Prediabetes in children and adolescents: a narrative review

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Abstract
Prediabetes and diabetes are important metabolic public health problems, especially among adolescents, which are being given little or no attention, especially in Sub-Saharan Africa (SSA). Prediabetes increases the risk of developing Type 2 Diabetes Mellitus (T2DM) and cardiovascular diseases. Despite being a high-risk state for developing diabetes, the diagnostic criteria for prediabetes are not uniform across various international professional organizations. Significant differences in prevalence can depend on the definition of prediabetes as Impaired Fasting Glucose (IFG) and/or Impaired Glucose Tolerance (IGT). Different studies have shown that prediabetes and its interactions with factors such as gender, age, ethnicity, environmental factors, genetics, and lifestyles do play a role in the pathogenesis and progression of diabetes. Prediabetes is a preclinical stage of DM and can be reversed with some lifestyle modifications. Therefore, there is a need to be informed about it such that active surveillance can be instituted to recognize it early and prevent its progression to T2DM and disease-associated health burden in adult life.

Introduction
Prediabetes is an important public health problem. It is an intermediate state of hyperglycemia with plasma glucose levels above normal but below the diabetic threshold.1,2 The diagnostic criteria of prediabetes are not uniform across various international professional organizations despite being a high-risk state for developing diabetes and its complications. It has a yearly conversion rate of 5-10%.3 Several studies have shown the efficacy of lifestyle interventions with regard to diabetes prevention, with a relative risk reduction of 40-70% in adults with prediabetes.4,5 Pharmacotherapy with metformin has also been shown to prevent the progression of diabetes in adults with prediabetes.3,5 Although secondary intervention with metformin therapy has been advocated for high-risk individuals, such as children,4 the criteria for determining its benefits remain unclear. Furthermore, outcomes such as benefits of early intervention, long-term cost-effectiveness, and end point of therapy have not been extensively studied.3 Hence, pharmacotherapy must be used with caution in such groups. There are no reports of systematic evaluation of health outcomes related to the pharmacotherapy of prediabetes in children.3

Definition of prediabetes
The definitions of prediabetes, which depend on the diagnostic criteria used, have changed over time and currently vary depending on the institution.5 The American Diabetes Association (ADA),6 in 1997, introduced Impaired Fasting Glucose (IFG) as a prediabetic state. It defined IFG as a Fasting Plasma Glucose (FPG) level of 110-125 mg/dL (6.1-6.9 mmol/L). This definition was also adopted by the World Health Organization (WHO).7 Six years later, the criterion of 110-125 mg/dL (6.1-6.9 mmol/L) was lowered to 100-125 mg/dL (5.6-6.9 mmol/L) by ADA.8 This decision was based on the observation that fewer persons with IFG above 6 mmol/L subsequently developed diabetes than those whose prediabetes was diagnosed as Impaired Glucose Tolerance (IGT) with a 2-hour postprandial glucose value of 140-199 mg/dL (7.8-11.0 mmol/L) on an Oral Glucose Tolerance Test (OGTT). This also means that individuals with IFG of 5.6-6.9 mmol/L, could have comparable risk to those with IGT of their progression to diabetes.7,8 This change was subsequently considered by a WHO expert committee, but it was preferred that the original lower limit of 110 mg/dL (6.1 mmol/L) be retained.8 Their decision was based on concerns about the significant increase in IFG prevalence, which would occur with lowering the cut-point, lack of evidence of any clinical benefit, and increase in the proportion of individuals with IFG and IGT but a decrease in the proportion of those with IFG who have IGT. ADA and the International Society for Paediatric and Adolescent Diabetes (ISPAD)6,9 further introduced Hemoglobin A1c (HbA1c) levels of 5.7-6.4% as a new criterion for prediabetes.

