,3] For brevity, we use the term prediabetes in this Series paper to refer to IFG, IGT, and high-risk HbA_{1c} concentrations.

Reproducibility of thresholds used to define prediabetes (around 50%) is lower than that for diabetes diagnostic criteria (>70%),[4] and each of the alternative definitions (based on IFG, IGT, or HbA_{1c}) produce overlapping groups with distinct and shared abnormalities. People with IFG can have different pathophysiological abnormalities from those with IGT—eg, in white people, overlap in abnormalities between those with IFG and those with IGT can be as low as 25%[5]—and those with both IFG and IGT tend to have more advanced disturbance of glycaemic homoeostasis.[5]

Individual risk factors for diabetes (eg, history of gestational diabetes or a first-degree relative with diabetes) or a combination of risk factors (eg, metabolic syndrome) can also be used to define populations at risk

Search strategy and selection criteria

We searched PubMed for work published up to and including January, 2012, with the terms "prediabetes", "impaired glucose tolerance", or "impaired fasting glucose". For the epidemiology section, we also searched with the terms "incidence" or "prevalence"; for the complications section, "nephropathy", "albuminuria", "microalbuminuria", "chronic kidney disease", "neuropathy", "autonomic", "heart rate variability", "orthostatic", "idiopathic neuropathy", "erectile dysfunction", or "Valsalva"; for the pathophysiology section, "pathophysiology", "clamp", "intravenous glucose tolerance test", "insulin secretion", or "insulin sensitivity"; and for the treatment section, "diabetes prevention", "lifestyle intervention", "metformin", "troglitazone", "rosiglitazone", "pioglitazone", "acarbose", "voglibose", "exenatide", "liraglutide", "nateglinide", "ramipril", "valsartan", "orlistat", "bariatric surgery", or "fibrate". We mainly selected publications from the past 5 years, but did not exclude widely referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. We have cited several review articles and book chapters to provide readers with more details and references. We modified our reference list on the basis of comments from peer reviewers and restricted it to 120 references.

	Venous plasma glucose
WHO, 1965	7·1–8·2 mmol/L (postload)
WHO, 1980	<8·0 mmol/L (fasting), ≥8·0 mmol/L and <11·0 mmol/L (2 h postload)
WHO, 1985	<7·8 mmol/L (fasting), ≥7·8 mmol/L and <11·1 mmol/L (2 h postload)
WHO, 1999 and 2006 (most recent)	IGT: <7·0 mmol/L (fasting), ≥7·8 mmol/L and <11·1 mmol/L (2 h postload); IFG: ≥6·1 mmol/L and <7·0 mmol/L (fasting), <7·8 mmol/L (2 h postload, if measured*)
ADA, 1997	IGT: <7·0 mmol/L (fasting), ≥7·8 mmol/L and <11·1 mmol/L (2 h postload); IFG: 6·1–6·9 mmol/L (fasting)
ADA, 2003	IGT: <7·0 mmol/L (fasting), 7·8–11·0 mmol/L (2 h postload, if measured); IFG: 5·6–6·9 mmol/L (fasting)†
ADA, 2010 (most recent)	IGT: <7·0 mmol/L (fasting), 7·8–11·0 mmol/L (2 h postload); IFG: 5·6–6·9 mmol/L (fasting)†; HbA_{1c}: 5·7–6·4%

One abnormal test result defines prediabetes; no repeat testing is required. IGT=impaired glucose tolerance. IFG=impaired fasting glucose. ADA=American Diabetes Association. HbA_{1c}=glycated haemoglobin A_{1c}. *Measurement is recommended to exclude diabetes or IGT. †2 h postload glucose measurement not recommended.

Table 1: **Diagnostic criteria for prediabetes**

for diabetes, but their predictive value is poorer than that of a prediabetes classification. Additionally, risk scores for incident diabetes based on a combination of non-invasive or blood-based risk factors are under development to identify individuals at high risk of developing diabetes.[6] In this Series paper we provide an updated review of the evidence of vascular complications and underlying pathophysiology of prediabetes, and discuss the clinical implications.

Epidemiology and temporal trends

Glycaemic concentrations are rapidly rising in people living in developed and developing countries.[7] Pooled data from 2·7 million adults participating in health surveys and epidemiological studies suggest that age-standardised mean FPG was 5·5 mmol/L in men and 5·4 mmol/L in women in 2008, a rise of 0·1 mmol/L since 1980. People living in Oceania had the highest mean FPG of any region (6·1 mmol/L for men and women), but mean FPG was also high in those from some other regions (south and central Asia, Latin America, the Caribbean, north Africa, and the Middle East).[7]

Increases in glycaemia have resulted in a rise in prediabetes prevalence, although in some populations IGT has not risen despite increasing diabetes incidence, probably because increases in obesity have affected FPG more than 2 h glucose, and because of improved detection of diabetes.[8] The population-based US National Health and Nutrition Examination Survey (NHANES) suggests that 35% of US adults older than 20 years and 50% of those older than 65 years had prediabetes in 2005–08, defined by FPG or HbA_{1c} concentrations.[9] Application of these percentages to the entire US population in 2010 yielded an estimated 79 million adults with prediabetes.[9] Prevalences of IFG and IGT vary between ethnic groups and both disorders are more common in people older than 40 years.[10] Additionally, IFG is more prevalent in men than in women, although the reasons for this difference are poorly understood.[10]

