POSITION STATEMENT

An Expert Group Consensus Statement on "Approach and Management of Prediabetes in India"

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Abstract

The prevalence of prediabetes, a forerunner of diabetes is very high, and its conversion to diabetes is also more rapid among Asian Indians. Prediabetes also predisposes to the development of macrovascular and to a lesser extent of microvascular complications of diabetes.

In a large community-based epidemiological study, the Indian Council of Medical Research–India Diabetes (ICMR–INDIAB), data reported an overall prevalence of prediabetes of 10.3%, derived from 15 Indian states. This shows that the diabetes epidemic is far from over as many of them may soon convert to diabetes.

Prediabetes, however, should not be considered a path to diabetes rather it should be a window of opportunity for the prevention of diabetes. This early screening, detection, and treatment of prediabetes should be made a national priority.

Several countries have introduced lifestyle programs to prevent diabetes and, when indicated, pharmacological intervention with metformin as well.

This consensus statement outlines the approaches to screening and lifestyle and pharmacological management of prediabetes in Asian Indians.

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Background

Prediabetes being a significant metabolic state is related to an increased risk of type 2 diabetes (T2D) and also the development of cardiovascular diseases (CVD). It has also been reported that in the prediabetic stage, complications in organs such as the eye, kidney, and nerve may also occur.[1] Hence, it is crucial to identify and treat individuals with prediabetes. However, being an asymptomatic condition, only regular screening of the population, especially the high-risk groups, can help to identify individuals with prediabetes.[2–5]

The prevalence of prediabetes can vary widely due to different definitions and screening criteria across guidelines.[2] Despite these differences, prediabetes in people is rising rapidly globally. As India being with the second-largest country of individuals with type 2 diabetes mellitus (T2DM) worldwide, we need to identify and manage prediabetes optimally so that risk of both future T2D and CVD can be mitigated. There is now strong epidemiological evidence that Asian Indians progress rapidly through the prediabetes phase to develop T2D in comparison to other ethnic populations.[6,7] Studies have also confirmed that nearly half of people with diabetes in the Indian population remain undiagnosed further emphasizing the need for increased awareness and screening.[2,8,9]

Thus, a better awareness of prediabetes could benefit early identification and timely management thereby lowering the development of diabetes and associated complications.[2] This consensus statement outlines the approaches to screening and management of prediabetes in the adult Indian population.

Defining Prediabetes

"Prediabetes" is also known as "nondiabetic hyperglycemia" or "intermediate hyperglycemia." It is the term used for individuals whose plasma glucose levels would be below diabetes levels, but above the normal threshold.[10,11]

The American Diabetes Association (ADA), World Health Organization (WHO), and International Diabetes Federation (IDF) provide criteria for screening individuals for prediabetes. There are two subtypes of prediabetes namely impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) and they can also coexist in the same individual. The levels of IGT are mutual across the guidelines, however, the ADA recommends lower levels only of IFG (Table 1).[2]

Prevalence of Prediabetes

Prediabetes is rising at an alarming rate in India even exceeding cases of diabetes in most states suggesting that in the near future large pool of the population could develop T2D. The prevalence of IGT worldwide in 2021 was found to be 541 million, or 10.6%, whereas, the prevalence of IFG worldwide was found to be 319 million adults, or 6.2%, according to IDF 10th edition (Table 2).[12]

The phased ICMR–INDIAB study was initiated that estimated the prevalence of prediabetes (IFG and/or IGT) and diabetes in India. The overall prevalence of prediabetes was reported at 10.3% in 15 states studied using WHO criteria. The range of prevalence was 6.0% in Mizoram to 14.7% in Tripura (Fig. 1). The prevalence of isolated IFG was 6.5% which was twice as higher as that of isolated IGT (2.8%) in all states except for Bihar, Manipur, and Meghalaya. If the ADA fasting glucose cutoff point of 100 mg/dL was used, the number of isolated IFG would increase to 20.8% and that of prediabetes to 24.7%. Male gender, obesity, age, family history of diabetes, and hypertension were independent risk factors for diabetes in both urban and rural areas.[13,14]

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Table 1: Diagnostic criteria for deflning prediabetes

