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Feature Review

Prediabetes remission to reduce the global burden of type 2 diabetes

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Prediabetes is a highly prevalent and increasingly common condition affecting a significant proportion of the global population. The heterogeneous nature of prediabetes presents a challenge in identifying individuals who particularly benefit from lifestyle or other therapeutic interventions aiming at preventing type 2 diabetes (T2D) and associated comorbidities. The phenotypic characteristics of individuals at risk for diabetes are associated with both specific risk profiles for progression and a differential potential to facilitate prediabetes remission and reduce the risk of future T2D. This review examines the current definition and global prevalence of prediabetes and evaluates the potential of prediabetes remission to reduce the alarming increase in the global burden of T2D.

Highlights

Prediabetes remission to normal glucose regulation (NGR), in addition to standard weight loss, lowers type 2 diabetes (T2D) risk more than standard weight loss alone.

Remission of prediabetes to NGR should be considered in guidelines and recommendations for the delay and prevention of T2D.

Future studies will provide evidence whether or not prediabetes remission can protect against incident T2D-related comorbidities such as cardiovascular and/or chronic kidney disease (CKD).

Need for prevention of T2D

One major global target for noncommunicable diseases is to halt the increase in the prevalence of T2D among adults, keeping the prevalence at 2010 levels. Yet, the number of people with T2D has nearly quadrupled since 1980, and incidence continues to rise, faster in low- and middle-income than in high-income countries and communities. Regions expected to experience very large increases in incident T2D are Latin America and the Caribbean, North Africa, the Middle East, and Southeast Asia. It will therefore be crucial to understand regional differences in individuals at risk of T2D and to define more effective strategies to prevent this large wave of incident T2D and its complications in the future [1–5].

In general, there are many conditions that predispose patients to developing T2D. One of the strongest risk factors is obesity, but also sedentary lifestyle, genetic predisposition, and history of gestational diabetes [6]. Other, less well-defined risk factors include chronic stress, certain infections, and specific drugs, such as certain checkpoint inhibitors in the treatment of cancer [7,8]. The best-studied condition with a high risk of progression to T2D is prediabetes – a condition affecting a highly heterogeneous group. Here, we will focus mainly on its different phenotypes and global pathophysiological aspects and discuss recent advances in prediabetes remission as an effective strategy to prevent incident T2D and potential complications.

Definitions and global epidemiology of prediabetes

Health organizations have proposed different definitions of prediabetes [9]. The American Diabetes Association (ADA, Box 1), defines prediabetes by at least one of the following conditions: fasting plasma glucose (FPG) between 100 and 125 mg/dl (6.5–6.9 mmol/l) [impaired fasting glucose (IFG)], 2-h plasma glucose in a 75 g oral glucose tolerance test (OGTT) between 140 and 199 mg/dl (7.8–11.0 mmol/l) [impaired glucose tolerance (IGT)], and/or hemoglobin A1c (HbA1c) between 5.7% and 6.4% (39–47 mmol/mol). The World Health Organization (WHO) uses the term 'intermediate hyperglycemia' instead of 'prediabetes'; one of its criteria is FPG between 110 and 125 mg/dl (6.1–6.9 mmol/l), without a reliable cut-off value of Hba1c as the WHO stresses the concept of

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Box 1. Mentioned studies, guidelines, and organizations

ADA: American Diabetes Association: one of the world's largest diabetes associations, founded in 1939

CATAMERI study: Catanzaro Metabolic Risk Factors study: an observational study enrolling White individuals with at least one cardiometabolic risk factor

Da Qing study: Da Qing Diabetes Prevention Study: aimed at investigating the effect of dietary and exercise intervention, on T2D incidence in people with impaired glucose tolerance in a randomized manner, starting in 1986 and including 577 adults

DCCPG: Diabetes Canada Clinical Practice Guidelines

DiRECT: Diabetes Remission Clinical Trial: open-label, cluster-randomized trial including 306 individuals with T2D from Scotland and the Tyneside region of the UK, starting in 2014

DPP: Diabetes Prevention Program: a study conducted from 1996 to 2001 in the USA comparing lifestyle intervention, metformin, or placebo, including 3234 individuals without T2D

DPPOS: DPP Outcome Study: further follow-up of 2776 individuals from DPP from 2002 to 2014 with semi-annually lifestyle reinforcement in the original lifestyle intervention group and unmasked metformin treatment in the original metformin group

Finnish DPS: Finnish Diabetes Prevention Study: lifestyle intervention study in 523 individuals with impaired glucose tolerance, recruited between 1993 and 1998 in Finland

IDF: International Diabetes Federation: world's largest diabetes organization, founded in 1950

IDPP: Indian Diabetes Prevention Program: comparing lifestyle modification, metformin, lifestyle modification, and metformin combined, with control in 531 Asian Indians with impaired glucose tolerance, recruited between 2001 and 2002

NDPP: National Diabetes Prevention Program: lifestyle intervention program established by the Centers for Disease Control and Prevention (CDC) in the USA since 2010

NHANES: National Health and Nutrition Examination Survey: program of the National Center for Health Statistics for assessing health and nutritional status of adults and children in the USA, started in 1960

NICE: National Institute for Health Care Excellence: publishes guidelines for the use of health technologies, clinical practice, guidance on health promotion and social care services in the UK

PLIS: German Prediabetes Lifestyle Intervention Study: conducted in Germany from 2012 to 2016 with ongoing follow-up, designed to investigate the effect of different intensities of lifestyle intervention in individuals with prediabetes

POP-ABC: Pathobiology of Prediabetes in a Biracial Cohort: prospective evaluation of the natural history of impaired glucose regulation that enrolled 376 individuals between 2006 and 2009 in the USA

RISC Study: European Relationship between Insulin Sensitivity and Cardiovascular Disease Study: enrolled 801 participants from 13 European countries between 2002 and 2004

TÜF study: Tübingen Family Study for T2D: enrolled 2600 individuals with normal glucose tolerance and with or without family history of T2D cross-sectionally

Whitehall II study: British study that included 10 308 civil servants to investigate social and occupational influences on health and disease from 1985 to 1988

WHO: World Health Organization: agency for global public health established in 1948

YMCA DPP: Young Men's Christian Association (YMCA) Diabetes Prevention Program: 12-month lifestyle intervention program for individuals at risk for T2D provided by the Young Men's Christian Association

Glossary

Glucagon-like peptide 1 (GLP-1): peptide hormone produced in the ileum and colon that regulates blood glucose level and satiety, amongst other functions.

Major adverse cardiac events (MACE): including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

Major adverse renal events (MARE): proposed to include new onset of kidney injury [persistent albuminuria/proteinuria and/or decreasing glomerular filtration rate (GFR) <60 ml/min/1.73 m^2], persistent signs of worsening kidney disease, development of end-stage kidney disease with estimated GFR <15 ml/min/1.73 m^2 without or with initiation of kidney replacement therapy, and death from renal cause [138].