Figure 1 shows worldwide projections of IGT prevalence for 2030, according to the International Diabetes Federation.[11] The number of adults with IGT is expected to increase worldwide, reaching 472 million by 2030. The greatest absolute rises are expected in southeast Asia and the western Pacific region.[11]

Progression from prediabetes to diabetes

Around 5–10% of people with prediabetes become diabetic every year, although the conversion rate varies with population characteristics and prediabetes definitions.[12,13] In a meta-analysis of prospective studies published between 1979 and 2004, annualised incidence rates of progression to diabetes in patients with isolated IGT (4–6%) or isolated IFG (6–9%) were lower than in those with both IFG and IGT (15–19%).[14] In subsequent major studies, progression estimates have been similar—annualised incidence was 11% in the Diabetes Prevention Program (DPP) outcomes study,[15] 6% in participants with IFG in the US Multi-Ethnic Study of Atherosclerosis,[16] and 9% in participants with IFG and 7% in those with HbA_{1c} 5·7–6·4% in a Japanese population-based study.[17] Data suggest that risk of diabetes development on the basis of FPG and 2 h postload glucose is broadly similar to that defined by HbA_{1c} concentration.[14,18]

According to an ADA expert panel, up to 70% of individuals with prediabetes will eventually develop diabetes. In a Chinese diabetes prevention trial,[19] the 20 year cumulative incidence of diabetes in controls with IGT defined with repeated OGTTs was even higher (>90%) than that predicted by previous studies. By comparison, women with gestational diabetes have a 20–60% risk of developing diabetes 5–10 years after pregnancy.[20–22] This large heterogeneity in estimates is probably caused by variation in criteria used to define gestational diabetes and type 2 diabetes in these studies. In a meta-analysis of 20 studies,[23] 13% of mothers with gestational diabetes developed diabetes after pregnancy compared with 1% of mothers without gestational diabetes.

Reversion to normoglycaemia

Several trials have reported reductions in the risk of diabetes development in prediabetic individuals after lifestyle and drug-based interventions.[15,24–28] Prediabetes can convert back to normoglycaemia. In a population-based observational study of the natural history of diabetes in England, 55–80% of participants with IFG at baseline had normal FPG at 10 year follow-up.[12] Other studies have reported lower conversion rates[29]—eg, 19% in controls in the DPP outcomes study.[15]

Risk prediction

As with prediabetic status, diabetes risk models provide methods for identification of individuals at risk of diabetes on the basis of indices available to family doctors. However, no diabetes prediction model has been universally accepted, and given that ethnic origin is strongly related to diabetes risk, recalibration of prediction algorithms might be necessary when models are applied to different populations.[30] Table 2 presents a selection of diabetes risk models used in Australia, Europe, and the USA. These models consist of many of the same risk factors, but they weigh these components differently.

In clinical practice, a two-stage process could be efficient—diabetes prediction models with non-invasive variables such as age, sex, body-mass index (BMI), blood pressure, diabetes family history, and lifestyle information allow a first assessment of diabetes risk with little effort and cost. Laboratory measures, particularly glucose values, can improve results of non-invasive models. Thus, for patients with an increased risk at first assessment, models consisting of routinely obtained blood measures can be applied for more precise risk estimation.

Classification of people as either healthy or prediabetic (those with IFG or IGT or both) neglects the fact that diabetes risk substantially increases for those with FPG values at the higher end of the normal range.[31] Thus, in diabetes risk prediction, glycaemic measures (fasting or 2 h glucose, or HbA_{1c}) might be more accurate if treated as continuous rather than categorical variables.[32,33] Furthermore, incorporation of postload glucose into a model that already includes FPG can improve prediction. The KORA (Cooperative Health Research in the Region of Augsburg) study[32] and the Framingham Offspring Study[33] reported the usefulness of straightforward clinical and laboratory measurements to derive diabetes prediction models suitable for general practice.[32,33] Derivation of both models suggested that some information about metabolic traits (eg, glucose, uric acid, and lipids) beyond personal diabetes risk factors is important to adequately establish future risk of type 2 diabetes. Most attempts to substantially improve diabetes prediction with measurements from genetics and transcriptomics have not been successful, and whether serial measurements might decrease variations in non-genetic biomarkers, resulting in a more precise estimation of their concentrations, is not known.[34–36]

Pathophysiology of prediabetes

Trajectories of glycaemic changes in prediabetes

In healthy people, blood glucose is strictly regulated. FPG is maintained at 3·9–5·6 mmol/L,[37] and postmeal increases rarely exceed 3 mmol/L.[38] During development of type 2 diabetes, homoeostasis of fasting and postload glucose becomes abnormal.[39]