Criterion	*ADA*	*WHO*	*IDF*
Terminology	Prediabetes	Intermediate hyperglycemia	Impaired glucose tolerance
IGT*		140–199 mg/dL (7.8–11.0 mmol/L)	
IFG**	100–125 mg/dL (5.6–6.9 mmol/L)	110–125 mg/dL (6.1–6.9 mmol/L)	
HbA1c	39–47 mmol/mol (5.7–6.4%)	ND	

*IGT is assessed using the 2-hour plasma glucose during a 75 gm oral glucose tolerance test; **IFG is assessed based on the FPG level; ADA, American Diabetes Association; FPG, Fasting plasma glucose; HbA1c, Glycated hemoglobin; IDF, International Diabetes Federation; IFG, Impaired fasting glucose; IGT, Impaired glucose tolerance; ND, Not defined; WHO, World Health Organization

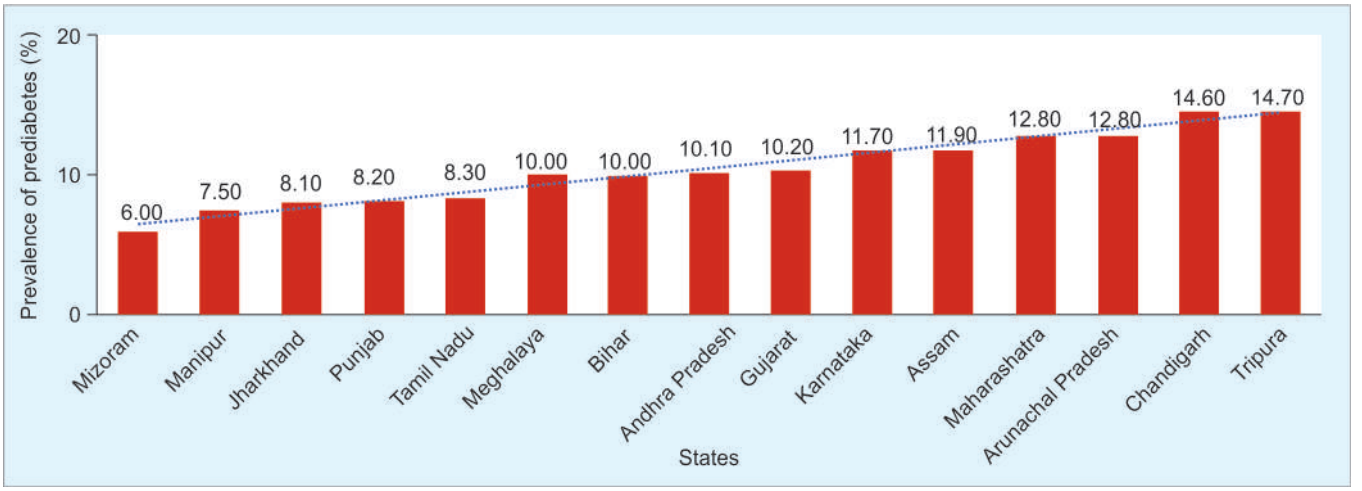

Fig. 1: Prevalence of prediabetes in 15 states sampled in phase II ICMR-INDIAB study[13]

A recent article by Kumar et al. stated a general prevalence of prediabetes/diabetes as 8.4 and 12.3% among adolescent girls and boys in India, respectively. Further, it was also demonstrated in the study that a person's subscapular skinfold thickness and body mass index (BMI) were positively associated with prediabetes/diabetes.[15]

Pathophysiology of Prediabetes

The pathophysiological defects that underlie T2D are also present in the prediabetes stage. In the prediabetes stage of IGT, significant abnormalities in insulin action and secretion are frequently visible. The transition from normal glucose tolerance (NGT) to prediabetes, according to longitudinal research by Weyer et al., was accompanied with an increase in body weight, an increase in insulin resistance, and a decrease in endogenous insulin production (β-cell dysfunction).[16]

The study also showed that increased weight gain, insulin resistance, and β-cell dysfunction were associated with the transition from prediabetes to T2DM. The main finding of the longitudinal observation was that β-cell failure and insulin resistance do not develop one after the other but rather concurrently. Loss of β-cell volume, increased lipolysis, decreased endogenous levels of glucagon-like peptide 1 (GLP-1), a poor incretin action, inadequate postprandial control of glucagon secretion, and perhaps hepatic glucose overproduction are further abnormalities in the prediabetic condition. The present disadvantages of prediabetes are made worse by the proinflammatory cytokine's abnormal expression (Fig. 2).[17,18]