Pathogenesis of prediabetes
Glucose concentrations are normally restricted within a narrow range between fasting and postprandial conditions.10 Maintenance of glucose concentrations within this range depends
on the complex interplay of harmonized hormonal (insulin and glucagon), neural, and metabolic activity in all organs and tissues involved in glucose metabolism.10 Normal glucose metabolism depends on the physiological interaction between insulin secretion and insulin action; for Type 2 Diabetes Mellitus (T2DM) to develop, defects in both are usually present.10

A key factor for the regulation of beta cell mass and function is glucose concentration.11 When hyperglycemia occurs, the pancreatic beta cells secrete enough insulin, which stimulates cellular uptake of glucose and suppresses hepatic gluconeogenesis. In insulin resistance, the action of insulin in tissues is impaired, resulting in postprandial hyperglycemia and hyperinsulinemia, which is the hallmark of prediabetes preceding T2DM.11 Insulin resistance in prediabetes occurs as a result of the interplay of pro-inflammatory adipocytokines such as tumor necrosis factor-α, interleukin-6, leptin, and macrophage migration inhibitor factor released as a result of excess adipose tissue and non-adipose tissue free fatty acids deposition.12 Although both IFG and IGT are insulin-resistant states, they differ in their site of insulin resistance.13 People with isolated IFG predominantly have hepatic insulin resistance with normal muscle insulin sensitivity, whereas individuals with isolated IGT have normal to slightly reduced hepatic insulin sensitivity and moderate to severe muscle insulin resistance.11,13 Therefore, individuals with both IFG and IGT manifest both muscle and hepatic insulin resistance.14 Brufani et al.14 showed that prediabetes was linked primarily to fasting insulin secretion in children with isolated IFG, while peripheral insulin resistance in children was seen in those with isolated IGT. Those with combined IFG and IGT had both reduced whole-body insulin sensitivity and an additional defect in the disposition index of insulin (which is the product of insulin sensitivity times the amount of insulin secreted in response to blood glucose levels).

Studies have also shown further differences between the two prediabetic states; Bacha et al.15 and Bock et al.16 showed that individuals with isolated IFG had greater impairment in their insulin secretion during both early and late phases of insulin secretion compared to those with isolated IGT who had impaired late insulin secretion.

Epidemiology of prediabetes

Globally, the number of individuals with prediabetes (IGT) in 2007 was 308 million among the age group 20-79 years. This number is expected to increase to 418 million by the year 2025.17 Prediabetes in children varies with the incidence of obesity, race, and other risk factors.18 The prevalence of prediabetes in obese children and adolescents ranges between 21% and 40% based on different studies.19,20 The prevalence in children in most developed countries ranges between 6% and 32%.19,20 It is high in most ethnic minorities in America, where there is an increase in T2DM among the adult population.22 In obese children and adolescents, the prevalence of prediabetes based on ethnicity, reported in a study from the United States of America, showed blacks to have the highest prevalence (54%), followed by Hispanics (28%), and then white youth (18%).23

Prediabetes has a higher prevalence rate in boys (1.7 to 2.4-fold) compared to girls.24 Sinha et al.21 reported the prevalence of IGT following an OGTT test to be 21% in obese adolescents aged 11-18 years attending the Yale Paediatric Obesity Clinic in the USA, irrespective of ethnicity.

Bahillo-Curieses et al.25,26 in a cross-sectional study of 100 obese Spanish children and adolescents, found that the prevalence rates of IFG and IGT were 2% and 15%, respectively. Wiegand et al.26 in Germany, studied T2DM and IGT in obese and other high-risk multi-ethnic European children and adolescents; they found the prevalence of IGT and IFG to be 11.8% and 36.3%, respectively. The higher prevalence figures obtained in the German study26 could be attributed to some factors, such as the prospective nature of the study (which could imply lower chances of missed cases) and the selection of only high-risk cases (positive family history of diabetes, signs of insulin resistance and ethnic predisposition), while Bahillo-Curieses et al.25 studied obese children irrespective of whether they have other risk factors or not. The sample size in the study by Wiegand et al.26 is larger than that by Bahillo-Curieses et al.25 Both studies included mainly Caucasian subjects, with only a few non-Caucasians, with the subjects in the Spanish study being only slightly younger. However, no significant ethnic differences were found.

Studies from Asia27-31 showed varied prevalence rates. Ghergherechi and Tabrizi, in 2008 in Iran,27 studied the prevalence of IGT and insulin resistance among obese Iranian children and adolescents aged 4-18 years. IGT was found to be 14.7% using OGTT, while Chahkandi and colleagues in Birjand, Iran,28 studied the prevalence rate of IFG to be 7.5%. The retrospective study by Ghergherechi and Tabrizi was conducted among 110 obese adolescents in an endocrinology clinic of a university located in a relatively high-end region of Iran, while that by Chahkandi et al. was conducted amongst 2,653 regular secondary and high school adolescent students living in a poor province in Iran. Although done in the same country, the differences in study settings, study designs, study populations, sample sizes, and glucose testing criteria used (IGT vs IFG) could account for the higher prevalence figure obtained in the study by Ghergherechi et al.