As proven by studies with repeat measures of glucose concentrations, insulin sensitivity, and insulin secretion, development of diabetes from normal glucose tolerance is a continuous process.[35,36,40,41] We described trajectories of fasting and postload glucose, and trajectories of insulin sensitivity and insulin secretion (β-cell function) measured by homoeostatic model assessment, preceding development of type 2 diabetes in the British Whitehall II study (figure 2).[36] In people who developed diabetes, increased glucose values were seen as early as 13 years before diagnosis, although glucose values seemed to be tightly regulated within the normal range until 2–6 years before diagnosis, when an abrupt increase was found. Other studies have confirmed this pattern of glycaemic changes.[35,40,41]

Figure 2 shows that insulin sensitivity was already reduced 13 years before onset of diabetes, with a steeper fall seen 5 years before diagnosis. Insulin secretion (β-cell function) was steady throughout the 13 year observation period and showed a substantial compensatory increase 3–4 years before diagnosis before decreasing steeply.[36] These results support the notion that insulin resistance starts years before diabetes development and that decreased β-cell function is already present in the prediabetic stage.[37,42]

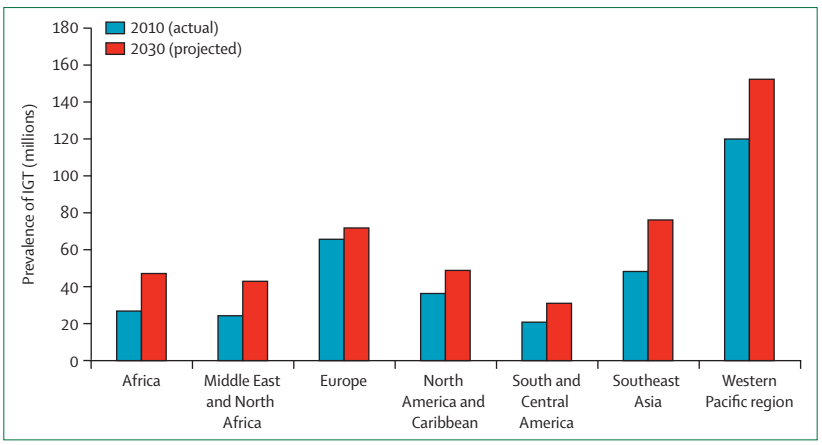

Figure 1: **Actual and projected prevalence of impaired glucose tolerance (IGT) by region in adults aged 20–79 years in 2010 and 2030**

Data are from the International Diabetes Federation Diabetes Atlas,[11] which provides a breakdown of the countries included in each of the geographical regions.

Multistage model of diabetes development

Weir coined a multistage model of diabetes development[43] that corresponds to these findings. The first stage is defined by a long period of insulin resistance accompanied by a compensatory increased rate of insulin secretion[44] and increased β-cell mass.[39] The second stage is the stable adaptation period when β cells are no longer fully compensating for increased insulin resistance; thus, fasting and postload glucose values are not completely maintained. This period probably starts when fasting and postload glucose levels are still within the normal range[36,39,43] and is usually accompanied by a decrease in acute insulin secretion at FPG concentrations of around 5·6 mmol/L.[39] Much of

	San Antonio	FINDRISK	ARIC	Framingham Offspring	Cambridge Risk Score	QDScore	AUSDRISK	KORA
Year	2002	2003	2005	2007	2008	2009	2010	2010
Country	USA	Finland	USA	USA	UK	UK	Australia	Germany
Age	✓	✓	✓	✓	✓	✓	✓	✓
Sex	✓	✓	✓	✓	✓	✓	✓	✓
Ethnicity	✓	×	✓	×	×	✓	✓	×
BMI	✓	✓	×	✓	✓	×	✓	✓
Waist circumference	×	✓	✓	×	×	×	✓	×
Height	×	×	✓	×	×	×	×	×
Family history of diabetes	✓	×	✓	✓	✓	×	✓	✓
Systolic blood pressure	✓	×	✓	✓	×	×	×	×
HDL cholesterol	✓	×	✓	✓	×	×	×	×
Triglycerides	×	×	✓	✓	×	×	×	×
Uric acid	×	×	×	×	×	×	×	✓
Antihypertensive treatment	×	✓	×	×	✓	✓	✓	×
Hypertension	×	×	×	×	×	✓	×	✓
Cardiovascular disease	×	×	×	×	×	✓	×	×
Use of corticosteroids	×	×	×	×	✓	✓	×	×
Diet	×	✓	×	×	×	×	×	×
Physical inactivity	×	✓	✓	×	×	×	✓	×
Smoking	×	×	×	×	✓	✓	✓	✓
Deprivation index	×	×	×	×	×	✓	×	×
Fasting glucose	✓	×	✓	×	×	×	✓	✓
HbA_{1c}	×	×	×	×	×	×	×	✓

FINDRISK=Finnish Diabetes Risk Study. ARIC=Atherosclerosis Risk in Communities study. AUSDRISK=Australian Type 2 Diabetes Risk Assessment Tool based on demographic, lifestyle, and simple anthropometric measures. KORA=Cooperative Health Research in the Region of Augsburg study. BMI=body-mass index. HbA_{1c}=glycated haemoglobin A_{1c}.

