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Prediabetes: A high-risk state for developing diabetes

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Summary

Prediabetes (or "intermediate hyperglycaemia"), based on glycaemic parameters above normal but below diabetes thresholds is a high risk state for diabetes with an annualized conversion rate of 5%–10%; with similar proportion converting back to normoglycaemia. The prevalence of prediabetes is increasing worldwide and it is projected that >470 million people will have prediabetes in 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 of prediabetes with early forms of nephropathy, chronic kidney disease, small fibre neuropathy, diabetic retinopathy, and increased risk of macrovascular disease. Multifactorial risk scores could optimize the estimation of diabetes risk using non-invasive parameters and blood-based metabolic traits in addition to glycaemic values. For prediabetic individuals, lifestyle modification is the cornerstone of diabetes prevention with evidence of a 40%–70% relative risk reduction. Accumulating data also suggests potential benefits from pharmacotherapy.

Introduction

Prediabetes, typically defined as blood glucose levels above normal but below diabetes thresholds, is a risk state that defines a high chance of developing diabetes. Diagnostic criteria for prediabetes have changed over time and currently vary depending on the institution (table 1).

According to the World Health Organization (WHO), high risk for developing diabetes relates to two distinct states, impaired fasting glucose (IFG) defined as fasting plasma glucose (FPG) of 6.1–6.9 mmol/L (in the absence of impaired glucose tolerance – IGT) and IGT defined as postload plasma glucose of 7.8–11.0 mmol/L based on 2-h oral glucose tolerance test (OGTT) or a combination of both.[1] The American Diabetes Association

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(ADA), although applying the same thresholds for IGT, uses a lower cut-off value for IFG (FPG 5.6–6.9 mmol/L) and has additionally introduced haemoglobin A1c levels of 5.7–6.4% as a new category of high diabetes risk.[2]

The term prediabetes itself has been critised on the basis that (1) many people with prediabetes do not progress to diabetes, (2) the term may imply that no intervention is necessary as no disease is present, and (3) diabetes risk does not necessarily differ between people with prediabetes and those with a combination of other diabetes risk factors. Indeed, the WHO used the term '*Intermediate Hyperglycaemia*' and an International Expert Committee convened by the ADA the '*High Risk State of Developing Diabetes*' rather than 'prediabetes'.[1,3] For brevity, we use the term prediabetes in this seminar to refer to IFG, IGT and high risk based on A1c.

The reproducibility of prediabetes (~50%) is lower than that for diabetes (>70%)[4] and the alternative definitions based on IFG, IGT and A1c define overlapping prediabetic groups with single or combined abnormalities. Isolated IFG and isolated IGT may define persons with different pathophysiological abnormalities and their combination marks a more advanced disturbance of glycaemic homeostasis.[5] In Caucasians, for example, the overlap between IFG and IGT can be as low as 25%.[5]

Individual risk factors for diabetes (eg history of gestational diabetes, first degree relative with diabetes) or a combination of risk factors (eg metabolic syndrome) can also be used to define populations at-risk for diabetes but their predictive value is poorer than that of prediabetes. In addition, 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] The aim of this seminar is to provide an updated review of the evidence of vascular complications and the underlying pathophysiology of prediabetes and to discuss the clinical implications.

Epidemiology and time trends

Glycaemic levels are rapidly rising in developed and developing countries.[7] According to pooled data from 2.7 million adults participating in health surveys and epidemiological studies, age-standardised mean fasting plasma glucose (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. Oceania had the highest mean FPG of any region (6.1 mmol/L for men and women), but mean FPG was also high in some other regions (South and Central Asia, Latin America, the Carribean, 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 influence FPG more than 2-h glucose and because of improved detection of diabetes.[8] The population-based U.S. National Health and Nutrition Examination Survey (NHANES) suggests that 35% of U.S. adults over 20 years of age and 50% of those over 65 had prediabetes in 2005–2008 based on fasting glucose or A1c levels.[9] Applying these percentages to the entire U.S. population in 2010 yields an estimated 79 million adults with prediabetes.[9] The prevalences of IFG and IGT vary between ethnic groups and both conditions are more common in older people.[10] In addition, IFG is more prevalent among men than women, although the reasons for this remain poorly understood.[10]

Figure 1 shows worldwide projections of IGT prevalence for the next twenty years according to the International Diabetes Federation.[11] The number of adults with IGT is

expected to increase globally, reaching 472 million by 2030. The greatest absolute rises are expected in South-East Asia and the Western Pacific Region.[11]