Risk Factors

The typical risk factors for the onset of prediabetes is as shown in Figure 3.[19]

Age, 2-hour plasma glucose, positive family history of diabetes, high glycated hemoglobin (HbA1c), inactivity, and poor high-density lipoprotein (HDL) are the common risk factors for the transition from NGT to dysglycemia, according to a 10-year follow-up of the Chennai Urban Rural Epidemiology Study (CURES). The same study also demonstrated that in those with NGT, sedentary lifestyles and low HDL cholesterol predicted the onset of prediabetes (but not diabetes). On the contrary, people with NGT were more likely to develop diabetes if their family had a history of the disease. As a result, it can be claimed that environmental variables like physical inactivity are associated to the development of prediabetes, but a combination of genetic and environmental factors may be responsible for the later development of diabetes. Therefore, to have the greatest benefit in this population, efforts to prevent diabetes would need to start before the onset of prediabetes.[20]

Recommended goal

A yearly diabetes development monitoring program should also screen for and treat modifiable CVD risk factors such as hypertension, dyslipidemia, smoking, and alcohol use.

The Madras Diabetes Research Foundation (MDRF) Indian Diabetes Risk Score, a simplified screening tool based on CURES, was created by Mohan et al. to test the general population for diabetes (Table 3).[21] Four basic factors—age, family history of diabetes, physical activity, and waist circumference—are used to calculate the score, which runs from 0 to 100. A score ≥60 indicates a high chance of developing diabetes in the future, a score of 30–60 indicates moderate risk, and a score of <30 indicates low risk.

Key point: Comparing neck circumference (NC) to conventional risk markers including BMI, waist circumference, and body fat percentage, NC is related to larger positive relationships with prediabetes and higher inverse connections with HDL cholesterol. In addition, NC is a simpler and more useful metric that is unaffected by attire or the most recent meal.[22]

Table 2: Estimated total number of adults with IGT and impaired fasting glucose in 2021 and 2045

	2021	*2045*
IGT	541 million	730 million
IFG	319 million	441 million

IGT, Impaired glucose tolerance; IFG, Impaired fasting glucose

Table 3: The MDRF Indian Diabetes Risk Score[18]

Particulars	*Score*
Age (years)	
<35 (reference)	0
35–49	20
≥50	30
Abdominal obesity	
Waist <80 cm (female), <90 (male) (reference)	0
Waist ≥80–89 cm (female), ≥90–99 cm (male)	10
Waist ≥90 cm (female), ≥100 cm (male)	20
Physical activity	
Exercise (regular) + strenuous work (reference)	0
Exercise (regular) or strenuous work	20
No exercise and sedentary work	30
Family history of diabetes	
No family history (reference)	0
Either parent	10
Both parents	20

Progression of Prediabetes to Diabetes

Asian Indians experience a rapid conversion from normoglycemia to dysglycemia and have one of the highest incidence rates of diabetes. This is related to the "Asian Indian" phenotype, which is distinguished by greater susceptibility to diabetes, hyperinsulinemia, and levels of total and visceral fat that are higher than those of white Caucasians with comparable BMIs. With a BMI of >23 kg/m^2 and a waist circumference of 85 cm for males and 80 cm for females, the development of diabetes is accelerated in Asian Indians. Therefore, it is crucial to recognize the circumstances as soon as possible and take proactive preventative actions.[23]

The incidence rates of diabetes, prediabetes, and "any dysglycemia" were found to be 22.2, 29.5, and 51.7 per 1,000 person-years, respectively, in a 10-year follow-up of the CURES. About 19.4% of NGT patients developed diabetes, whereas 25.7% developed prediabetes, for a total conversion rate to dysglycemia of 45.1%. In this cohort, there were 78.9 new cases of diabetes per 1,000 person-years among those with prediabetes.[20]