Metabolic dysfunction-associated steatotic liver disease (MASLD): steatotic liver disease associated with cardiometabolic risk factors without elevated alcohol consumption.

Metabolically healthy obesity (MHO): individuals with obesity with a relatively low risk for cardiometabolic abnormalities.

Raster scan optoacoustic mesoscopy (RSOM): a method used for microvascular structure assessment with a laser.

Reactive oxidative species (ROS): highly reactive chemicals formed from oxygen that can exert damaging effects.

Sodium-glucose cotransporter 2 (SGLT2): a protein of the renal proximal tubule that helps reabsorbing glucose.

metabolic diseases as a continuum. Both the Diabetes Canada Clinical Practice Guidelines (DCCPG) and the National Institute for Health and Care Excellence (NICE) are aligned with the WHO in its FPG thresholds, but add HbA1c levels between 6.0% and 6.4%. Overall, the

ADA proposes the lowest cut-off values for prediabetes, allowing for identification of at-risk individuals at an early stage [10].

Recent observations show the age-adjusted global prevalence of IGT to be at 9.1% (464 million people) and of IFG to be at 5.8% (298 million people) in 2021 based on WHO criteria in the International Diabetes Federation (IDF) Diabetes Atlas [11]. The global prevalence of IGT is projected to increase to 10.0% (638 million people) and IFG to 6.5% (414 million people) in 2045. Applying ADA criteria, the same estimate may be up to 60% higher[i]. Until 2045, the largest relative growth in cases of IGT and IFG is projected to occur in low-income countries, with a 12% and 6.7% increase, respectively (WHO criteria) [11]. While the prevalence of IGT is currently highest in North America and Caribbean regions (13.1%) and lowest in Southeast Asia (4.5%), Southeast Asia had the highest age-adjusted prevalence of IFG (9.4%) in 2021, reflective of genetic and environmental differences (Figure 1) [12,13]. Importantly, race- and ethnicity-specific prevalences of prediabetes in the USA do not differ between persons of non-Hispanic Asian (37.3%), non-Hispanic Black (NHB) (39.2%), Hispanic (35.4%), or non-Hispanic White (NHW) (38.7%) ancestry. These data suggest that local environmental factors might overrule genetic background in an obesogenic environment.

In the USA, one-third of the population lives with prediabetes, as diagnosed by ADA cut-offs, with NHW men being least aware of their condition, followed by NHB, Hispanic, and Asian people. Overall, prediabetes prevalence shows a clear association with age, with prevalence increasing from 27.8% in 18–44 years olds to 48.8% in >65 years olds in the USA (ADA). Similar to the differing definitions by health organizations, prediabetes prevalence greatly depends on applied thresholds [14,15]. The regional prevalence of IFG differs markedly from IGT. This could either result from differing diagnostic tools, for example, sole measurements of fasting glucose instead of performance of whole OGTT, and/or reflect differential pathophysiological patterns and/or ethnicity. Sensitivity of HbA1c testing was 83% in NHB, while being only 20% in NHW in the National Health and Nutrition Examination Survey (NHANES) [16]. However, sensitivity of IFG testing was only around 50% in NHB. This is partly associated with differing prevalences: IFG rate in NHB was 18%, while elevated HbA1c rate was 29.8%.

Progression to T2D differs between regions, which is reflected by the distribution of known T2D genetic variants [17,18]. In Asian Indians, T2D occurs at an earlier age than in Caucasian Whites [19]. A decreasing beta-cell function seems to play a major role in Asian Indians with impaired glucose regulation, specifically with IFG and IGT [12]. The progression rate of IGT to T2D is higher in Asian Indians, with a cumulative incidence of 55.0% in 3 years (18.3% per year) compared with Chinese (11.3% per year), Finnish (6.0% per year) and, American individuals (11 per 100 person-years) [20–22]. Furthermore, the risk thresholds of anthropometric measures are lower in Asian people compared with Caucasian Whites, as the risk of T2D increases already at a body mass index (BMI) of >23 kg/m^2 and a waist circumference of 85 cm for men and 75–80 cm for women [23]. For a given BMI, Asian Indians have been found to have a higher central adiposity accompanied by insulin resistance [24]. Moreover, recent elegant studies provide evidence that South Asians differ from White Europeans in the adipose tissue physiology of weight gain. Accordingly, differences in adipocyte morphology are associated with greater adverse metabolic changes with weight gain in South Asians [25]. In Black African individuals with prediabetes or T2D, beta-cell failure without significant insulin resistance was more frequent than insulin resistance while the insulin resistant phenotype showed a higher T2D prevalence [26]. As body weight, being a key indicator of insulin resistance, is increasing in most countries, the prevalence of prediabetes is expected to rise even faster than T2D prevalence [11,27,28].

Sex-specific considerations

Prediabetes affects females and males differently at different stages of life. Yet, high-quality data are still rare. In the USA, more males [41.0 (37.3–44.8%)] than females [32.0 (28.9–35.2%)] have