Progression from prediabetes to diabetes

Around 5–10% of people with prediabetes become diabetic annually although conversion rate varies by population characteristics and the definition of prediabetes.[12,13] In a meta-analysis of prospective studies published up to 2004, annualised incidence rates of diabetes for isolated IGT (4–6%) and isolated IFG (6–9%) were lower than those for IFG and IGT combined (15–19%).[14] In more recent major studies, progression estimates have been similar: the annualised incidence was 11% in the Diabetes Prevention Program (DPP) Outcomes Study,[15] 6% among participants with IFG in the US Multi-Ethnic Study of Atherosclerosis (MESA),[16] 9% among participants with IFG and 7% among those with an A1c 5.7–6.4% in a Japanese population-based study.[17] Studies suggest that the risk of diabetes development on the basis of FPG and 2-h postload glucose is broadly similar to that posed by A1c.[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, the 20-year cumulative incidence of diabetes was even higher (>90%) among controls with an IGT defined with repeated OGTTs.[19] For comparison, women with gestational diabetes have been suggested to have a 20%–60% risk of developing diabetes 5 to 10 years after pregnancy.[20–22] This large heterogeneity in the estimates is probably due to the variation in the criteria used to define gestational diabetes and type 2 diabetes in these studies. In a recent meta-analysis of 20 studies, 13% of mothers with gestational diabetes developed diabetes after pregnancy compared to 1% of mothers without gestational diabetes.[23]

Reversion to normoglycaemia

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

Risk prediction

As with prediabetic status, diabetes risk models provide a method for identifying individuals at risk of developing diabetes based on parameters available to the general practitioner. There is no single universally accepted diabetes prediction model and given that ethnicity is strongly related to diabetes risk, recalibration of prediction algorithms may be necessary when they are applied to different populations.[30] Table 2 presents a selection of current diabetes risk models used in the US, Europe, and Australia. These models include a broadly similar combination of risk factors but they weigh these components differently.

In clinical practice, a two-stage process could be efficient: diabetes prediction models with non-invasive parameters such as age, sex, BMI, blood pressure, diabetes family history and lifestyle information allow a first assessment of diabetes risk with little effort and costs. Laboratory measures, in particular glucose values, can improve the performance of non-invasive models. Thus, for patients with an increased risk at the first stage, models including routinely collected blood measures can be applied for a more precise risk estimation.

A categorisation of persons as either 'normal' or 'prediabetic' (IFG, IGT) neglects the fact that diabetes risk significantly increases for FPG values within the normal range.[31] Thus, in diabetes risk prediction, glycaemic measures (fasting and 2-h glucose, A1c) may perform better if treated as continuous traits rather than categorical variables.[32,33] Furthermore, there is some evidence to suggest that incorporating postload glucose into a model that already includes FPG improves prediction. The Framingham Study and the KORA Study demonstrated the utility of simple clinical and laboratory measurements to derive diabetes prediction models suitable for general practices.[32,33] The derivation of both models indicated that some information on metabolic traits (eg, glucose, uric acid, lipids) beyond personal diabetes risk factors is important to adequately determine the future risk of type 2 diabetes. Most recent attempts to improve diabetes prediction using measurements from genetics and transcriptomics have not shown significant improvements in predictive performance but it is unknown whether serial measurements may decrease variations in non-genetic biomarkers allowing for a more precise estimation of their levels.[34–36]

The pathophysiology of prediabetes

In healthy people blood glucose is strictly regulated. Fasting glucose is maintained between 3.9 and 5.6 mmol/L[37] and the post-meal increases rarely exceed 3 mmol/L.[38] During the development of type 2 diabetes, the homeostasis of fasting and postload glucose becomes abnormal.[39]

As evidenced by studies with repeat measures of glucose levels, insulin sensitivity and insulin secretion, the development of diabetes from NGT is a continuous process.[35,36,40,41] Recently we described trajectories of fasting and postload glucose in addition to trajectories of HOMA insulin sensitivity and insulin secretion (β-cell function) preceding the development of type 2 diabetes in the British Whitehall II study (figure 2).[36] In people who developed diabetes, increased glucose values were observed already at the beginning of the follow-up, 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. This pattern of glycaemic changes was confirmed by others.[35,40,41]

Figure 2 shows that insulin sensitivity was reduced already 13 years before the onset of diabetes, with a steeper decline observed 5 years before diagnosis. Insulin secretion was elevated throughout the 13-year observation period and showed a marked increase 4-3 years before diagnosis, followed by a steep decrease until diagnosis.[36] This is in line with the notion that insulin resistance starts years before diabetes development and that decreased beta-cell function is already present in the prediabetic stage.[37,42]

Multistage model of diabetes development

Weir coined a multistage model of diabetes development[43] that corresponds to the above-described findings. The first stage of diabetes development is a long compensatory period when insulin resistance is present and accompanied by increased rates of insulin secretion[44] and an 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/or postload glucose values are not completely maintained. This period is likely to start when fasting and postload glucose levels are within the normal range[36,39,43] and is usually accompanied by a decrease in acute insulin secretion that is present at FPG levels around 5.6 mmol/L.[39] Much of the first and second stages therefore occur before the prediabetic phase is achieved.