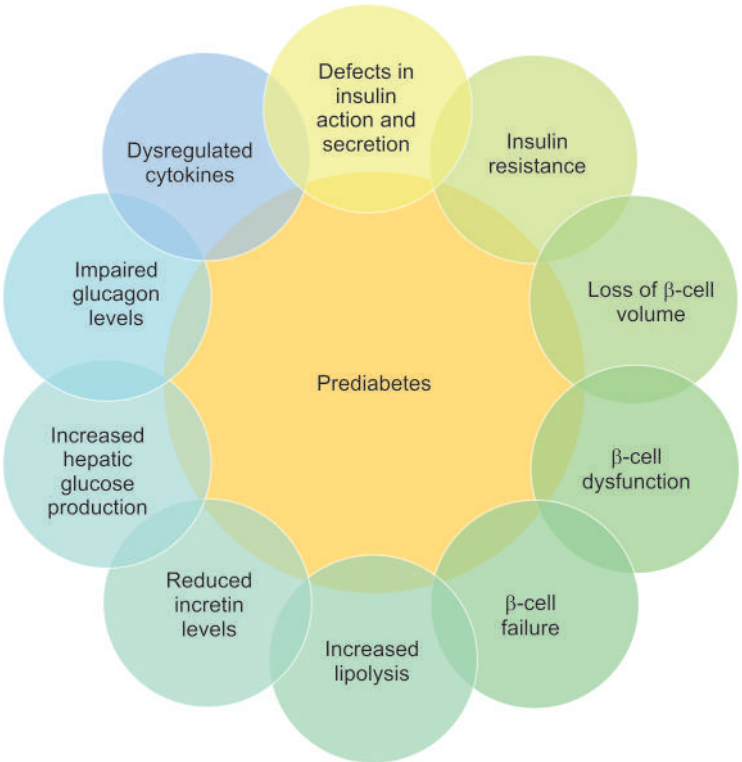

Fig. 2: Pathophysiological defects in prediabetes

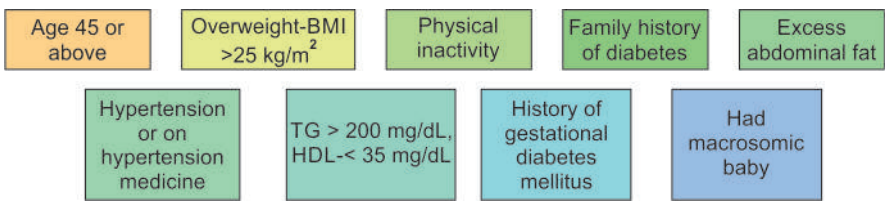

Fig. 3: Risk factors for the development of prediabetes. HDL, High-density lipoproteins; TG, Triglyceride

In both rural and urban areas, diabetes and prediabetes are becoming more common, according to the Secular TRends in DiabEtes in India (STRiDE-I) study. It was stated that all areas had higher rates of prediabetes and diabetes, but only towns and peri-urban villages had higher rates. There was a rise in abdominal obesity among rural villagers as well.[24]

In comparison to rates reported in small, isolated, and homogenous populations like the Pima Indians (87.3 per 1,000 person-years), the Micronesian population of Nauru (62.8 per 1,000 person-years), and Native Americans in the Strong Heart Study (66.1 per 1,000 person-years), the rate of conversion from prediabetes to diabetes in the CURES follow-up is one of the highest reported in a large country (49.0 per 1,000 person-years) (Fig. 4).[20,22]

It can be suggested that there has already been significant β-cell loss and disease progression by the time prediabetes develops because the incidence of T2D among people with NGT reported in the CURES follow-up was 22.2 per 1,000 person-years, which is significantly lower than the rates seen in people with prediabetes.[25]

Kristian and Gottwald-Hostalek[26] reported a linear fall in β-cell function and approximately 50% β-cell function is lost at diagnosis of prediabetes. Staimez et al. demonstrated that independent of age, obesity, insulin sensitivity, or family history, Asian Indians with mild dysglycemia showed noticeably impaired β-cell function. NGT had the greatest levels of the major indicator of β-cell function, the unadjusted mean of oral disposition index (DIo), compared to patients with more severe diseases (IFG plus IGT and diabetes). IFG and IGT had 25 and 23%, respectively, larger homeostasis model assessments of insulin resistance (HOMA-IR) compared to NGT (both $p = 0.0001$) (Fig. 5).[27]

Another study investigated the link between incident diabetes with IGT and DIo obtained from an oral glucose tolerance test in Asian Indian males. The development of incident diabetes