Narayanappa et al. in India30 studied 726 school children aged 5-10 years and found the prevalence of IFG to be 3.7%. Ranjani et al.31 studied 1519 children and adolescents aged 6-19 years in South India using OGTT. They got the prevalence rate of IGT to be 3.4%. Both studies were done in urban areas. The prevalence rates in the two studies were similar even though Ranjani et al. had a larger sample size with a wider age range, and stricter diagnostic criteria. While Narayanappa et al. used the ADA criteria. The ADA criteria have a wider FPG range than the WHO criteria, hence likely to identify more children with IFG.

In China, Zhang et al.32 reported the prevalence of IFG to be 0.7% in 3644 Uygur children aged 0-17 years. The prevalence was highest in those 0-8 years of age, while none of the children aged 14-17 years had IFG, and this was probably due to the small sample size (n=86) of the 14-17 years age group. It was found in this study that overweight and obesity were independent risk factors for diabetes in their study cohort; however, no explanation was given as to why the prevalence figures of both IFG and diabetes were highest in the 0-8 years age group. The study also did not report the proportions of children in each age group who were overweight or obese.

The differences in the prevalence rates of prediabetes from the different Asian countries could be due to differences in the prevalence of obesity and cardio-metabolic risk factors, which are caused by lifestyle, diet, ethnic and cultural differences, and other environmental factors in the different countries.

Data from Africa are limited. Sunwaiye15 reported an IFG of 3.3% using WHO criteria and 11.5% using the ADA/ISPAD criteria in 305 Ghanaian children and young adults aged 5-20 years in a cross-sectional study on the prevalence of prediabetes and diabetes among children and young adults in the Kassena Nankana district of Ghana. This finding is slightly lower than the 14.5% of IFG reported by Agbre-Yace et al.,33 who studied 1572 children
aged 2-19 years in Abidjan Cote d’Ivoire. The differences in the two studies could be explained by the larger sample size of 1572 from the Ivorian study since both used the ISPAD criteria. Different environmental risk factors and lifestyles may have also contributed. Jaja and colleagues in Port Harcourt, South-South Nigeria, reported IFG and IGT to be 17% and 15%, respectively, in adolescents aged 10-19 years. The higher IFG was obtained using the ISPAD criteria, while 4% was obtained using the WHO criteria. The lower prevalence of IGT compared to the IFG was because OGTT was done only on those with an abnormal IFG, in which case, the test may have missed many children who had isolated IGT with normal FPG. Arigbede and colleagues from Ibadan, Southwest Nigeria, reported the prevalence of prediabetes as 4% when they studied 500 secondary school adolescents using the WHO criteria. Also from the Southwest, Oluwayemi and colleagues in Ado Ekiti studied the fasting blood glucose profile among 628 secondary school adolescents and found a prevalence of 28.7% for IFG using the ADA criteria. The higher prevalence was seen more in females aged 10-14 years, who were obese and had a family history of diabetes. Although the two studies involved the same age group of adolescents and studied similar factors, Oluwayemi et al. found a significant association between the risk factors (female gender, obesity, and a positive family history of diabetes) studied and the development of IFG while Arigbede et al. in Ibadan did not find any such association. Oluwayemi et al. also used the ADA criteria, which could have identified more participants with prediabetes.

Risk factors of prediabetes

Prediabetes is usually related to some risk factors and research has showed that intensive lifestyle (defined as a minimum of 7% weight loss or maintenance and a minimum of 150 min of physical activity similar in intensity to brisk walking) and pharmacological interventions can prevent or delay progression to T2DM. Factors that increase insulin resistance and increase the risk for prediabetes and diabetes include obesity, gestational diabetes, puberty, physical inactivity, race, family history of T2DM, prenatal and childhood malnutrition, gender, age, and some environmental factors (Figure 1).37

Prediabetes and obesity

Globally, childhood obesity has dramatically increased to reach epidemic proportions in the last decades, raising concerns about the increased prevalence of T2DM in children.38 Obesity is the most frequent cause of peripheral insulin resistance in childhood.39 Many of the metabolic and cardiovascular complications associated with obesity occur early during childhood and are closely linked to concomitant insulin resistance/hyperinsulinemia and the degree of obesity.40