During the unstable early decompensation period, the third stage of diabetes development, the β-cells become unable to compensate for a given insulin resistance and consequently glucose levels start to increase rapidly[39,43] as it 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, insulin resistance and β-cell dysfunction

Fasting plasma glucose values are determined by endogenous glucose production (EGP) that is mostly dependent on the liver. The product of EGP and fasting insulin is used as a marker of hepatic insulin resistance and it shows a relatively strong relationship with fasting glycaemia.[38,39,45]

During absorption of a glucose-containing meal, changes in glucose levels are determined by intestinal absorption, suppression of EGP and by total body glucose uptake.[38,39] EGP is markedly suppressed in people with NGT after glucose ingestion while this suppression is less pronounced in prediabetes and diabetes.[38,39] In type 2 diabetes, total body glucose disposal is also decreased and 85–90% of this impairment is related to muscle insulin resistance.[46]

If insulin secretion were able to compensate for insulin resistance perfectly, no observable changes in glucose levels would occur. This means that, by definition, β-cell dysfunction is already present in the prediabetic phase. β-cell function however cannot be characterised solely on the basis of insulin secretion without the consideration of the underlying insulin resistance. The β-cell responds to a given increase in glucose level with a given rise in insulin secretion that is conditioned on whole body insulin sensitivity. According to this concept, the relation between insulin secretion and insulin sensitivity is hyperbolic; the ratio of incremental insulin over incremental glucose divided by insulin resistance is described by a constant, the disposition index.[39,47] The disposition index therefore is a measure of insulin secretion after accounting for the underlying degree of insulin resistance that is higher for healthy people and lower for prediabetic and diabetic individuals.

Studies using different measures of β-cell function have reported severely abnormal (up to 80% decreased) insulin secretion in prediabetic people.[37,42,48] This observation is supported by autopsy studies reporting a 50% decrease in β-cell volume among those with glucose values within the IFG range.[49]

Specific differences between subjects with isolated IFG and isolated IGT

Subjects with isolated IFG and isolated IGT differ in their fasting and 2-h postload glucose values and by the shape of the glucose concentration curves during the OGTT.

Both IFG and IGT subjects present with insulin resistance, however the site of insulin resistance is different: High hepatic insulin resistance is a typical finding in IFG with almost normal values in skeletal muscle.[38,39,45] In IGT, the main site of insulin resistance is the muscle with only modest changes in liver insulin sensitivity.[37,38] This notion is reflected by the finding that total body glucose disposal gradually worsens from NGT to IFG to IGT and type 2 diabetes.[48]

β-cell dysfunction is present both in people with isolated IFG and isolated IGT. IFG people have severely impaired early insulin response during OGTT but their insulin secretion

improves during the second phase of the OGTT. In contrast, IGT people present with impaired early 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 observations requires further clarification.

Nephropathy and kidney disease in prediabetes

People with prediabetes may have concomitant damage to end organs, such as eyes, kidneys, blood vessels and the heart that are traditionally considered to be complications of diabetes. In the following, we briefly review evidence on complications that are particularly relevant to prediabetes: (1) nephropathies and chronic kidney disease, (2) neuropathies, (3) diabetic retinopathy, and (4) macrovascular diseases.

There is evidence to link prediabetes to increased risk of early forms of nephropathy and chronic kidney disease (CKD), defined based on methods such as urinary albumin excretion rate (AER) and estimated glomerular filtration rate (eGFR).[51–55] The NHANES 1999–2006 showed increasing frequency of albuminuria in tandem with the glycaemia range when classified from normoglycaemia through IFG, undiagnosed diabetes and diagnosed diabetes for both microalbuminuria, which may also relate to hypertension and is therefore an imprecise marker of diabetes-related early nephropathy (6%, 10%, 29% and 29%, respectively) and macroalbuminuria (0.6%, 1.1%, 3.3% and 7.7%).[54] Other data on increased albuminuria and glomerular filtration rates, an early marker of a kidney involvement in hyperglycaemia, also support the concept that some nephropathic changes may be present already in the prediabetic stage before the onset of diabetes.[51,53,56–58] In contrast, evidence of a cross-sectional association between prediabetes and eGFR, a late marker of CKD, is mixed, including both studies with positive[54] and null findings.[55,57] Longitudinal studies suggest that prediabetes is a risk factor for subsequent CKD but it is unclear 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.[59,60]

Neuropathies in prediabetes

Neuropathies can be further divided into subcategories; the strongest supportive evidence relates to autonomic neuropathy, although the method of detection seems to be critical. Prediabetes has been found to be associated with decreased heart rate variability[61] (HRV – a marker of parasympathetic function),[62–65], decreased postural changes in heart rate,[62] increased prevalence of erectile dysfunction among 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 measurements of orthostatic blood pressure changes,[63] which is a late marker of diabetic neuropathy,[61] or with decreased expiratory-inspiratory ratio or change in heart rate during breathing.[63]

Studies in prediabetes and sensorimotor neuropathy [68–70] suggest that IGT and early diabetic neuropathy may involve small demyelinated fibres.[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; classical nerve conduction tests; vibration and temperature perception threshold may not capture neuropathy among prediabetic people.