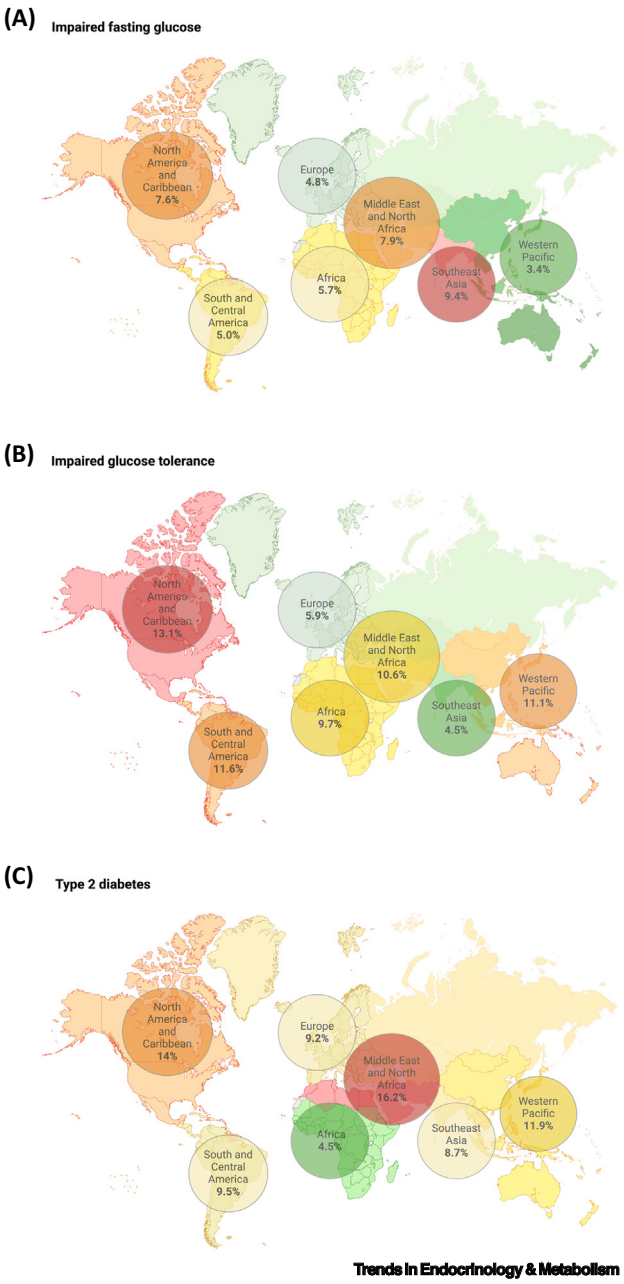

Figure 1. Color-coded age-adjusted prevalence for impaired glucose tolerance (IGT), impaired fasting glucose (IFG), and type 2 diabetes (T2D) in adults aged 20–79 years by International Diabetes Federation (IDF) region. Dark red: highest prevalence; dark green: lowest prevalence. (B) Based on data from Rooney *et al*. [11], (C) based on data from IDF Diabetes Atlas 2021[ii]. IFG was defined as fasting plasma glucose levels of 6.1 to 6.9 mmol/l (110–125 mg/dl). Figure created using BioRender.

prediabetes; however females were more aware of living with prediabetes than males [29]. Moreover, females with prediabetes had a greater increase in metabolic syndrome severity and central adiposity compared with males over time, which may, together with elevated coronary heart disease risk factors and stronger endothelial dysfunction already in the prediabetic state, contribute to the higher risk for cardiovascular diseases (CVDs) in females with T2D in the USA [30–33].

By contrast, in India, a larger proportion of people with prediabetes has IFG or even isolated impaired fasting glucose (i-IFG), with more than 70% being female, while IGT is more frequent

among males than among females [34]. In a Chinese cohort, physical activity favored remission from prediabetes to normal glucose tolerance (NGT) in males, while in females, lower waist circumference seemed to be more important. Here, high 2-h glucose in men, as opposed to high fasting glucose levels in females, were associated with a high risk for the progression to T2D [35].

While males with prediabetes seem to be more susceptible to develop T2D at a younger age than females [36], in the Rotterdam Study, lifetime risk of progression to T2D after 45 years of age was higher in females than in males, which may be explained by a diverging vulnerability of females and males to the effects of obesity and ageing [37,38].

Taken together, our knowledge on ethnic- and race-specific as well as sex-specific differences in people at risk for diabetes is still incomplete; it is imperative to conduct further investigations aiming at a comprehensive understanding of risk differences for developing T2D and the means of preventing it. This will be crucial for meeting the demands of modern medicine.

Pathophysiology and natural history of prediabetes

Obesity

Once prediabetes develops, glucose homeostasis is already strongly, but partly still reversibly, dysregulated. Its pathophysiology seems to be to some extent specific to the individual at-risk condition, including BMI category, body composition, and genetic risk.

Elegant cross-sectional studies have examined persons with obesity with NGT, some of whom are classified as people with so-called **metabolically healthy obesity (MHO)** (see Glossary), compared with lean persons with normal glucose regulation (NGR [39,40]. People with metabolically unhealthy obesity with NGT are characterized by whole-body insulin resistance with skeletal muscle and hepatic insulin resistance, higher insulin secretion, and reduced insulin clearance rate, leading to an increase in basal insulin values of >100% [40]. In these people, visceral adipose tissue (VAT), hepatic and skeletal muscle fat content, *de novo* lipogeneses, and cholesterol- and saturated fatty acid-triglyceride secretion rates are higher compared with those of people who are healthy and normal weight. Since insulin secretion rate, and thus beta-cell function, is reduced (while insulin secretion is increased), this may indicate that insulin secretion reaches a plateau [39,41,42]. Interestingly, recent data show that insulin secretion remains elevated in persons with obesity compared with lean people, even when matched for insulin sensitivity in a cross-sectional setting [43]. However, these data remain to be corroborated in longitudinal trials.

Ethnicity-specific differences seem to contribute to the heterogeneity, with a faster reduction in beta-cell function in African Americans and increased hepatic lipid accumulation and muscle insulin resistance despite lower body weight in Asian Indians [44–46].

In order to unravel early mechanisms of insulin resistance, young, lean, sedentary individuals without prediabetes have been examined upon high-carbohydrate mixed meals [47]. From this group, insulin-resistant individuals showed post-prandial skeletal muscle insulin resistance, which led to higher hepatic *de novo* lipogenesis by redirecting glucose from muscle to liver, where glucose uptake is not insulin dependent, and consequently, these young lean insulin-resistant individuals had higher hepatic and circulating triglyceride levels, compared with insulin-sensitive individuals. Prediabetes in the context of overweight/obesity is in most cases associated with increased energy intake, possibly from saturated fat sources and monosaccharides, which can cause ectopic lipid storage in VAT and numerous other organs. *De novo* lipogenesis in the liver and low-grade inflammation in adipose tissue contribute to ectopic lipid storage [48–52], while the regional distribution of ectopic lipid disposition in the body is, to an important extent,

genetically determined [53,54]. Ectopically stored lipids, especially diacylglycerols and ceramides, can lead to hepatic insulin resistance together with an adipose tissue–liver crosstalk via FFA/acetyl-Co [55–57]. Free fatty acids (FFAs) from VAT can drain via the portal vein directly to the liver, possibly exposing it to high concentrations of FFAs and glycerol [58]. So far, the contribution of FFAs drained from VAT to the portal vein has not been quantified in a longitudinal manner after weight loss, while in cross-sectional studies, FFAs drained from VAT to the liver were quantitatively lower than FFA from subcutaneous white adipose tissue. High FFAs in the pancreatic circulation, which may stem from very-low-density lipoproteins (VLDL) secreted by the liver and/or dietary and adipose tissue-derived sources, may hamper beta-cell function by impairment of beta-cell gene transcription and elevation of oxidative stress via **reactive oxygen species (ROS)** [59–61].

A liver fat content above 1.85% is already associated with hepatic insulin resistance [55,62,63]. As a consequence, an elevated fasting hepatic glucose production can result in IFG. However, the absolute level of liver fat at which metabolic deterioration begins varies from person to person. Studies have shown that people with obesity but a rather healthy metabolic phenotype have a reduced prevalence of **metabolic dysfunction-associated steatotic liver disease (MASLD)** compared with those with an unhealthy metabolic phenotype [64].

In people with prediabetes and obesity, the prevalence of visceral obesity, MASLD, and both insulin resistance and relative insulin secretion failure is high [65]. This is often accompanied by three or more criteria of the metabolic syndrome, reflecting a high-risk phenotype to develop T2D and complications.