Table 2: **Examples of externally validated diabetes risk models[6]**

the first and second stages therefore occur before the prediabetic phase. During the unstable early decompensation period—the third stage of diabetes development—β cells become unable to compensate for insulin resistance and consequently glucose concentrations start to increase rapidly,[39,43] as was seen in Whitehall II and other longitudinal studies.[36,41] This period probably extends from prediabetes to manifest diabetes. The subsequent two stages of diabetes development (stable decompensation and severe decompensation) relate to manifest diabetes and thus are beyond the scope of this review.[43]

Glucose dysregulation

FPG values are determined by endogenous glucose production (EGP), which depends mostly on the liver. EGP and fasting insulin are used as markers of hepatic insulin resistance and show a strong relation with fasting glycaemia.[38,39,45] During absorption of a glucose-containing meal, changes in glucose concentrations are caused by intestinal absorption, suppression of EGP, and total body glucose uptake.[38,39] EGP is greatly suppressed in people with normal glucose tolerance after glucose ingestion, whereas this suppression is less pronounced in prediabetes and diabetes.[38,39] In type 2 diabetes, total body glucose disposal is decreased, and 85–90% of this impairment is related to muscle insulin resistance.[46] If insulin secretion was able to compensate for insulin resistance perfectly, no observable changes in glucose concentration would occur. This factor means that, by definition, β-cell dysfunction is already present in the prediabetic phase. However, β-cell function cannot be characterised solely on the basis of insulin secretion without consideration of underlying insulin resistance. β cells respond to an increase in glucose concentration with a rise in insulin secretion that is dependent on whole body insulin sensitivity. Accordingly, the relation between insulin secretion and insulin sensitivity is hyperbolic, and the ratio of incremental insulin to incremental glucose divided by insulin resistance is described by a constant known as the disposition index.[39,47] This index, therefore, is a measure of insulin secretion after the underlying degree of insulin resistance (higher for healthy people and lower for prediabetic and diabetic individuals) has been accounted for. Studies using different measures of β-cell function have reported severely abnormal (up to 80% decreased) insulin secretion in prediabetic people.[37,42,48] These findings are supported by autopsies

reporting a 50% decrease in β-cell volume in those with IFG.[49]

IFG versus IGT

Patients with isolated IFG differ from those with isolated IGT in their fasting and 2 h postload glucose values and by the shape of their glucose concentration curves during OGTT. Both groups present with insulin resistance, but the site of their insulin resistance is different. High hepatic insulin resistance is a typical finding in patients with IFG, with almost normal values in skeletal muscle.[38,39,45] In patients with IGT, the main site of insulin resistance is muscle, with only small changes in liver insulin sensitivity.[37,38] This notion is supported by the finding that total body glucose disposal can gradually worsen from normal glucose tolerance to IFG to IGT and then to type 2 diabetes.[48] β-cell dysfunction is present both in people with isolated IFG and those with isolated IGT. Individuals with IFG have severely impaired early insulin responses during OGTT, but their insulin secretion improves during the second phase of the test. By contrast, people with IGT present with impaired early-phase and late-phase insulin secretion.[38,39,50] These findings suggest distinct pathophysiological mechanisms of isolated IFG and isolated IGT, although the clinical relevance of these results needs further clarification.

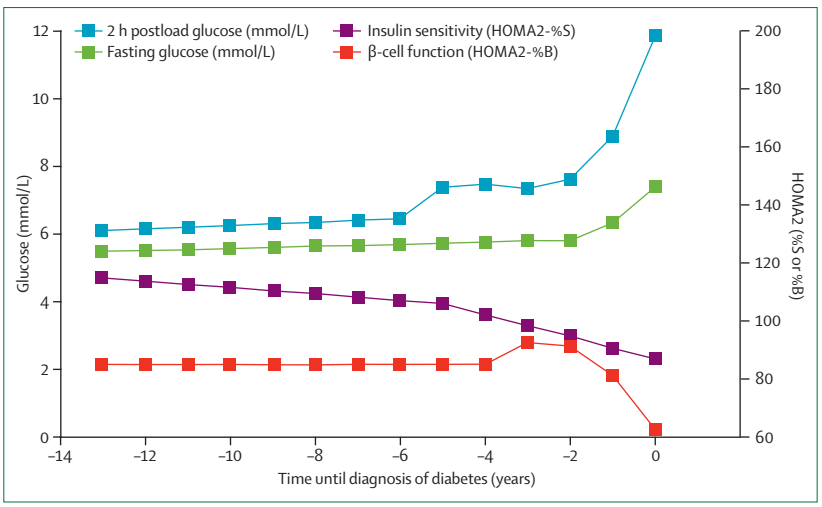

***Figure 2*: Fasting and 2 h postload glucose, insulin sensitivity, and β-cell function trajectories before the diagnosis of diabetes**

Data are from the British Whitehall II study of 505 diabetes cases.[36] Time 0 is diagnosis of diabetes. The updated homoeostasis model assessment (HOMA2) was used to calculate insulin sensitivity (HOMA2-%S) and β-cell function (HOMA2-%B) trajectories. Adapted from figures 1 and 2 of Tabák and colleagues,[36] by permission of Elsevier.