Finally, evidence is accumulating on increased prevalence of idiopathic polyneuropathy (eg, idiopathic sensory/painful neuropathy,[73–78] and sensory/small fibre only neuropathy)[73,75,78]

among prediabetic individuals with IGT being more strongly related to painful than non-painful neuropathy.[73,75,78]

Diabetic retinopathy

Prediabetes status may be associated with an increased risk of diabetic retinopathy although the findings vary depending on the method of detection.[51,79–83] In a study of >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*, increased *retinal arteriole or venular calibre*, have also been shown to be related to prediabetes or increased risk of diabetes, but the evidence is not entirely consistent.[81–83]

Macrovascular disease

Prediabetes is linked with increased risks of major manifestations of vascular disease, but it remains unclear whether the elevated disease risks depend on development of clinical diabetes.[84,85] Cross-sectional studies argue in favour of vascular risk effects of mild or moderate hyperglycaemia as there is an excess prevalence of coronary disease in those with fasting or postload hyperglycaemia below the diabetic level.[86,87] Compared with coronary disease, there is less certainty with respect to cerebrovascular disease and aortic aneurysm.[87] Diabetes is a known risk factor for ischaemic and haemorrhagic stroke, but it remains to be established whether risk increases before development of diabetes. [84]

The dose-response effect of the degree of fasting hyperglycaemia for vascular mortality may be weaker than is the case for postload glucose. The DECODE pooling study of European cohorts found IGT to be associated with increased risk of coronary death and total cardiovascular death, independent of the level of FPG, while the converse was not the case.[88] Whether it is the basal or the challenged blood glucose level that is more important for atherogenesis, average glucose levels, indexed by HbA1c concentration, predict incident coronary disease at least as well as fasting and postload glucose, though there are comparatively few prospective studies of HbA1c.[89]

The epidemiological relation between prediabetes and macrovascular disease may be confounded by clustering of vascular risk factors within individuals. Blood glucose in the prediabetic range is modestly correlated with many risk factors, including general and central obesity, blood pressure, triglyceride and lipoprotein levels.[84] In consequence the strength of the glycaemia effect in itself depends on the extent to which related vascular risk factors are taken into account. A recent individual-level evidence from prospective studies suggests that fasting hyperglycaemia (figure 3), postload glucose, and A1c 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

The reasons for treating prediabetes include prevention of progression to diabetes, mitigation of some of the potential consequences of progression to diabetes as well as prevention of the potential consequences of prediabetes itself. Majority of the studies in this field of research have focused on diabetes incidence among prediabetic individuals and support the concept that lifestyle change should be the cornerstone for diabetes prevention. Evidence is also accumulating to demonstrate potential benefits from pharmacotherapy.

Lifestyle intervention

The primary aim of lifestyle interventions is to prevent or delay the 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 largest to date, the US DPP with a 3-year follow-up found a 58% risk reduction after interventions aimed at weight loss, dietary change and increase in physical activity.[25,28] In the first trial, the benefits were dependent on the number of goals achieved by the participant (weight reduction >5%, fat intake< 30%, saturated fat intake < 10%, fiber intake >15g/1000 kcal, exercise > 4h/week),[28] while in the DPP the most important determinant of risk reduction was weight loss (each 1-kg decrease reduced the risk by 16%).[90] The beneficial effect of lifestyle interventions has also been confirmed among Asian populations.[26,91] Successful lifestyle interventions seem to improve insulin sensitivity and β-cell function.[92,93]

Pharmacological intervention based on antidiabetic drugs

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

(2) Thiazolidinediones—The glitazones, such as troglitazone, rosiglitazone and pioglitazone, act through the PPAR-γ receptor 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 this drug was also associated with significant weight increase (~2 kg compared to placebo) and increased risk of heart failure (0.1% vs. 0.5% in controls).[24,97] Pioglitazone showed effectiveness in the ACT NOW Study on obese people with IGT. The risk of diabetes decreased by >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 greater with pioglitazone (~3 kg compared to placebo) and edema was more frequently reported (13% vs. 6%).[29] There is also some suggestion of a possible link between pioglitazone and bladder cancer and therefore individuals with a history of bladder cancer or unexplained hematuria should probably not receive this drug.[98,99] In the Indian DPP-2 study no difference in the rate of diabetes development was found between lifestyle intervention alone and lifestyle intervention plus pioglitazone during a 3-year trial.[100]