In people with prediabetes and normal weight, however, relative beta-cell dysfunction occurs frequently, while insulin resistance is only present in around one-third of individuals. Rates of visceral adiposity are relatively low and of MASLD even lower.

Still, these phenotypes do not necessarily reflect the development of overall prediabetes, but rather different pathophysiological subgroups and traits of prediabetes [66]. Interestingly, the relationship between mortality and BMI just before incident T2D has been found to be J-shaped, with the highest hazard ratio for all-cause mortality in the normal weight (18.5–22.4 kg/m^2) and the obese (≥35.0 kg/m^2) BMI category [67].

Progression from NGR to prediabetes

In the postabsorptive state, approximately two-thirds of glucose uptake is independent of insulin [68]. To avoid resulting hypoglycemia, an equilibrium between the rate of glucose uptake and endogenous glucose production is achieved, mainly by the liver. Thus, FPG is primarily determined by hepatic glucose production, further being adapted by glucagon secretion [69,70]. In the postprandial state, carbohydrates are absorbed into circulation, stimulating insulin secretion, together with the gastrointestinal incretin receptor hormones **glucagon-like peptide 1 (GLP-1)** and glucose-dependent insulinotropic polypeptide (GIP). Both high glucose and insulin levels suppress hepatic glucose production and stimulate glucose uptake into peripheral tissues, mainly skeletal muscle, leading to high glucose disposal and, ultimately, normoglycemia [71]. Recent studies have shown that elevation of 1-h plasma glucose (1-h PG) seems to precede IGT, thereby suggesting that 1-h PG may be employed as an early marker of impaired glucose metabolism [72].

Impaired glucose regulation

Changes in glucose homeostasis are a continuum, probably starting years before prediabetes is diagnosed (Figure 2). While numerous studies focused on the conversion from prediabetes

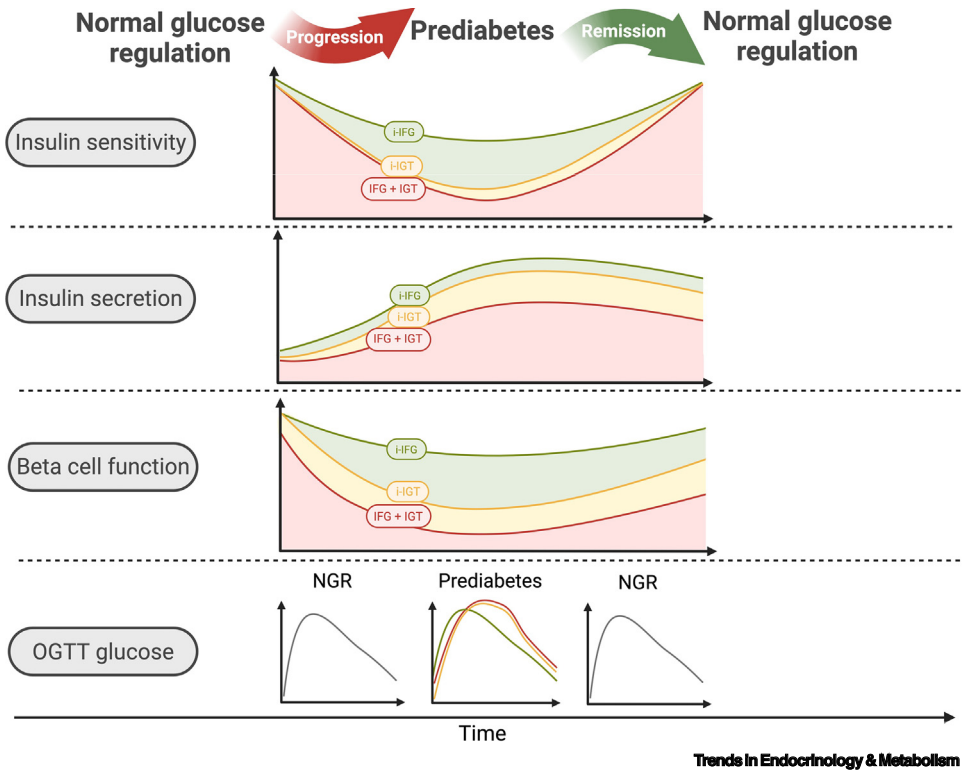

Figure 2. Natural history of the transition from normal glucose regulation (NGR) to prediabetes subtypes [isolated impaired fasting glucose (i-IFG), isolated impaired glucose tolerance (i-IGT), and impaired fasting glucose (IFG)/impaired glucose tolerance (IGT) combined] and remission of prediabetes to NGR due to lifestyle changes. Top: insulin sensitivity reflected by oral glucose tolerance test (OGTT)-derived indices [oral glucose insulin sensitivity (OGIS); insulin sensitivity index; Matsuda index] and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Center: insulin secretion, reflected by Homeostasis Model Assessment of Beta-cell Function (HOMA-B) and/or area under the curve $(AUC)_{c\text{-}pep0\text{–}30}/AUC_{gluc0\text{–}30}$ as an index of glucose-stimulated insulin secretion levels during a 75-g OGTT. Bottom: beta-cell function reflected by insulin secretion relative to insulin sensitivity (adaptation index and disposition index) [127,139,140]. OGTT glucose: OGTT-derived glucose curves in NGR and in prediabetes, divided in i-IFG (green line), i-IGT (yellow line), and IFG + IGT (red line). Figure created using BioRender.

to T2D, few studies have focused on the transition from NGR to prediabetes (i.e., i-IFG, i-IGT, or both). In a study of Pima Indians who are at high risk of developing T2D, individuals who progressed to T2D had beta-cell dysfunction even before the plasma glucose level rose into the prediabetic range, and beta-cell dysfunction worsened with rising plasma glucose levels [73,74].

The POP-ABC (Pathobiology of Prediabetes in a Biracial Cohort) study has identified several risk factors for the development of prediabetes. These include higher age, male sex, higher BMI, waist-to-hip ratio (WHR), plasma glucose levels, impaired insulin secretion and beta-cell dysfunction, higher triglycerides, lower adiponectin, higher alanine aminotransferase (ALT) levels, and higher blood pressure, amongst others [75,76]. People who progressed from NGR to prediabetes had lower insulin sensitivity compared with non-progressors, as measured by the gold standard technique hyperinsulinemic-euglycemic clamp, and a steeper decrease of insulin sensitivity over the years [77,78].

i-IFG

People with i-IFG are characterized by an elevated FPG (>100 mg/dl according to ADA criteria), an exaggerated early rise in plasma glucose concentration following glucose ingestion, and a 2-h glucose level similar to NGT. Most data indicate that people with i-IFG are primarily characterized by adipose tissue and hepatic insulin resistance with normal muscle insulin sensitivity, resulting in increased hepatic glucose output and increased fasting glucose levels [68,79–81]. The reason for the ability of people with i-IFG to maintain NGR after a glucose challenge is that muscle glucose disposal is not or only slightly impaired. Additionally, only first phase, but not second phase insulin secretion is mildly impaired and glucagon suppression by glucose stimuli is reduced, which is not specific to i-IFG only [82–84]. By contrast, the role of gut-derived incretins in i-IFG is less well understood and clearly needs further study [85].