Nephropathy and kidney disease in prediabetes

People with prediabetes can have concomitant damage to end organs such as eyes, kidneys, blood vessels, and heart, which is traditionally thought to be a complication of diabetes. Here, we briefly review evidence for complications that are particularly relevant to prediabetes: nephropathies and chronic kidney disease; neuropathies; diabetic retinopathy; and macrovascular diseases.

Prediabetes has been linked to increased risk of early forms of nephropathy and chronic kidney disease, defined by methods such as urinary albumin excretion rate and estimated glomerular filtration rate.[51–55] NHANES, 1999–2006, showed that the prevalences of microalbuminuria and macroalbuminuria increase as glycaemia worsens—ie, from normoglycaemia (6% prevalence of microalbuminuria and 0·6% prevalence of macroalbuminuria), to IFG (10% and 1·1%), undiagnosed diabetes (29% and 3·3%), or diagnosed diabetes (29% and 7·7%).[54] Of note, microalbuminuria can be indicative of hypertension and is therefore an imprecise marker of diabetes-related early nephropathy.[54] Other data for increased albuminuria and glomerular filtration rate—an early marker of kidney involvement in hyperglycaemia—also support the notion that some nephropathic changes might be present in the prediabetic stage before onset of diabetes.[51,53,56–58] By contrast, evidence of a cross-sectional association between prediabetes and decreased estimated glomerular filtration rate—a late marker of chronic kidney disease—is mixed, consisting of studies with both positive[54] and null findings.[55,57] Longitudinal studies suggest that prediabetes is a risk factor for chronic kidney disease, but whether this prospective association is attributable to the effects of prediabetes itself, increased incidence of diabetes, or common causes contributing to both hyperglycaemia and kidney pathology is unclear.[59,60]

Neuropathies in prediabetes

The strongest supportive evidence is for the association between prediabetes and autonomic neuropathy in particular, although the method used to measure autonomic neuropathy seems to be crucial. Prediabetes is associated with decreased heart-rate variability[61] (a marker of parasympathetic function),[62–65] decreased postural changes in heart rate,[62] increased prevalence of erectile dysfunction in men,[66] and a worse profile in tests of sympathetic and parasympathetic function.[67] No consistent evidence is available to suggest that prediabetes is associated with orthostatic blood pressure[63] (a late marker of diabetic neuropathy[61]), decreased expiratory-to-inspiratory ratio, or changes in heart rate during breathing.[63]

Studies of prediabetes and sensorimotor neuropathy[68–70] suggest that small demyelinated fibres might be implicated in IGT and early diabetic neuropathy.[61] Distal intraepidermal nerve fibre density, quantitative sudomotor testing, total sweat volume and arm-to-foot sweat responses, deep tendon reflexes, and temperature sensation are sensitive markers of sensorimotor neuropathy,[71,72] whereas tests such as the Michigan neuropathy screening instrument, calibrated tuning fork, and classical nerve conduction tests, and vibration and temperature perception thresholds, might not detect neuropathy in prediabetic people.

Finally, evidence is accumulating for increased prevalence of idiopathic polyneuropathy (eg, idiopathic sensory or painful neuropathy,[73–78] and sensory or small-fibre-only neuropathy)[73,75,78] in individuals with prediabetes, with IGT more strongly related to painful than non-painful neuropathy.[73,75,78]

Diabetic retinopathy

Prediabetes might be associated with an increased risk of diabetic retinopathy, although findings vary depending on how diabetic retinopathy is detected.[51,79–83] In a study of more than 5000 Pima Indians, retinopathy ascertained by direct ophthalmoscopy was associated with prediabetic status.[51] Measures of retinal vascular changes, such as lower arteriole-to-venule ratio and increased retinal arteriole or venular calibre, have also been related to prediabetes or increased risk of diabetes, although evidence is not entirely consistent.[81–83]

Macrovascular disease

Prediabetes is linked with increased risks of major manifestations of vascular disease, but whether raised disease risks depend on development of clinical diabetes is unclear.[84,85] Cross-sectional studies provide evidence in favour of vascular risk effects of mild or moderate hyperglycaemia because an excess prevalence of coronary disease is reported in people with fasting or postload hyperglycaemia lower than the diabetic threshold.[86,87] Compared with coronary disease, less certainty exists with respect to cerebrovascular disease and aortic aneurysm.[87] Diabetes is a known risk factor for ischaemic and haemorrhagic stroke, but whether risk increases before development of diabetes remains to be established.[84]

The dose–response effect of fasting hyperglycaemia for vascular mortality might be weaker than the effect of postload glucose. The DECODE (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe) pooling study of European cohorts showed that IGT was associated with increased risk of coronary death and total cardiovascular death, independent of the concentration of FPG, although the converse was not the case.[88] Irrespective of whether basal or challenged blood glucose concentration is more important for atherogenesis, average glucose concentrations, indexed by HbA_{1c} concentration, predict incident coronary disease at least as well as fasting and postload glucose, although prospective studies of HbA_{1c} are fairly rare.[89]