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

(3) α-glucosidase inhibitors—α-glucosidase inhibitors reduce the rate of polysaccharide digestion from the proximal small intestine. They primarily lower postprandial glucose without causing hypoglycaemia. Since their effect on A1c 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 support the effectiveness of these drugs in the prevention of diabetes and importantly one of them also shows evidence of decreased CVD and hypertension risk among treated IGT patients.[102,103] In the STOP-NIDDM trial, a 25% relative risk reduction for diabetes was found among people with IGT who were randomised to either acarbose 100 mg t.i.d. or identical placebo during 3.3 years of follow-up,[103,104] but almost one 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, another α-glucosidase inhibitor, found a 40% reduction in incident diabetes risk over 48 weeks of follow-up among high-risk Japanese individuals with IGT. Although the gastrointestinal side effects were similar as reported in previous trials, more people completed that study.[102]

(4) The GLP-1 analogues—Exenatide and liraglutide were both found to produce sustained weight loss among obese subjects and were associated with increased reversion from prediabetes to normoglycaemia over 1–2 years of follow-up. The most frequent side effects were nausea and vomiting in these studies.[105–107]

(5) Insulin secretagouges—A multicentre multinational study investigated the effect of nateglinide (a short-acting insulin secretagogue) in over 9000 persons with IGT and found no effect on the rate of diabetes or the cardiovascular outcomes during 6.5 years of follow-up.[108]

Pharmacological interventions based on non-antidiabetic drugs

(1) Anti-obesity drugs—The anti-obesity drug orlistat is a gastrointestinal lipase inhibitor. In a post hoc analysis of obese people, this drug was associated with greater weight loss (6.7 vs. 3.8 kg) compared to placebo with a significantly reduced conversion from IGT to diabetes (7.6% vs. 3.0%) in a 1.5-year follow-up.[109] This finding is consistent with the 4-year XENDOS trial that reported a 37% reduction in relative risk of diabetes among obese people treated with orlistat although in that study only 52% completed treatment compared with 34% of placebo recipients. An explanatory analysis suggested that the preventive effect was mainly confined to subjects with IGT.[27]

There is at least one randomised trial with 6-month duration in people with prediabetes and hypertriglyceridemia that found higher rates of regression to normoglycaemia among fenofibrate (>50%) treated subjects compared to placebo (30%). Lipotoxicity is thought to be an important factor in the development of diabetes that makes these findings attractive.[110]

(2) Renin-angiotensin-aldosteron system blockers—Secondary analyses of hypertension trials have suggested lower incidences of diabetes among people with high cardiovascular risk who receive ACE (angiotensin converting enzyme) inhibitors, or ARBs (angiotensin receptor blockers).[111] However, these findings may be biased as the comparator active treatment groups had different proportions of other antihypertensive treatments that are known to increase the risk of diabetes (β-blockers, thiazide diuretics).[112,113] Furthermore, in the DREAM trial, there was no significant association between ramipril, another renin-angiotensin-aldosteron system blocker, and new-onset diabetes.[113] In light of current evidence, the effect of these drugs is much smaller than that of the antidiabetic drugs and they are not recommended for the treatment of prediabetes.

Other treatments that reduce diabetes risk

In morbidly obese people, bariatric surgery was associated with a sustained weight loss, a substantial reduction in 2- and 10-year incidence of type 2 diabetes[114] and among individuals with blood glucose above 4.5 mmol/L 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 the 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, for example, those receiving a lifestyle intervention had a 43% reduced risk of diabetes, translating to a mean 3.6 year delay in the development of diabetes.[119]

The Diabetes Prevention Program Outcomes Study 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. Those who remained prediabetic despite intensive lifestyle treatment had an even higher risk of developing diabetes than those on metformin or placebo treatment.[120]

In the 20-year follow-up of the DaQing Study, the lifestyle intervention was also associated with an almost 50% reduction in the relative risk of incident severe retinopathy, while the rates of other microvascular complications, such as nephropathy and neuropathy, were similar as in controls.[119]

The evidence of intervention effects on macrovascular complications is not consistent. In a recent meta-analysis of trials among prediabetic people, lifestyle and drug-based interventions had no significant effect on the risk of all-cause mortality or cardiovascular death during the mean follow-up of 3.8 years, except for a borderline significant reduction in stroke risk.[116] All-cause mortality was lower in the diet and exercise intervention group compared to the control group during a 12-year follow-up in the Malmö Preventive Project, but in this study participation in intervention was not randomised.[121]

Clinical and public health implications

The concept of prediabetes (also known as Intermediate Hyperglycaemia or High Risk for Diabetes) identifies a heterogeneous patient population that is characterized by the simultaneous presence of insulin resistance and β-cell dysfunction. Multifactorial diabetes risk scores are promising tools to further improve identification of individuals at high risk of developing diabetes although it is not yet known whether use of risk scores would help in the prevention of diabetes above the classical definition of prediabetes.