Natural history of i-IFG

In the Inter99 study [86], 5 years before the progression to i-IFG, beta-cell function was already significantly impaired in normoglycemic individuals. Yet, during the development of i-IFG, beta-cell function did not decline further, indicating that a decreasing insulin secretion ability is not a major feature in the early stages of fasting hyperglycemia. Instead, these longitudinal data suggest that a steady decline in hepatic, but not muscle, insulin sensitivity, causes the development of prediabetes. However, muscle insulin sensitivity was already low at baseline in people progressing to i-IFG. The prediabetic state, i-IFG, therefore appears to be caused by a low baseline beta-cell function in combination with a progressive decline in hepatic insulin sensitivity. Indeed, a family history of T2D was more common in the i-IFG cohort than in the NGT group, suggesting a genetic or epigenetic impact in the development of i-IFG.

i-IGT

When glucose tolerance during OGTT is impaired, insulin secretion is not sufficient to lower plasma glucose to normal values within the normal timeframe. A lower insulin sensitivity has been consistently demonstrated in individuals with i-IGT in comparison to those with NGT [87–89]. An impairment in insulin-stimulated whole-body glucose disposal, which is mainly determined by skeletal muscle glucose uptake, but further contributed to by adipose tissue and hepatic glucose output, was observed in all ethnic groups studied, including Pima Indians, Hispanics, and Japanese [87,89–92]. High FFA levels can induce muscle insulin resistance [93] and defects in muscle glycogen synthesis occur in insulin resistance and contribute to elevated glucose levels by increasing the hepatic energy burden already at early stages [47].

Natural History of i-IGT

In the transition from NGT to prediabetes to T2D, peripheral insulin resistance can first be compensated by an increased insulin secretion by pancreatic beta cells. When prediabetes occurs, beta cells reach a plateau of their insulin secretion capacity and fail to lower plasma glucose levels into the normal range. People with i-IGT exhibit impairments in early and late phases of insulin secretion as well as alpha-cell function with reduced glucagon suppression by glucose stimuli [83,84]. The role of gut-derived incretins in i-IGT is less well understood and requires further investigation [85]. Several studies have shown that in individuals with i-IGT or IFG/IGT, the modulation of insulin secretion by incretins is impaired, further contributing to the progression towards T2D [94,95].

Combined IFG and IGT

In cross-sectional studies, people with obesity and IFG/IGT, a phenotype also referred to as metabolically unhealthy obesity, have severe metabolic disturbances as a combination of the single attributes of people with i-IGT and i-IFG [39].

Analysis of the natural history shows that people developing IFG/IGT within 5 years from NGT are able to increase a previously low insulin secretion rate (either determined by fasting insulin levels or by insulin levels during the 75-g OGTT), while beta-cell function (evaluated as insulin secretion rate relative to insulin sensitivity) declines, and hepatic- as well as skeletal muscle insulin sensitivity, which are low already at baseline, further decline.

Interesting to note is that individuals who develop IFG/IGT have more characteristics in common with those who developed i-IFG than with those who developed i-IGT, both in terms of sex distribution and family history of diabetes [86].

Natural history of i-IFG and i-IGT

Observation of the natural history of i-IFG highlights that 5 years prior to the development of IGT, beta-cell function was already lower compared with that of people with NGT and further declined over time, while insulin sensitivity was lower already at baseline but did not decline further [86]. The progressive reduction in beta-cell function over time may therefore be secondary to the insulin resistance observed at baseline. Together, this leads to increased basal and post-challenge insulin levels, which initiate a vicious cycle of insulin resistance and glucose toxicity. Factors such as lower physical activity and/or food quality, but also genetic or epigenetic factors, such as *in utero* programming, may contribute to lower insulin sensitivity [96,97].

Taken together, both i-IFG and i-IGT are conditions with impaired insulin sensitivity, yet, the site of insulin resistance, namely liver versus muscle, seems to differ. In this regard, i-IFG is mainly characterized by impaired hepatic insulin sensitivity, while i-IGT is associated with low whole-body insulin sensitivity [86,87]. Also, while mild impairments of mainly the early phase of insulin secretion seem to characterize beta-cell function in i-IFG, both phases are impaired in i-IGT.

High 1-h PG level

Earlier interventions are more successful in reverting pathophysiological changes such as beta-cell dysfunction. Therefore, since many people with prediabetes will inevitably progress to T2D due to the substantial decline in insulin sensitivity and beta-cell function already present at the time of diagnosis, earlier identification of people at high risk is required. In the Botnia Prospective Study, people with NGT had a low risk of roughly 2% for developing T2D. By contrast, people with NGT and a 1-h PG >155 mg/dl (8.6 mmol/l) had a roughly fivefold higher risk (8.5%) for future T2D compared with people with NGT and a 1-h PG <155 mg/dl (1.3%) [98].

Individuals with high 1-h PG can meet IFG, IGT, or both criteria, and/or NGT, partly reflecting differing metabolic endotypes and risk stages [99–102]. People with IFG and high 1-h PG had a significantly increased risk (11.4%) for future T2D compared with people with IFG and low 1-h PG (1.8%). People with IGT and high 1-h PG had a significantly higher risk (14%) for future T2D compared with people with IGT and low 1-h PG level, in which the risk of developing diabetes is nearly absent.

The European Relationship between Insulin Sensitivity and Cardiovascular Disease (RISC) study compared pathophysiological features of persons with NGT with low and high 1-h PG as well as IGT. They found that people with NGT and high 1-h PG had a larger waist circumference, higher BMI, lower insulin sensitivity, higher FPG, and higher insulin secretion than people with low 1-h PG. Compared with people with IGT, most glucose measurements of people with 1-h PG were in between NGT and IGT. Thus, people with NGT but high 1-h PG seem to be, both pathophysiologically as well as risk-wise, in a state between NGT and IGT. Most people with IGT also have high 1-h PG and recent regression models of longitudinal examinations show that elevation of 1-h PG seems to precede elevation of 2-h PG [72]. This stratification therefore

holds the potential to identify people at risk earlier than with conventional measures, opening up the possibility to implement preventive strategies earlier and therefore likely more successfully [103–105]. This has recently been underscored by findings from the Catanzaro Metabolic Risk Factors (CATAMERI) study, where high 1-h PG reflected reduced insulin sensitivity accompanied by impaired beta-cell function and identified individuals with an unfavorable cardiometabolic risk profile [106]. Still, whether or not people with elevated 1-h PG have a higher chance for remission to NGR needs to be formally proven.