The epidemiological relation between prediabetes and macrovascular disease can be confounded by clustering of vascular risk factors within individuals. Blood glucose in the prediabetic range is correlated with many risk factors, including general and central obesity, blood pressure, and triglyceride and lipoprotein concentrations.[84] As a result, the strength of the glycaemia effect depends on the extent to which related vascular risk factors are taken into account. Individual-level evidence from prospective studies suggests that fasting hyperglycaemia (figure 3), postload glucose, and HbA_{1c} are all robust predictors of vascular mortality[86,88,89] and, according to multivariable adjusted analyses, these associations are independent of vascular risk factors such as obesity, blood pressure, triglyceride, and lipoproteins.[84,85,87]

Treatment

Lifestyle intervention

Prediabetes should be treated to prevent progression to diabetes, mitigate some of the potential results of progression to diabetes, and prevent the potential effects of prediabetes itself. Most studies in this research specialty have focused on diabetes incidence in prediabetic individuals, and support the notion that lifestyle change should be the cornerstone for diabetes prevention.

The primary aim of lifestyle interventions is to prevent or delay development of type 2 diabetes and its complications[13,45] by targeting obesity and physical inactivity, the two most important modifiable risk factors of diabetes development.[3,25] The Finnish Diabetes Prevention Study and the US DPP (the largest so far) with a 3 year follow-up reported a 58% risk reduction after interventions aimed at weight loss, dietary change, and increased physical activity.[25,28] In the first trial, benefits were dependent on the number of goals achieved by the participant (weight reduction >5%, fat intake <30%, saturated fat intake <10%, fibre intake >15 g/1000 kcal, exercise >4 h/week),[28] whereas in the DPP the most important determinant of risk reduction was weight loss (every 1 kg decrease reduced risk by 16%).[90] The beneficial effect of lifestyle interventions has also been confirmed in Asian populations.[26,91] Successful lifestyle interventions seem to improve insulin sensitivity and β-cell function.[92,93]

Pharmacological intervention based on antidiabetic drugs

Evidence of potential benefits from pharmacotherapy is accumulating. The biguanides are a class of drug that include metformin, used for decades to treat diabetes. Metformin has beneficial effects on BMI and lipid concentrations and has been proven to be safe by trial evidence showing no serious adverse effects (only minor gastrointestinal side-effects were detected).[94] It reduces fasting glucose mainly through its effect on hepatic glucose output.[95] According to trial evidence in people with IGT, metformin lowers risk of type 2 diabetes by 45%.[96] Its effect was similar to lifestyle intervention in the Indian DPP-1 study,[26] although in the US DPP it was less effective than lifestyle.[25] The beneficial effect of metformin was greater in prediabetic people with a higher baseline BMI and higher FPG than in their leaner counterparts with lower FPG concentrations.[25] Gastrointestinal side-effects of the drug were mostly mild to moderate, so the intervention seemed to be safe.[25,26]

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Thiazolidinediones, such as troglitazone, rosiglitazone, and pioglitazone, act through the peroxisome proliferator-activated receptor-γ by increasing hepatic and peripheral insulin sensitivity and preserving insulin secretion.[45,95] Rosiglitazone was effective in a 3 year randomised trial that showed a 60% reduction in incident diabetes risk, but it was also associated with a statistically and clinically significant weight increase (roughly 2 kg) compared with placebo and increased risk of heart failure (0·1% *vs* 0·5% in controls).[24,97] Pioglitazone showed effectiveness in the ACT NOW study[29] in obese people with IGT. The risk of diabetes decreased by more than 70% and the drug was associated with improved diastolic blood pressure, improved HDL cholesterol, and a reduced rate of carotid intima-media thickening. However, weight gain was about 3 kg greater with pioglitazone than with placebo, and oedema was more frequently reported (13% *vs* 6%).[29] A possible link between pioglitazone and bladder cancer has been suggested and therefore individuals with a history of bladder cancer or unexplained haematuria should probably not receive this drug.[98,99] In the Indian DPP-2 study,[100] no difference in the rate of diabetes development was noted between lifestyle intervention alone and lifestyle intervention plus pioglitazone during a 3 year trial.

Two thiazolidinedione drugs were withdrawn from the European market: troglitazone for probable serious hepatotoxicity, and rosiglitazone because of possible increases in cardiovascular risk.[45,95] In the CANOE (CAnadian Normoglycemia Outcomes Evaluation) trial,[101] low doses of rosiglitazone (2 mg twice a day) in combination with metformin were tested against placebo to examine whether lower doses would cause reduced side-effects. The risk of incident diabetes was reduced by 66% in the active treatment group with no significant difference in weight gain compared with controls. However, more people complained of diarrhoea in the active treatment group (16% *vs* 6%).