Prediabetes is not only related to an increased risk of diabetes and its complications but there is also accumulating evidence to suggest damage on kidney and nerves already at the prediabetic stage. Identification and treatment of prediabetic individuals is therefore crucial. Recent evidence suggest that preventing progression of prediabetes to diabetes is possible although evidence of reduced cardiovascular disease risk is limited. Based on randomized trials that show the effectiveness of lifestyle intervention and several antidiabetic drugs in the prevention of diabetes, lifestyle intervention aimed at >7% of weight reduction and 150 minutes/week of moderate intensity physical activity is recommended for all subjects with prediabetes. Based on the decades long safety information on metformin, this drug could also be used in people that are unable to comply with lifestyle advice. For the other potential

drugs, further long-term studies are required on safety and on vascular outcomes before lifelong treatment could be safely recommended.

Economic considerations are important for policy makers, public health agencies, insurers, health care providers and consumers, but currently there are little data assessing different prediabetes screening and treatment strategies in terms of cost-effectiveness and health benefits. The fact that diabetes is projected to be within the 5 leading causes of death in high-income countries by 2030 and within the 10 leading causes of death globally highlights the public health importance of reducing diabetes risk at the population level. Strategies targeting interventions at the entire population in order to shift the distribution of key diabetes risk factors, such as adiposity and physical inactivity, are important. However, our seminar has shown that these need to be complemented with diabetes prevention strategies based on interventions specifically aimed at prediabetic and other high-risk individuals.

Search strategy

We searched Pubmed (from inception to January 2012). In the *epidemiology* section, we used the search terms “incidence” or “prevalence”, in the *complications* section “nephropathy” or “albuminuria” or “microalbuminuria” or “chronic kidney disease” or “neuropathy” or “autonomic” or “heart rate variability” or “orthostatic” or “idiopathic neuropathy” or “erectile dysfunction” or “Valsalva”, in the *pathophysiology* section “pathophysiology” or “clamp” or “intravenous glucose tolerance test” or “insulin secretion” or “insulin sensitivity”, in the *treatment* section “diabetes prevention” or “lifestyle intervention” or “metformin” or “troglitazone” or “rosiglitazone” or “pioglitazone” or “acarbose” or “voglibose” or “exenatide” or “liraglutide” or “nateglinide” or “ramipril” or “valsartan” or “orlistat” or “bariatric surgery” or “fibrate” in combination with the terms “prediabetes”, “impaired glucose tolerance” or “impaired fasting glucose”. We primarily selected publications in the past 5 years, but did not exclude commonly 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. Review articles and book chapters are cited to provide readers with more details and more references than this Seminar has room for. Our reference list was modified on the basis of comments from peer reviewers and was limited to 120 references.

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Abbreviations

A1c	hemoglobin A1c
ADA	American Diabetes Association
ACE inhibitors	angiotensin converting enzyme inhibitors
AER	albumin excretion rate
ARB	angiotensin receptor blockers
ARIC	Atherosclerosis Risk in Communities study
AusDiab	Australian, Diabetes, Obesity, and Lifestyle Study
CKD	Chronic kidney disease

CVD	cardiovascular disease
DPP	Diabetes Prevention Programme
eGFR	estimated glomerular filtration rate
EGP	endogenous glucose production
FPG	fasting plasma glucose
HRV	heart rate variability
IFG	impaired fasting glucose
HOMA	homeostatic model assessment
IGT	impaired glucose tolerance
IENFD	intraepidermal nerve fibre density
MESA	Multi-Ethnic Study of Atherosclerosis
NGT	normal glucose tolerance
NHANES	National Health and Nutrition Examination Survey
OGTT	oral glucose tolerance test
WHO	World Health Organization

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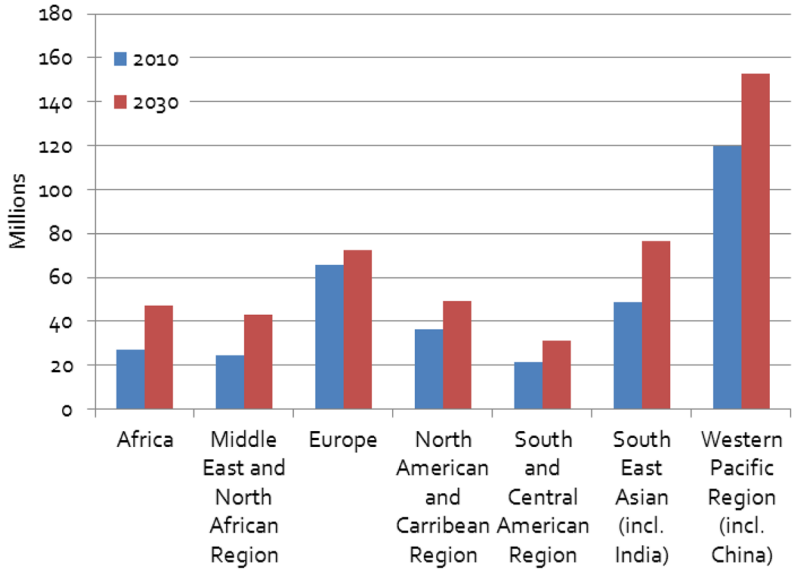