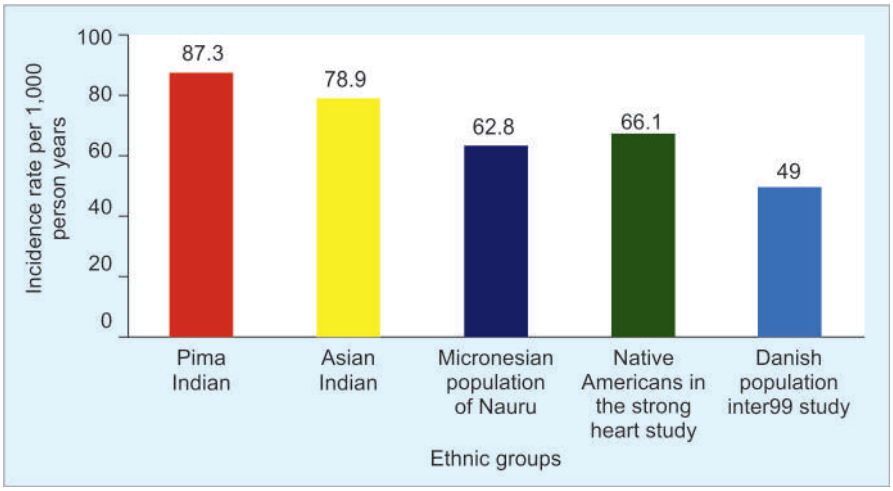

Fig. 4: Rate of conversion of prediabetes to diabetes in different ethnic groups across different studies[20,22]

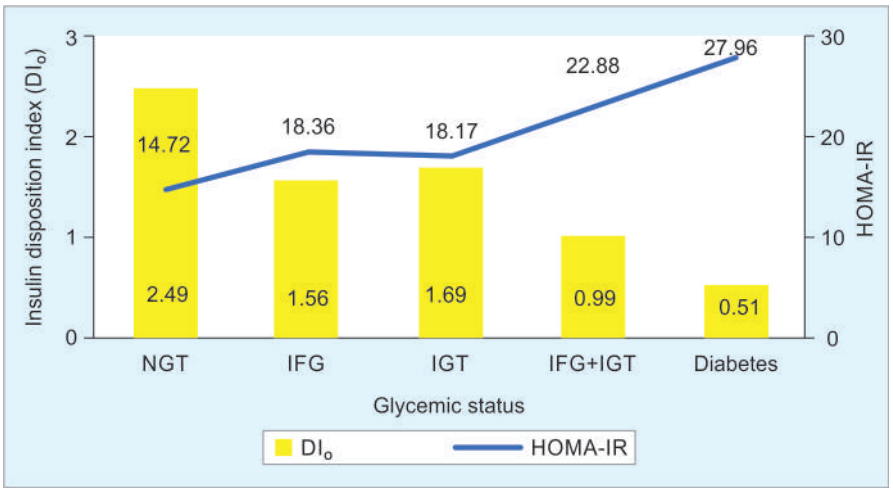

Fig. 5: Age- and sex-adjusted mean DIo and mean HOMA-IR across the glycemic status.[27] HOMA-IR, Homeostasis model assessment of insulin resistance; IFG, Impaired fasting glucose; IGT, Impaired glucose tolerance; NGT, Normal glucose tolerance

was found to have an inverse association with DIo at the final follow-up, making DIo the best indicator of incident diabetes among the surrogate indices investigated.[28]

Key point: According to several studies, 1-hour post-load plasma glucose is a stronger predictor of dysglycemia than fasting plasma glucose (FPG), 2-hour plasma glucose, and glycated hemoglobin (HbA1c). It also predicts not only the development of T2D but also CVD and mortality.[29]

Biomarkers of Prediabetes

The gradually rising glucose levels appear rather late in the course of T2D development, by which time the β-cell function may already be significantly diminished. Therefore, it is essential to find more accurate and sensitive biomarkers that can anticipate the onset of dysglycemia early on when β-cell function is essentially at its peak.[30] Some of these biomarkers are discussed below:

Clinical relevance of biomarkers

- Help identify people with significant diabetes risk.
- May help to identify subjects at risk of developing macro and microvascular complications.
- Can be added to conventional risk variables and improve the power of prediction.