A positive association between overweight and obesity and the risk of T2DM has been established repeatedly in many cross-sectional and prospective studies.37,38 Prevalence of prediabetes in obese children and adolescents is shocking, with the rate ranging from 21% to 40% based on different studies.41 In obese children and adolescents from the United States, the prevalence of prediabetes by ethnic group is as follows: highest in blacks (54%), followed by Hispanics (28%), and then white youth (18%).39 There was a twofold increase in the prevalence of IFG in a population-based U.S. National Health and Nutrition Examination Survey (NHANES) study between 1999-2006, and this was attributed to the rapid rise in the prevalence of obesity among adolescents.5

Reinhr and colleagues2 studied a group of 169 obese European children and, after a year of follow-up, revealed IGT in 11.2% and IFG in 2.4% of them.

Here in Nigeria, Jaja and colleagues found a higher prevalence of IFG to be among overweight and obese subjects. The reason for the higher prevalence in those subjects was due to the presence of insulin resistance and toxicity to beta cells from high levels of free fatty acids in obese individuals.

Prediabetes and puberty

Puberty is a risk factor for prediabetes and T2DM. This has been noted by the peak age at diagnosis of T2DM to be 13.5 years of age,6 corresponding to peak adolescent growth and development. During puberty, rapid and dynamic changes occur in various metabolic systems, such as hormonal regulations, variations in body fat and its distribution, and increasing insulin resistance. Insulin sensitivity is highest before the beginning of puberty (Tanner stage 1), approaching near pre-pubertal levels at the end of maturation (Tanner stage 5).6,29 Puberty is associated with drastic changes in size, shape, and body composition. While girls have higher total body fat percentage during puberty, boys suffer more increase in their central obesity.29 In a study conducted in Gorgan city in northern Iran by Qorbani and colleagues,44 it was found that FBS was significantly higher in boys than in girls, while in a study by Guerrero-Romero and colleagues45 on Mexican children aged 6-18 years, the mean FBS was slightly higher in girls.

In a study by Chahkandi and colleagues29 on the prevalence of IFG in adolescents in Birjand city in eastern Iran, mean blood glucose at all ages except at 11 years of age was higher in boys. After 12 years of age, there was no significant change in blood glucose in both sexes. They attributed this to pubertal changes, which occur earlier in girls. Possibly, the variation in blood glucose levels at different ages and in both sexes corresponds with pre to post-puberty hormonal changes. Three cohort studies have assessed insulin sensitivity at different Tanner stages, which demonstrated conflicting results.46,47 Goran et al. showed a decrease in insulin sensitivity and an increase in acute insulin response throughout the pubertal stages. Ball et al. showed a decrement in insulin sensitivity, at onset and subsequent recovery at the end of puberty. In contrast, Hoffman et al. demonstrated greater insulin sensitivity in early pubertal boys than in girls, which was primarily attributed

Figure 1. Type 2 Diabetes Mellitus risk factors (source: idf.org).
to the effects of body fat mass differences and/or peripheral Growth Hormone (GH) action. Studies on prediabetes in children in developing countries are scarce. Jaya and colleagues\textsuperscript{18} in Port Harcourt found the incidence of prediabetes was highest amongst those participants who were in early and mid-adolescence, coinciding with the early Tanner stage, which is associated with an increase in insulin resistance.

**Prediabetes and physical inactivity**

World Health Organization defines physical activity as any bodily movement produced by skeletal muscles that require energy expenditure, including activities undertaken while working, playing, carrying out household chores, traveling, and engaging in other recreational activities.\textsuperscript{49} The WHO recommends that children and adolescents aged 5-17 years do at least 60 minutes of moderate to vigorous-intensity physical activity daily. Physical activity of amounts greater than 60 minutes daily will provide additional health benefits. This should include activities that strengthen muscles and bones at least three times per week.\textsuperscript{49}