α-glucosidase inhibitors reduce the rate of polysaccharide digestion from the proximal small intestine. They mainly lower postprandial glucose without causing hypoglycaemia. Since their effect on HbA_{1c} is smaller than that of other oral antidiabetic agents, they are seldom used in the treatment of type 2 diabetes.[95] However, two large trials[102,103] support their effectiveness in the prevention of diabetes and, importantly, one of them (STOP-NIDDM [Study to Prevent Non-Insulin-Dependent Diabetes Mellitus])[103] shows evidence of decreased cardiovascular disease and hypertension risk in treated IGT patients. In this trial, a 25% relative-risk reduction for diabetes was reported in people with IGT who were randomly assigned to either acarbose (100 mg three times a day) or identical placebo during 3·3 years of follow-up,[103,104] but almost a third of the acarbose group could not complete the trial because of gastrointestinal side-effects such as flatulence and diarrhoea.[103] A recent study investigating voglibose,[102] another α-glucosidase inhibitor, reported a 40% reduction in incident diabetes risk during 48 weeks of follow-up in high-risk Japanese individuals with IGT. Although gastrointestinal side-effects were similar to those reported in previous trials, more people completed that study.

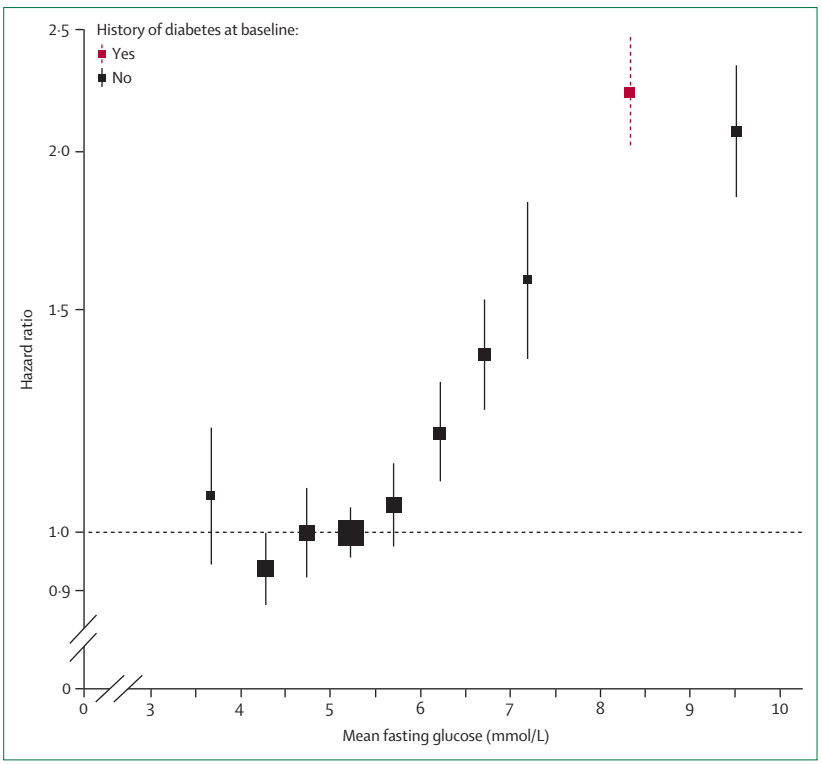

Figure 3: **Hazard ratios for vascular death according to baseline concentrations of fasting glucose**
Data are from 50 studies and include 16 211 vascular deaths. Glucose concentrations for participants without a known history of diabetes at baseline were classified into several groups (<4·0 mmol/L; 4·0 mmol/L to <4·5 mmol/L; 4·5 mmol/L to <5·0 mmol/L; 5·0 mmol/L to <5·5 mmol/L; 5·5 mmol/L to <6·0 mmol/L; 6·0 mmol/L to <6·5 mmol/L; 6·5 mmol/L to <7·0 mmol/L; 7·0 mmol/L to <7·5 mmol/L, and ≥7·5 mmol/L). Hazard ratios are plotted against mean fasting glucose concentration in each group (reference category, 5·0 to <5·5 mmol/L). Error bars show 95% CIs. Reproduced from Seshasai and colleagues[85] of the Emerging Risk Factor Collaboration, by permission of Massachusetts Medical Society.

The glucagon-like peptide-1 analogues exenatide and liraglutide both produced sustained weight loss in obese patients and were associated with increased reversion from prediabetes to normoglycaemia during 1–2 years of follow-up. The most frequent side-effects were nausea and vomiting.[105–107] A multicentre multinational study investigated the effect of nateglinide (a short-acting insulin secretagogue) in more than 9000 people with IGT and reported no effect on the rate of diabetes or cardiovascular outcomes during 6·5 year follow-up.[108]

Pharmacological interventions based on non-antidiabetic drugs

The anti-obesity drug orlistat is a gastrointestinal lipase inhibitor. In a post-hoc analysis of obese people,[109] orlistat was associated with greater weight loss than was placebo (6·7 kg *vs* 3·8 kg) and significantly reduced the conversion rate from IGT to diabetes (7·6% *vs* 3·0%) in a 1·5 year follow-up. This finding is consistent with the