Figure 1.
The number of people with IGT (in millions) by region among adults aged 20–79 years for the years 2010 and 2030[11]

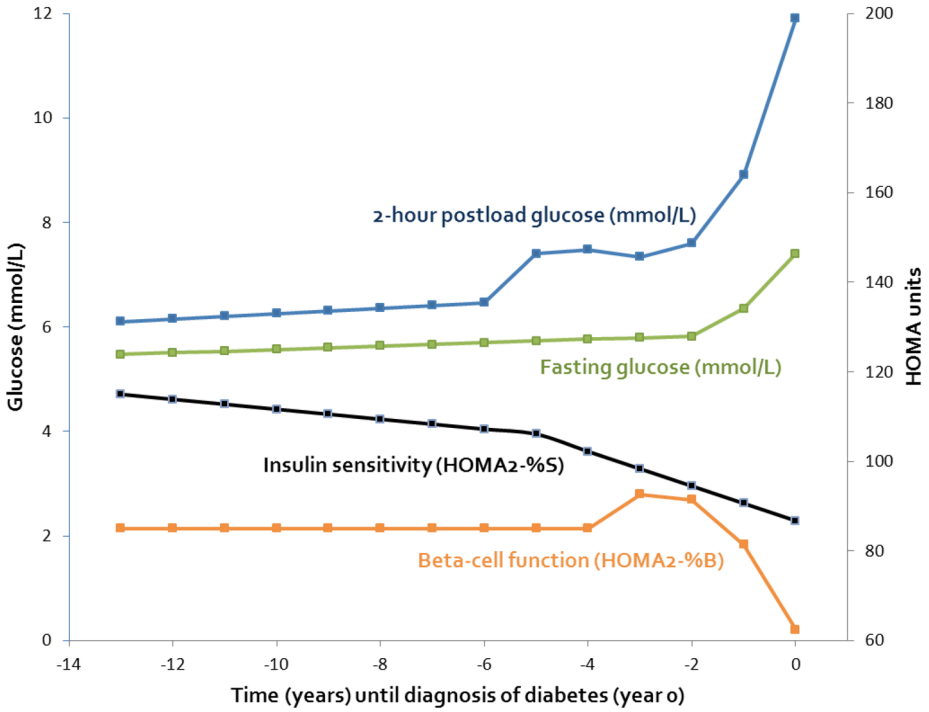

Figure 2.

Fasting and 2-hour postload glucose, Homeostasis model assessment insulin sensitivity (HOMA2-%S) and HOMA β-cell function (HOMA2-%B) trajectories before the diagnosis of diabetes mellitus in the British Whitehall II study

Redrawn with permission from [36]