Adiponectin

Adiponectin is derived from adipose tissues and has anti-inflammatory, antiatherogenic, and insulin-sensitizing effects. Adiponectin has been identified as an independent predictor of diabetes in a preliminary investigation of Asian Indians. A low level of adiponectin was strongly predictive of the onset of diabetes and significantly correlated with HbA1c.[31]

Independent of racial or gender variations, adiponectin levels are inversely related to the likelihood of incident prediabetes and are directly correlated with insulin sensitivity and indirectly correlated with insulin secretion. The area under the curve was demonstrated to be improved by the addition of adiponectin to HbA1c, however, the predictive power of HbA1c alone was not improved by the addition of interleukin-6 (IL-6).[30,32]

Retinol-binding Protein 4 (RBP4)

The novel adipokine RBP4, which is released by adipocytes and hepatocytes, is the particular transport protein for retinol (vitamin A) in the blood. A favorable correlation exists between RBP4 levels and metabolic risk factors such as BMI, waist circumference, hypertension, and lipid markers. Concentrations of RBP4 are significantly correlated with prediabetes.[33]

Gamma-glutamyl Transferase (GGT) and Alanine Transaminase (ALT)

Particularly when fasting, the liver is crucial in the regulation of blood glucose levels. T2DM is more common when there has been liver damage, which is indicated by an increase in blood ALT or GGT levels.[34]

After adjusting for potential confounders known to affect circulating GGT, such as alcohol consumption and insulin resistance, a 2-year prospective, randomized, controlled primary prevention study of diabetes among Asian Indians revealed that higher concentrations of GGT were significantly associated with an increased risk of developing diabetes.[35]

Leptin

Leptin is a crucial hormone that controls energy intake and expenditure by regulating appetite and glucose metabolism. It is largely secreted by adipocytes, and the amount of circulating leptin is directly correlated with the overall amount of body fat. In addition to atherosclerosis, hypertension, and coronary vascular disease, leptin insufficiency or resistance causes uncontrolled eating, obesity, and diabetes mellitus. Leptin levels are considerably greater in patients with diabetes than in those without ($p = 0.001$) in both males and females, according to a cross-sectional observation research by Diwan et al.[36]

Inflammatory Markers

An ideal degree of inflammation is necessary for enhancing immunity, and inflammation plays a crucial role in human health. However, there are a number of metabolic illnesses like T2D, obesity, CVD, etc. that are linked to chronic inflammation.[37]

Serum IL-6 levels were shown to be considerably higher in the IFG population compared with the normoglycemic population in an Indian patient research by Upadhyaya et al.[37] (2.00 ± 0.14 pg/mL vs 1.77 ± 0.23 pg/mL,

$p = 0.05$). The increase was statistically significant when compared between the hyperglycemic and normoglycemic populations (2.84 ± 0.62 pg/mL vs 1.77 ± 0.23 pg/mL, $p = 0.01$). However, IFG and hyperglycemic groups did not significantly differ from one another.[37]

A study by Deepa et al. showed that in Asian Indians, inflammatory markers such as IL-6, C-reactive protein, and vascular adhesion molecule 1 increase as the degree of glucose intolerance increases.[38]

Complications of Prediabetes

The risk of CVD events including myocardial infarction, stroke, or CV death is increased by prediabetes.[18] The mean carotid intimal medium thickness (IMT) values in the CURES participants with glucose intolerance were substantially higher than those in the subjects with NGT (NGT 0.69 ± 0.12 mm, IGT 0.75 ± 0.16 mm, newly diagnosed diabetes 0.79 ± 0.19 mm, and known diabetes (0.87 ± 0.24 mm, $p = 0.001$) (Fig. 6). Even after correcting for age and gender, regression analysis revealed a linear increase in mean IMT values with increasing severity of glucose intolerance.[39]

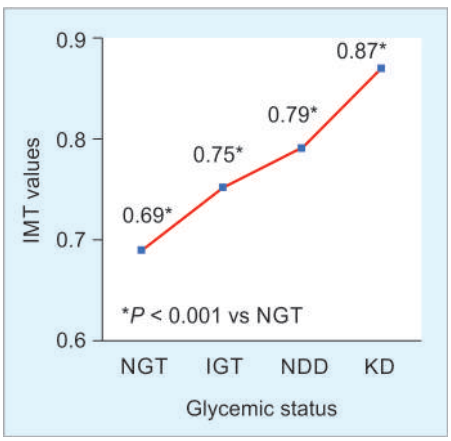

Fig. 6: IMT values across glycemic status[39]