Tübingen Clusters of people at risk for diabetes

Prediabetes has been linked to coronary artery disease, CKD, and all-cause mortality [2,3,107,108]. Still, the individual risk profile and severity of the developed type of prediabetes is not fully understood. A novel classification derived from the Tübingen Family Study (TÜF) of people at risk for T2D (Tübingen Clusters) includes people with a history of prediabetes, of gestational diabetes mellitus, with family history of T2D, and/or a BMI > 27 kg/m^2 (Figure 3) [107,109]. Initial hierarchical data-driven clustering used specific variables for risk cluster assignment, including OGTT-based indices of insulin sensitivity (Matsuda-index) and insulin secretion [area under the curve (AUC)$_{0–30}$c-peptide/AUC$_{0–30}$glucose] as well as AUC$_{0–120}$glucose for glycemia. Furthermore, VAT and subcutaneous adipose tissue volume from magnetic resonance imaging (MRI) measurements, intrahepatic lipid content from ^{1}H-magnetic resonance spectroscopy (^{1}H-MRS), high-density lipid (HDL)-cholesterol and triglycerides, and a genome-wide polygenic risk score for the differentiation between genetically determined beta-cell dysfunction and acquired beta-cell dysfunction were applied. In order to facilitate cluster assignment in clinical settings, clustering was reproduced with easy-to-assess clinical proxy parameters in the Whitehall II cohort. Individuals were thus clustered according to differences in BMI, FPG, 2-h PG, fasting insulin, 2-h insulin, and HDL-cholesterol and triglyceride levels. Amongst those individuals, six risk clusters with distinct phenotypes have been identified. Clusters 1, 2, and 4 have been identified to be low-risk clusters for T2D or related complications. Clusters 3, 5, and 6, however, have been identified as high-risk clusters. Individuals from cluster 3 have rather low insulin secretion, but a high genetic risk of T2D, leading to a high risk for T2D and CVD. Individuals from cluster 5 have a high liver fat content and a high risk for CVD, CKD, and T2D. Finally, individuals from cluster 6

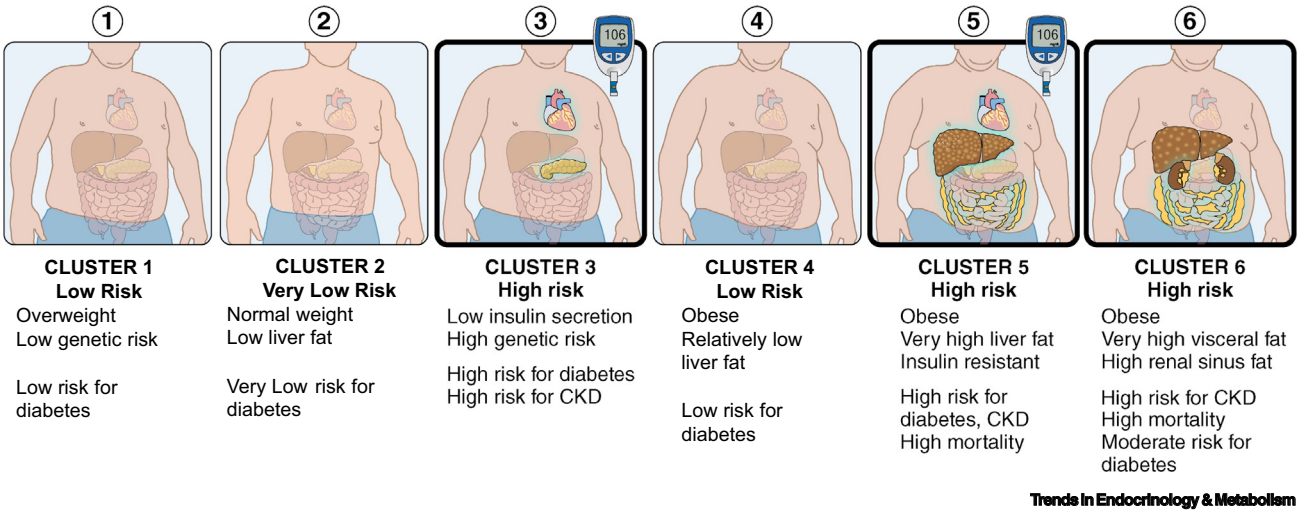

Figure 3. Overview with six risk clusters of people at risk for diabetes. In people with prediabetes, six risk clusters have been identified. Low-risk clusters are 1, 2, and 4 and high-risk clusters are 3, 5, and 6. All clusters are shown with phenotypic (within schematic person) and complications profile. Figure adapted from [141]. Clusters can be assigned by using the app of the Institute for Diabetes Research and Metabolic Diseases Tübingen[iii]. Abbreviation: CKD, chronic kidney disease.

are characterized by a high VAT volume. As opposed to the other high-risk clusters, however, they have an intermediate T2D risk but high CKD risk. This reduced T2D risk can likely be explained by a high capability to secrete insulin, which overcomes insulin resistance, yet exposes individuals to high intrinsic insulin concentrations.

Therapeutic considerations: current approaches

Prevention of T2D

Several major randomized controlled lifestyle intervention (LI) trials examining the prevention of T2D have been conducted, including the Diabetes Prevention Program (DPP), the Finnish Diabetes Prevention Study (DPS), the DaQing Diabetes Prevention Study (DQDPS), and the Indian Diabetes Prevention Program (IDPP) [20–22,110]. The DPP examined >3000 individuals with IFG and IGT without T2D. Individuals were randomized to 850 mg of orally taken metformin once daily or placebo or LI with an aim of 7% body weight loss and at least 150 min of physical activity per week. Participants were followed up semi-annually for 4 years. Even though both LI and metformin were effective in preventing T2D, the LI group showed the lowest diabetes progression rates and the strongest weight loss, with one case of T2D prevented per seven persons treated for 3 years [28]. The Finnish DPS showed comparable results upon LI both after 4 years of active intervention and until 3 years after intervention [111]. A 6-year LI could reduce cardiovascular and all-cause mortality and diabetes incidence in Chinese individuals, achieving significance after a follow-up period of 23 years [112]. The IDPP showed a lower relative risk reduction of 28.5% over a median follow-up period of nearly 3 years with no additional benefit of metformin treatment in Indian individuals [108,110]. A recent study in Chinese individuals, however, showed that the combination of LI and metformin was even more effective than LI alone in preventing the progression from prediabetes to T2D [113].