4 year XENDOS (XENical in the prevention of Diabetes in Obese Subjects) trial[27] that reported a 37% reduction in relative risk of diabetes in obese people given orlistat, although in that study only 52% of people on the drug and 34% of placebo recipients completed treatment. An explanatory analysis suggested that the preventive effect was mainly confined to participants with IGT. At least one randomised 6 month trial in people with prediabetes and hypertriglyceridaemia has reported higher rates of regression to normoglycaemia in patients given fenofibrate (>50%) than in those given placebo (30%). Lipotoxicity is thought to be an important factor in development of diabetes, so these findings might have important clinical implications.[110]

Whether or not inhibitors of the renin–angiotensin–aldosterone system have an effect on the development of diabetes is the subject of debate. Secondary analyses of hypertension trials have suggested that people with high cardiovascular risk who receive angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers have lower incidences of diabetes than do those receiving different active treatments or placebo.[111] However, these findings might be biased because the comparator active treatment groups had different proportions of other antihypertensive treatments known to increase diabetes risk (eg, β blockers and thiazide diuretics).[112,113] Furthermore, in the DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) trial,[113] ramipril, another renin–angiotensin–aldosterone system blocker, did not significantly reduce incidence of new-onset diabetes. In view of the evidence, the effect of these drugs is much smaller than that of antidiabetic drugs, and they are not recommended for treatment of prediabetes.

Other treatments that reduce diabetes risk

In morbidly obese people, bariatric surgery is associated with sustained weight loss; a substantial reduction in 2 year and 10 year incidence of type 2 diabetes;[114] and, in individuals with blood glucose greater than 4·5 mmol/L, a reduced risk of cardiovascular disease.[115] Corresponding benefits have not been reported for other weight-loss interventions.

Long-term effects of lifestyle and antidiabetic drug interventions

Several trials support a long-term reduction in diabetes risk or a delay in onset of the disease as a result of lifestyle and drug-based interventions.[15,19,116–118] In the 20 year follow-up of the DaQing Diabetes Prevention Study,[119] for example, those receiving a lifestyle intervention had a 43% reduced risk of diabetes, translating to a mean 3·6 year delay in development of diabetes. In the same study, lifestyle intervention was also associated with an almost 50% reduction in relative risk of incident severe retinopathy, whereas rates of other microvascular complications, such as nephropathy and neuropathy, were similar to those seen in controls.[119]

The DPP outcomes study[120] found that reversion from prediabetes to normoglycaemia during the randomised phase of the study, even if transient, was associated with a 56% reduced risk of future diabetes, independent of whether the reversion occurred spontaneously or during lifestyle or metformin therapy during the 5·7 year follow-up (hazard ratio=0·44, 95% CI 0·37–0·55; p<0·0001).

In the 20 year follow-up of the DaQing Study, the evidence of intervention effects on macrovascular complications is not consistent. In a recent meta-analysis of trials in prediabetic people,[116] lifestyle and drug-based interventions had no significant effect on the risk of all-cause mortality or cardiovascular death during mean follow-up of 3·8 years, except for a borderline significant reduction in stroke risk. All-cause mortality was lower in the diet and exercise intervention group than in the control group during a 12 year follow-up in the Malmö Preventive Project,[121] but this study was not randomised.

Clinical and public health implications

By defining people as prediabetic (also known as intermediate hyperglycaemia or high risk for diabetes), a heterogeneous patient population is identified, characterised by the simultaneous presence of insulin resistance and β-cell dysfunction. Multifactorial diabetes risk scores are promising approaches to further improve identification of individuals at high risk of diabetes development, although whether risk scores will help prevent diabetes more than the classic definition of prediabetes is unknown.

Prediabetes is not only related to an increased risk of diabetes and its complications, but also might cause damage to kidney and nerves, according to accumulating evidence. Identification and treatment of prediabetic individuals is therefore crucial. Recent evidence suggests that prevention of progression to diabetes is possible, although evidence of reduced cardiovascular disease risk is scarce. On the basis of randomised trials that show the effectiveness of lifestyle intervention and several antidiabetic drugs in the prevention of diabetes, lifestyle intervention aimed at achieving more than 7% weight reduction and 150 min per week of moderate intensity physical activity is recommended for all people with prediabetes. In view of long-standing safety information about metformin, this drug could be given to people who are unable to comply with lifestyle advice. For other potential drugs, further long-term studies are needed on safety and vascular outcomes before lifelong treatment can be safely recommended.

Economic considerations are important for policy makers, public health agencies, insurers, and health-care providers and consumers, but few studies have assessed different prediabetes screening and treatment strategies in terms of cost-effectiveness and health benefits. Diabetes is projected to be one of the five leading causes of death in high-income countries by 2030 and one of the

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ten leading causes of death worldwide, which emphasises the public health importance of reducing diabetes risk at the population level. Strategies targeting interventions aimed at the entire population to reduce key diabetes risk factors, such as adiposity and physical inactivity, are important. However, these need to be complemented with diabetes prevention strategies specifically aimed at prediabetic and other high-risk individuals.

Contributors
All authors contributed to the search of published work and wrote parts of the paper. AGT and MK wrote the first draft and all authors contributed to the final version.

Conflicts of interest
We declare that we have no conflicts of interest.

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