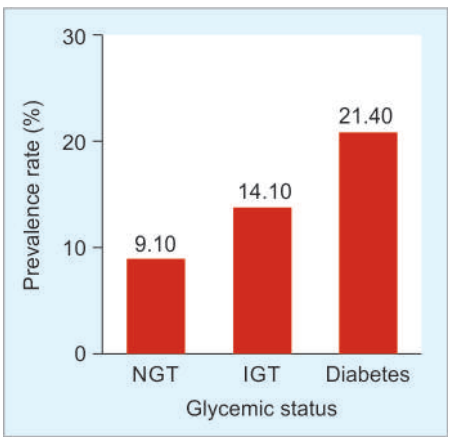

Fig. 7: Prevalence rate of CAD in the Indian population.[40] IGT, Impaired glucose tolerance diabetes; NGT, Normal glucose tolerance

The prevalence rates of coronary artery disease (CAD) were 9.1, 14.9, and 21.4% in people with NGT, IGT, and diabetes, respectively, as studied in the Chennai Urban Population Study (CUPS). As compared to NGT, subjects with IGT had a □5% additional risk of CAD (Fig. 7).[40]

According to the Multi-Ethnic Study of Atherosclerosis (MESA), prediabetes is linked to a prevalence of undiagnosed myocardial infarction that is approximately three times greater than that of NGT (3.5 vs 1.4%). Following multiple risk factor adjustments, those with IFG had higher risks of an undetected myocardial infarction than those with NGT [odds ratio (OR): 1.60 (95% confidence interval (CI): 1.0–2.5); $p = 0.048$].[41]

In addition to established T2D, prediabetes has also been associated to retinopathy, neuropathy, and nephropathy, however, these conditions typically manifest in milder forms. Retinopathy is thought to affect 8–12% of adults with prediabetes. Peripheral neuropathy affects 11–25% of those with prediabetes, and neuropathic pain affects 13–21% of them. In a study by Bahar et al., it was discovered that 15.5% of prediabetic participants had microalbuminuria ($p = 0.005$). The prevalence of diabetic kidney disease in prediabetics ranged from 4.5 to 26.0% across the papers examined by Branda et al.[42–45]

Management of Prediabetes

Preventing the onset of diabetes and its effects, and reducing the complications of prediabetes itself are the guiding ideas underlying the treatment of prediabetes. It may be possible to understand potential actions that could halt prediabetes from developing into diabetes by raising knowledge and risk classification of people with the condition. It should be attempted in every way to bring prediabetes to a normal glucose condition. The most effective strategy for managing prediabetes is lifestyle modification. Pharmacological treatment comes next, and in cases of severe obesity, bariatric surgery may be an option.[46–48]

Lifestyle Intervention

Dietary changes, exercise, and quitting smoking and drinking, among other lifestyle interventions, are included. Despite their relatively low BMI and highly insulin-resistant features, the Indian Diabetes Prevention Program (IDPP) intervention research conducted among Asian Indians showed that it was able to prevent diabetes in participants with IGT utilizing lifestyle change. Each subject was advised to change their diet to consume fewer calories overall, fewer refined carbohydrates and fats (20 gm/day), avoid sugar, and consume more fiber-rich foods. They were also encouraged to engage in physical activity for at least 30 minutes each day, including occupational- and transportation-related physical activity. Following a 3-year follow-up, lifestyle changes significantly lower the chance of developing diabetes by 28.5%.[48,49]

Preventing the development of diabetes also requires a sustained impact of lifestyle changes. The ongoing positive benefits of lifestyle modification have been investigated in the Indian SMS diabetes prevention trial. The study's findings showed that after a 2-year text messaging period, the effects of lifestyle adjustments in lowering the incidence of diabetes are maintained for an additional 3 years. Text messaging offers the advantages of little disturbance to patients' lives, convenience of delivery, relatively high retention rates, cheap cost, and continuous benefits in support of lifestyle modifications.[50] The relative risk reduction for the incidence of diabetes in major diabetes prevention trials is demonstrated in Figure 8.