When comparing different LI studies, the German Prediabetes Lifestyle Intervention Study (PLIS) was the first to investigate the intensity of LI in high- and low-risk phenotypes as a first step to individualized therapy [114,115]. PLIS has been conducted as a multicenter study by the German Center for Diabetes Research in nine clinical centers in Germany in the years 2012 to 2016, with follow-up still ongoing. A high-risk phenotype was characterized by relative beta-cell dysfunction and/or insulin resistance combined with MASLD and assigned individuals had higher BMI and higher age than low risk individuals. Low-risk participants were randomized to control LI or conventional (DDP-like) LI, whereas high-risk individuals were randomized to conventional or intensified LI. No medical intervention was performed, thereby being an easy-to-introduce program in the clinical outpatient setting. Individuals at high risk benefitted more from intensified LI but could not surpass individuals at low risk with standard LI only in terms of remission to NGT [114]. Thus, individuals at high risk can achieve a stronger risk reduction by adhering to intensive LI than to less intensive LI, but cannot reduce the risk to similarly low levels as persons at low risk with a standard therapy. These data suggest that preventive interventions in people with prediabetes need to start as early as possible to have the strongest effect on the absolute risk of progressing to T2D. When the PLIS intervention was evaluated within the Tübingen Clusters, high-risk clusters 3 and 6 benefitted particularly, which was dependent on the change in liver fat content in cluster 5 [116]. These data suggest that the amount of liver fat content and the change during a preventive LI plays an important role in mediating the success of the preventive strategy in high-risk cluster 5.

Prevention studies have been able to show the effectiveness of LI in diabetes prevention. Thus, two community-based programs have been set up in the USA: Young Men's Christian Association (YMCA) Diabetes Prevention Program (DPP)and the National Diabetes Prevention Program (NDPP) [117,118]. Even though LIs do not achieve as much weight loss in the participants as medical interventions, they bring less harm with them and might be more cost effective [119]. Recent studies have shown that incretin-based therapies are effective in inducing weight loss

mediating the reversal to NGR in individuals with obesity and prediabetes [120,121]. Still, maintaining NGR seems to remain challenging, specifically in the off-treatment period. Furthermore, the amount of required weight loss seems to differ between individuals [122].

Prediabetes remission

In light of the fact that a prediabetes diagnosis already indicates the presence of significant pathophysiological alterations, such as insulin resistance and/or beta-cell dysfunction, as discussed earlier, it is crucial to reverse these changes as early as possible to safeguard beta-cell function early and sustainably and to reduce the sequelae of long-standing insulin resistance (i.e., organ damage).

Therefore, while the remission of prediabetes indicates that most of these pathophysiological alterations have been (at least temporarily) reversed, weight loss without reversion to NGR is not associated with the same risk reduction as weight loss in combination with reversion to NGR [123]. The term remission has been proposed in T2D for reverting glucose levels to non-diabetic ranges (HbA1c < 6.5%) by an ADA expert group [124]. In people with T2D, DiRECT allowed for in-depth mechanistic insight into remission of T2D. Here, the increase in insulin secretion plays a major role [125]. Interestingly, both first-phase and maximal insulin secretion were increased in individuals who returned from T2D to prediabetes or NGT ('diabetes responders'). DiRECT reported a reduction in hepatic and pancreatic fat content upon LI but no differences between responders and non-responders in the context of T2D remission [126]. In prediabetes, pioneering work from the DPP Outcome Study (DPPOS) was the first to describe the effect of returning 2-h plasma glucose or fasting plasma glucose levels in people with prediabetes to normal levels (<140 mg/dl, <7.8 mmol/l) or normal FPG (<100 mg/dl, <5.6 mmol/l) on the risk of developing T2D. T2D incidence remained 56% lower after 3 years in people who regressed at least once to normal 2-h glucose levels. Nevertheless, longitudinal mechanistic insight, as in DiRECT, was not provided by DPPOS. Moreover, people reverting to NGR in DPPOS lost nearly twice as much body weight during the DPP phase, compared with those not reverting to NGR. Therefore, the impact of weight loss compared with reaching NGR was not finally solved.

To close this gap in our understanding of prediabetes remission and to identify underlying mechanisms, these mechanisms were investigated in PLIS, as described earlier [114]. Deep phenotyping, including five-point OGTT, whole-body MRI to assess body fat distribution, and ^{1}H-MRS to assess liver fat content was conducted in all patients at baseline and at the end of the LI at 12 months. To understand pathophysiological mechanisms that drive weight loss-induced remission of prediabetes, in participants who achieved the weight loss goal of at least 5% body weight loss, those who returned to NGR ('responders') were defined, compared with those who stayed in the prediabetic range ('non-responders'). This was termed prediabetes remission, defined by normal FPG (<100 mg/dl, <5.6 mmol/l), NGT (2-h plasma glucose level <140 mg/dl, <7.8 mmol/l), and HbA_{1c} <39 mmol/mol (<5.7%), without glucose-lowering medication for at least 3 months, according to ADA criteria [127]. Responders and non-responders had similar BMI, fat mass, and WHR at baseline. Weight loss was similar between responders and non-responders and hepatic fat content and skeletal muscle fat mass were reduced in a comparable manner in both groups. Still, responders showed a stronger reduction of both WHR and VAT than non-responders. Stronger VAT reduction was associated with higher proportions of prediabetes remission in a 'dose-dependent' manner (i.e., the stronger the VAT loss, the higher the prediabetes remission rate). Improvement in insulin sensitivity as determined by OGTT-derived indices was stronger in responders than in non-responders (Figure 4, Key figure). These findings were validated in a comparable subgroup of DPP participants who lost at least 5% of the initial body weight. While insulin secretion did not change in both groups, beta-cell function increased numerically, but not significantly, in responders. Thus, the major driver of prediabetes remission seems to be insulin sensitivity, which is an important difference to remission of T2D. It seems to open a window of

opportunity to tackle metabolic disease at a time-point when beta cells are not yet severely and persistently damaged.

Importantly, in PLIS participants who returned to NGR, the risk of developing T2D within 3 years after study initiation was reduced by 73% (Figure 4). Urine albumin-to-creatinine ratio was lower in responders at 3 years after study initiation, possibly reflecting a lower risk for future nephropathy. Furthermore, **raster scan optoacoustic mesoscopy (RSOM)** as a measurement of epidermal small-vessel morphology revealed more junction-to-endpoint branches and dermis-vessel density, reflecting a better small-vessel integrity in responders compared with non-responders in a subgroup of PLIS participants after the intervention.

Weight loss and glycemic goals for the prevention of T2D

The presented data prompt the question of whether prediabetes remission is more effective than the currently recommended strategies for the prevention of T2D and its associated complications in the ADA Standards of Care for the prevention and delay of T2D [29]. Here, individuals with overweight and obesity and at risk of developing T2D are advised to lose a minimum of 7% of body weight.