Insufficient physical activity is a key risk factor for Non-Communicable Diseases (NCDs) such as cardiovascular diseases, cancer, and diabetes.\textsuperscript{45,50} Globally, 81% of adolescents aged 11-17 years were reported to be insufficiently physically active in 2010.\textsuperscript{49} Adolescent girls were less active than adolescent boys, with 84% vs 78% not meeting WHO recommendations for physical activity. The drop in physical activity is partly due to inaction during leisure time and sedentary behaviour in the workplace and also at home. Likewise, an increase in the use of ‘passive’ modes of transportation, such as being driven to school rather than using a bicycle or walking to school, also contributes to insufficient physical activity.\textsuperscript{51} Physical inactivity alone accounts for 7% of T2DM cases in Europe.\textsuperscript{52} It is also linked to higher levels of insulin resistance and subsequently poor glycaemic control.\textsuperscript{52}

**Prediabetes and family history of diabetes**

A family history of DM is a very important risk factor for the development of T2DM.\textsuperscript{43} A study done on adolescents in Port Harcourt\textsuperscript{48} showed that approximately one out of every ten participants had a positive family history of DM. The finding in this report is, however, much lower than a report from a Brazilian study where about half of the children studied had a positive family history. Rodriguez- Moran et al.\textsuperscript{53} conducted a multicenter study on school-aged children and adolescents in central and northern Mexico. They found that 88% of the studied population with a family history of diabetes had IFG, compared to only 1.9% of those who had IFG without a family history of diabetes. Ranjani et al. in India\textsuperscript{28} also found that a positive family history of diabetes in their study participants doubles the risk of glucose intolerance. A comparative study on African American children with and without a family history of T2DM in a children’s hospital in Pittsburgh\textsuperscript{54} showed that pre-pubertal children who had a family history of T2DM had a lower insulin-stimulated glucose disposal than those without a family history.

**Diagnosis of prediabetes**

Prediabetes is a preclinical condition not associated with overt symptoms. The diagnosis of prediabetes depends on blood glucose levels. Diagnosis can be made using either Fasting Blood Glucose (FBG), OGTT or Glycated Haemoglobin (HbA1c).

The FBG is the preferred test for diagnosing diabetes and prediabetes because of its ease of use, acceptability to patients, and lower cost.\textsuperscript{55} The FBG measures the blood glucose in a person who has fasted for at least 8 hours and is more reliable when done in the morning. According to the ISPAD\textsuperscript{6} and ADA,\textsuperscript{8} prediabetes is defined as FBG of 100 to 125 mg/dL (5.6-6.9 mmol/L) while, by WHO/IDF,\textsuperscript{7} it is defined as FBG of 110 to 125 mg/dL (6.1-6.9 mmol/L).

The OGTT is the gold standard for diagnosing prediabetes and diabetes.\textsuperscript{7} It involves measuring blood glucose after an overnight fast of at least 8 hours, and thereafter, a drink containing 1.75 g/kg of glucose dissolved in water to a maximum glucose of 75 grams is given.\textsuperscript{7} The blood glucose level is then tested after 2 hours of the glucose drink. Two hours of blood glucose level between 140 and 199 mg/dL is regarded as Impaired Glucose Tolerance (IGT).

OGTT has some limitations such as being costly, time-consuming, requires testing at least twice and has lower reproducibility compared with FPG.\textsuperscript{56}

The HbA1C test is a blood test that reflects the average of a person’s blood glucose levels over three months.\textsuperscript{57} The HbA1C is more convenient for patients than the conventional glucose tests because it does not require fasting and can be performed anytime. According to the A1C guideline, a normal HbA1C level is below 5.7%, while an HbA1C of 5.7 to 6.4% indicates prediabetes.\textsuperscript{57,58} When the HbA1C test is used for the diagnosis of prediabetes or diabetes, the blood sample must be sent to a laboratory using a method with certified National Glycohemoglobin Standardization Program (NGSP) to ensure results are standardized to international standards.\textsuperscript{58} Blood samples analysed as point of care test, are not standardized for diagnosing diabetes or prediabetes. The test is less sensitive and detects fewer cases of prediabetes/diabetes than tests that measure glucose.\textsuperscript{59} Genetic differences in people of African, Asian, and Mediterranean origin; certain haemoglobinopathies; heavy bleeding or blood transfusion; iron deficiency anaemia, and conditions that increase the red blood cell turnover rate; liver or kidney disease may affect the result of HbA1C. It is also costly and not readily available in most developing countries.\textsuperscript{50}