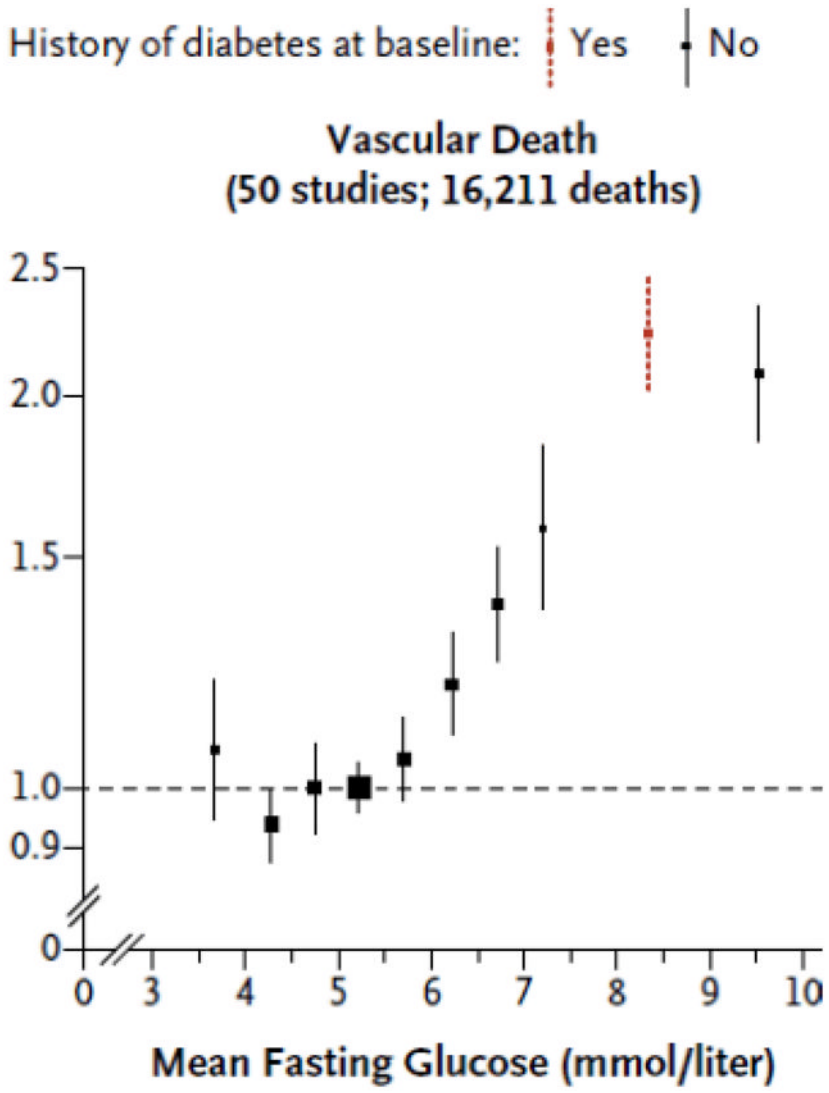

Figure 3.
Hazard ratios for vascular death according to baseline levels of fasting glucose
Glucose levels for participants without a known history of diabetes at baseline were classified as <4.5, 4.5 to less than 5.0, 5.0 to less than 5.5, 5.5 to less than 6.0, 6.0 to less than 6.5, 6.5 to less than 7.0, 7.0 to less than 7.5 mmol/l.
Reproduced with permission from[85]

Table 1

Diagnostic criteria for prediabetes

Authority, year	Venous plasma
WHO 1965	Postload: ~7.1–8.2mmol/L
WHO 1980	Fasting: <8.0mmol/L and 2-h postload: ≥8.0 and <11.0mmol/L
WHO 1985	Fasting: <7.8mmol/L and 2-h postload: ≥7.8 and <11.1mmol/L
WHO 1999 & 2006 (most recent)	IGT Fasting: <7.0mmol/L and 2-h postload: ≥7.8mmol/L and <11.1mmol/L IFG Fasting: ≥6.1 and <7.0mmol/L and 2-h postload: <7.8mmol/L (if measured) (2-h postload glucose measurement recommended to exclude diabetes or IGT).
ADA 1997	IGT Fasting: <7.0mmol/L and 2-h postload: ≥7.8mmol/L and <11.1mmol/L IFG Fasting: 6.1 – 6.9mmol/L
ADA 2003	IGT Fasting: <7.0mmol/L and 2-h postload: 7.8 – 11.0mmol/L (if measured) IFG Fasting: 5.6 – 6.9mmol/L (measurement of 2-h postload glucose not recommended)
ADA 2010 (most recent)	IGT Fasting: <7.0mmol/L and 2-h postload: 7.8 – 11.0mmol/L IFG Fasting: 5.6 – 6.9mmol/L (measurement of 2-h postload glucose not recommended) HbA1c (a new category of high risk for diabetes): 5.7 – 6.4%

Abbreviations: ADA, American Diabetes Association; A1c, Haemoglobin A1c; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; WHO, World Health Organization.

One abnormal test result defines prediabetes, no repeat testing is required.

Table 2

Examples of externally validated diabetes risk models

Study/score	Year	Country	Age	Sex	Ethnicity	BMI	Waist circumference	Height	Family history of diabetes	Systolic blood pressure	HDL-cholesterol	Triglycerides	Uric acid	Antihypertensive medication	Hypertension	Cardiovascular disease	Use of corticosteroids	Diet	Physical inactivity	Smoking	Deprivation index	Fasting glucose	Hemoglobin A1c
San Antonio	2002	USA	+	+	+	+			+	+	+											+	
FINDRISK	2003	Finland	+	+		+	+							+				+	+				
ARIC	2005	USA	+	+	+		+	+	+	+	+	+							+			+	
Framingham Offspring	2007	USA	+	+		+			+	+	+	+											
Cambridge Risk Score	2008	UK	+	+		+			+					+			+			+			
QDScore	2009	UK	+	+	+									+	+	+	+			+	+		
AUSDRISK	2010	Australia	+	+	+	+	+		+					+					+	+		+	
KORA	2010	Germany	+	+		+			+				+		+					+		+	+

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; AUSDRISK, an Australian Type 2 Diabetes Risk Assessment Tool based on demographic, lifestyle and simple anthropometric measures; BMI, body mass index; FINDRISK, Finnish Diabetes Risk Study, KORA, Cooperative Health Research in the Region of Augsburg Study.[6]