Key figure

Weight loss induced prediabetes remission and related risk reduction through returning to normal glucose tolerance

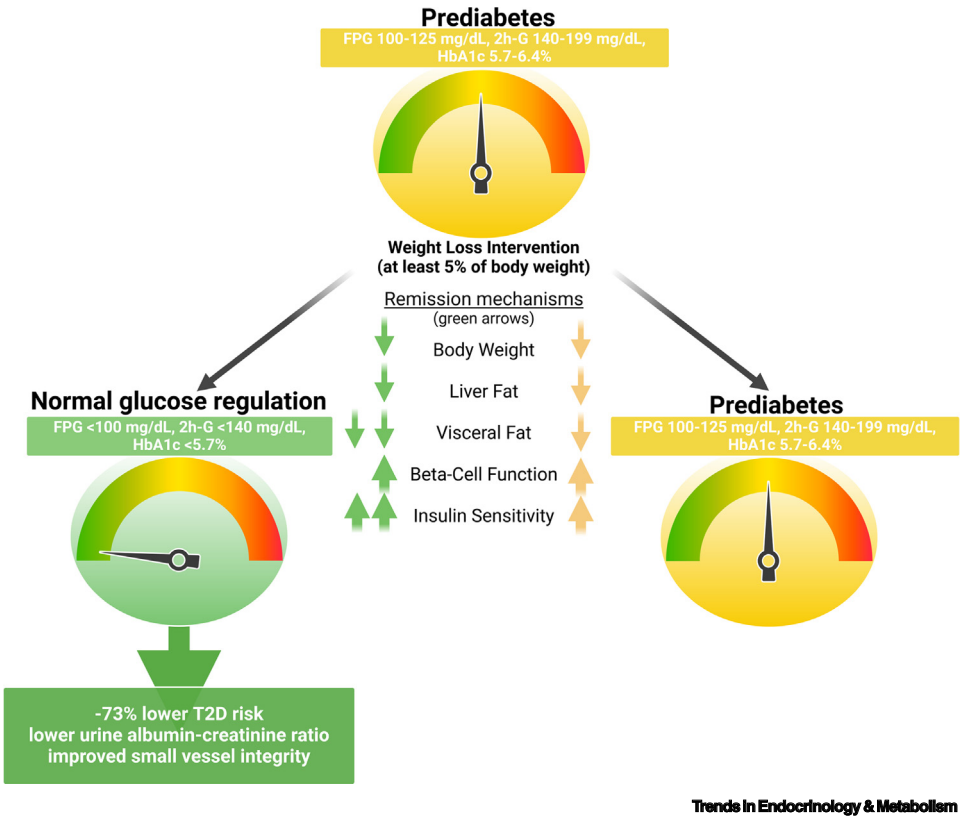

Figure 4.

This notion is primarily based on findings from DPP and comparable studies. It was thus tested if guideline-based weight loss of ≥7% with targeted prediabetes remission to NGR is more effective than the same weight loss without remission in individuals with prediabetes in DPPOS. Results indicate that weight loss and targeted prediabetes remission reduced the relative risk of developing T2D by 76% (absolute risk: –10.1%). It would be of high clinical relevance to determine if prediabetes remission to NGR in conjunction with guideline-recommended weight loss also reduces the incidence of complications compared with similar weight loss without remission [128]. Thus, not only weight loss, but also targeting NGR should be considered in the treatment of prediabetes to prevent T2D. To achieve this goal, additionally increasing physical exercise needs to be considered, as positive effects of exercise on reducing VAT have also been shown [127,129,130]. As weight loss is an effective and straightforward way to achieve prediabetes remission, a general aim of losing at least 7% body weight and further until the personal threshold of the return to NGR is reached has been proposed [122,131]. Given these data, prediabetes remission holds the potential to be more effective than current concepts in the global fight against the ever-increasing incidence of T2D. Prediabetes remission as a treatment target is a clear goal assessable on a global scale [103,123].

Concluding remarks and future perspectives

Prediabetes is a condition associated with heterogeneous complications. Some individuals with prediabetes are at elevated risk for complications such as CVD and CKD, even without the progression to T2D, and others have a high risk of developing overt T2D over the course of their lifetime [107]. The individual risk profile is associated with specific phenotypic characteristics such as high visceral and/or high liver fat, but also with brain insulin resistance, often in connection with a chronic inflammatory state. These phenotypic alterations may be influenced by lifestyle aspects such as nutrition and physical activity, but can partly be determined by genetic disposition. As peripheral and brain insulin resistance seem to influence each other, manipulation of brain insulin signaling has been shown to regulate and/or disrupt glucose and lipid metabolism in several peripheral tissues [132]. Upon LI, brain insulin sensitivity is a significant predictor for VAT loss and individuals with higher brain insulin sensitivity maintain this reduction for a longer period of time than brain insulin-resistant persons [133]. First evidence shows that brain insulin resistance can be overcome by physical exercise and pharmacological interventions, such as **sodium-glucose co-transporter 2 (SGLT2)** inhibition, making it an important target for future interventional strategies [134,135].

To reduce the risk of complications and T2D, targeted prediabetes remission or NGR together with guideline-based weight loss should be the primary therapeutic objective in the future [123]. Intervention programs, taking cultural and socio-economic factors into account, should be made broadly accessible. Depending on the individual phenotype and risk profile, specific therapeutic interventions could be considered, while low-risk individuals may benefit from close monitoring [136]. In this regard, it will be important to determine the precise responses of the Tübingen Clusters of people at risk for diabetes for preventive measures and therapeutic interventions. As weight loss remains the most effective strategy, different means to induce weight reduction are currently being investigated in these clusters [137]. Furthermore, knowledge is needed on how prediabetes remission impacts long-term outcomes such as **major adverse cardiovascular events (MACE)**, **major adverse renal events (MARE)**, cancer incidence, and mortality (see Outstanding questions). Finally, one of the most pressing questions is how ethnicity-related and cultural differences in the risk of T2D can be addressed by prediabetes remission to NGR and if and how prediabetes remission can be implemented in different parts of the world. Potentially, the 1-h PG threshold may help improve remission responses. In order to facilitate its implementation, it will be important to determine if a single, cheap, and readily available biomarker can be used in the future to ascertain that prediabetes remission was achieved. Current studies addressing this pressing question are ongoing.

Outstanding questions

Can we establish effective, population-specific predictive biomarkers for prediabetes remission in people of different ancestries?

How can population-specific differences in the risk of diabetes be addressed by deploying precision medicine?

How can preventive prediabetes remission strategies be implemented, also taking cultural and socio-economic factors into account?

Can prediabetes remission reduce long-term vascular, malignant, and neurodegenerative outcomes?

Does prediabetes remission have a 'legacy' (preventive) effect on future comorbidities?

Can prediabetes remission to normal glucose regulation be cost-effective to prevent T2D and its comorbidities?

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Declaration of interests

No interests are declared.

Resources

[i]www.cdc.gov/diabetes/php/data-research/index.html

[ii]https://diabetesatlas.org/atlas/tenth-edition/

[iii]https://prediabclusters.idm-tuebingen.org

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