Several studies have shown poor correlation between HbA1C and IFG and IGT.\textsuperscript{5,60} Lee et al.\textsuperscript{61} found that HbA1C had less than acceptable test performance for children with dysglycaemia than blood glucose tests. They screened 254 overweight and obese children and adolescents from Michigan with dysglycaemia using non-fasting tests. In contrast, in a community-based study of African American and non-Hispanic white adults without diabetes, baseline HbA1C was a stronger predictor of subsequent diabetes and cardiovascular events than fasting glucose.\textsuperscript{62}

**Instruments for measuring blood glucose**

The first use of a glucose meter is found in papyrus documents dating back to 1550 BC, which depict Egyptian physicians using ants to determine glycosuria in patients suspected of having diabetes. Jules Maumene was the first to develop a simple urine reagent “strip” in 1850 made of sheep’s wool containing starchous chloride. The pursuit for a more convenient method culminated in a “dip and read” urine reagent strip, the clinistix.\textsuperscript{63} The major breakthrough came in 1965 when the first Blood Glucose (BG) test strip, the dextrostix, was developed by Ernie Adams.\textsuperscript{63} It is a “visually interpreted” paper reagent strip that uses the Glucose Oxidase (GO) reaction method. Five years later, a reflectance meter was developed. The meter assesses quantitative BG from the dextrostix. However, the meter was bulky and expensive and was available only in clinics and emergency departments, thus heralding the beginning of the era of Point-Of-Care Testing (POCT) for BG for clinicians but not for patients. Subsequently, over the next 40 years, technology evolved into the small, lightweight, portable...
meters (as small as to weigh only 9 grams) for use by patients and at the hospital bedside. Blood glucose meters have gained acceptance as a tool for patients and clinicians because they provide immediate information and may improve patients' management of diabetes. All current glucose measurement systems, including clinical laboratory testing and POCT use indirect enzymatic techniques. Three enzymatic techniques are in use: namely Hexokinase (HK), Glucose Oxidase (GO), and Glucose-1-Dehydrogenase (GDH).

In 1987, the ADA developed a consensus statement which recommends that glucose values determined with portable meters should fall within ±15% of the laboratory values for meters available at that time. Subsequently, this guideline was reduced to within ±5% of laboratory values for future glucose meters. Several studies done on different meters, showed that it is difficult to achieve this recommendation. Cheney et al. from Baptist Medical Center in North Carolina, studied the performance of three blood glucose meters: One Touch II, Glucometer Elite, and Accu-chek Advantage glucometers. The majority (75%) of the blood glucose values from all 3 meters fell within 20% of the standard laboratory reference method. Ninety-seven percent of the values obtained with One Touch II and Glucometer Elite were within 30% of the laboratory standard values, while 25% of Glucometer Elite values were found to be within 5% of the laboratory standard.

Glucose may be measured in plasma, serum, whole blood, or de-proteinised samples, and the values obtained will depend on the type of sample collected. Values in plasma are approximately 12-13% higher than in whole blood. Measurement differences may also arise depending on the blood sample collection site. Venous and capillary samples will give the same result in the fasting state, but in the non-fasting state, capillary will give higher results than venous samples. Boyd et al. in South Australia reported on blood glucose values based on capillary vs venous bedside blood glucose estimation using Medisense Precision glucometer on 20 individuals aged 13-88 years who presented to the Emergency Department of Elizabeth Vale Health Center. They found that the capillary blood glucose values correlated well with that of the venous blood sample using the same glucometer. However, the timing for the test, whether fasting, random, or 2-hour postprandial, was not stated. When the capillary or venous blood samples were compared to values from venous laboratory samples of the same patients, it was observed that the values from the bedside test (either capillary or venous) were higher than those obtained from the laboratory, and the finding was statistically significant. Similarly, Kumar et al. in Singapore studied the correlation of capillary and venous blood glucometry with laboratory determination in a multicentre study. They studied 270 individuals using glucometer Elite. They found that the capillary bedside values approximate the venous laboratory blood glucose levels, though the capillary blood glucose test may be inaccurate at lower glucose levels of 3-4 mmol/L. Their study also showed that the venous bedside test tends to overestimate the blood glucose compared to that of the laboratory.

Treatment of prediabetes

A number of studies have looked at lifestyle and pharmacologic interventions in people with prediabetes to determine if progression to frank diabetes can be prevented. The preferred treatment approach is intensive lifestyle modification, because of its safety and efficacy in improving glycaemia and in reducing cardiovascular risk factors.

Two diabetes prevention studies; the United States Diabetes Prevention Program (DPP) and the Finnish Diabetes Prevention Study (DPS) have both shown beneficial effects of lifestyle and pharmacological (metformin) interventions. The DPP study, which was done in overweight and obese adults after a 2.8-year follow-up, showed Intensive Lifestyle Interventions (ILS) were associated with a 58% risk reduction, while the metformin group had a 31% risk reduction. The biggest determinant of risk reduction was noted to be weight loss. The study showed that for every 1-kilogram decrease in weight, there is a 16% reduction in the risk of developing diabetes.

In DPS, the benefits were found to be dependent on the achievement of the number of pre-defined goals of the intervention by the participant. These goals consisted of weight reduction greater than 5%, total fat intake less than 30% of energy intake, saturated-fat intake less than 10% of energy intake, fibre intake greater than or equal to 15 g per 1000 kcal, and exercise greater than 4 hours per week over a six-year period. They deduced that these lifestyle interventions have a 58% risk reduction for diabetes. While both of these studies were largely among Caucasians, studies in Asian population have also shown similar benefits. Xiao-Ren and colleagues in Daqing China, studied the effect of diet and exercise in preventing diabetes on 577 adults with IGT over a 6-year period. They found that there was a 25-50% reduction in the risk of diabetes in those patients with IGT subjected to dietary modification and/or exercise compared to control who were not given any formal dietary or physical activity advice. There is strong evidence to support pharmacological therapy with antidiabetic drugs such as metformin, acarbose, or thiazolidinediones in preventing the progression of prediabetes to diabetes. From both DPP and DPS studies, there was a 25% reduction in the risk of diabetes in patients with IGT given metformin. Acarbose was associated with a 25% reduction in progression from IGT to diabetes after three years in the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial. This effect disappeared with discontinuation of the acarbose, suggesting that acarbose may have masked the progression to diabetes.

Complications of prediabetes

Prediabetes alone is associated with a fivefold increase in the development of T2DM, while in combination with other cardiometabolic risk factors, is associated with a 20-fold increase in diabetes and other cardiovascular complications. Research has shown, as reported by Abdul-Ghani and colleagues, that subjects with isolated IFG and isolated IGT have a 4% to 6% annual risk for progression to T2DM compared with less than 0.5% in Normoglycaemic (NGT) individuals. Individuals with combined IFG/IGT have approximately 10% annual risk for conversion to T2DM, indicating a synergistic effect. These findings have been reported in an epidemiological study reviewed by Abdul-Ghani and colleagues, where they reviewed some studies that compared the values of isolated IFG vs combined IFG and IGT. The values of isolated IFG vs IGT varied from 21.6% to 38.1% among Mauritians, 31% to 41.2% among Pima Indians and 9% to 44.4% among Italians. The highest proportion of diabetes development was 64.3% to 72.7% seen among Brazilian-Japanese population. The differences in the rate of progression to diabetes may be due to differences in race, sample size, and duration of the study, which varied in the different studies they reviewed. Prediabetes is also associated with an increased risk for both early microvascular and macrovascular complications. It has been linked to increased risk of early forms of nephropathy and chronic kidney disease, defined by methods such as urinary albumin excretion rate and...
estimated glomerular filtration rate. NHANES 1999–2006 showed that the prevalence of both micro and macro-albuminuria increases as glycaemia worsens; from normoglycaemia (6% and 0.6% prevalence for micro and macro-albuminuria respectively), to IFG (10% and 1-1%), undiagnosed diabetes (29% and 3-3%), or diagnosed diabetes (29% and 7-7%) respectively.5

Conclusions

IGT and IFG have been shown to be associated with an increased risk for cardiovascular events, with IGT being a slightly stronger risk predictor.54 The increased risk is thought to be due to metabolic abnormalities (hypertension and dyslipidaemia) associated with insulin resistance, as well as differences in the pathophysiology of IFG/IGT. The Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) pooling study of European origin showed that IGT was associated with an increased risk of coronary death and total cardiovascular death, irrespective of the fasting blood glucose level.13

References

Tolerance: the Da Qing IGT and Diabetes Study. Diabetes Care 1997;20:537-44.