The Da Qing Diabetes Prevention Study, the United States DPP, and the Finnish Diabetes Prevention Study (DPS), these three large studies on diabetes prevention have all demonstrated positive effects of lifestyle changes.

The goal of the DPP study was a 6-month weight decrease of more than 7%. Dietary solutions focused on lowering energy consumption and limiting fat intake to 25% of total energy. The subjects were given access to structured meal programs and meal replacement products. A goal of more than 150 minutes per week of moderate-intensity exercise was established, and twice-weekly supervised exercise sessions were made available. Although encouraged, lifestyle physical activity did not count against the 150 minutes per week of physical activity objective (e.g., taking the stairs instead of the elevator).[51] It is imperative that physical activity be included in daily life.

After a 3-year follow-up, the study indicated a 58% risk decrease with lifestyle modifications. The study also found that the chance of having diabetes decreased by 16% for every kg of weight lost.[52]

In the Da Qing trial, which compared diet, exercise, and diet combined with exercise to a control group receiving no therapy, it was discovered that each lifestyle choice decreased the risk of acquiring diabetes by 31–46%.[53]

The cumulative incidence of T2D in the intervention group in the Finnish DPS research was 11% compared to 23% in the control group after 4 years of active intervention. There was a 58% decrease in the prevalence of diabetes overall.[54]

A moderate-intensity exercise, just 150 minutes per week of brisk walking, has

been found to enhance insulin sensitivity and reduce belly fat in adolescents and young adults, and people with prediabetes. An exercise program intended to prevent diabetes may also incorporate resistance training in addition to aerobic exercise. It is also recommended to avoid spending too much time sitting down because doing so is linked to somewhat lower postprandial glucose levels.[55]

Recommendations to prevent T2D in those with prediabetes

- 6–8 hours daily sleep

Diet

- Important factors to control:
  - Attempts to lose 5–10% of body weight if overweight or obese
  - Maintaining the ideal body weight, right from the time of pregnancy, counting and watching calories
- Refined food grains, juices, and trans fat should be limited
- Saturated fats and simple sugars should be limited
- Ample quantity of fiber be included in all the meals
- Important to individualize the percent of calories from fat and carbohydrate based on clinical goals for each individual

Regular exercise

- Brisk walking, swimming, dancing, cycling, or outdoor sports that can give exercise to your body should be done every day
- Exercise should be performed for 30 minutes 5 days a week
- It is necessary to walk around generally at least five times every week to keep your mobility
- Yoga is a promising adjunct along with exercise

Pharmacological Intervention

Recommendation: The threshold for the action of pharmacological therapy should be based upon:

- Severity of the hyperglycemia
- Self-perception of severity
- Susceptibility of a person like those subjects who are more susceptible to worsening of dysglycemia, developing diabetes, developing CV complications, or having positive family history should be treated differently than less susceptible patients
- Support from the system like economic support to the patient

Metformin in Prediabetes

The management of prediabetes has been researched using a variety of antidiabetic and non-antidiabetic medications, such as anti-obesity medications. The only pharmaceutical now indicated for the prevention or delaying of T2D is metformin. Large, randomized clinical trials have provided evidence that metformin is effective in preventing diabetes, particularly in younger, heavier patients. Additionally, metformin has a strong safety record, with positive benefits on lipid levels and BMI.[56]

It is proposed that the role of metformin in clinical practice can be divided into the following:

- Primary prevention of diabetes when metformin is given from the perspective of diabetes prevention.
- Secondary prevention of prediabetes when metformin is given in prediabetes patients.
- Primordial prevention of vascular ill health when metformin is given to all prediabetes patients to prevent vascular complications.

Thus, to simplify, the following terminologies are suggested to support the role of metformin in the management of prediabetes: glycemic hygiene,vascular hygiene, andvasculometabolic hygiene.

The ADA and IDF recommend individuals with any form of prediabetes (IGT, IFG, or IFG + IGT) to avoid diabetes gradually by changing their lifestyles in addition to taking metformin when their risk is still high. The Diabetes Community Lifestyle Improvement Program (D-CLIP) was a randomized controlled, diabetes prevention trial in overweight/obese Asian Indian adults with IGT, IFG, or IFG + IGT. The U.S. DPP lifestyle recommendation was given to those who were eligible for it for 6 months, along with a step-by-step addition of metformin (500 mg, twice daily), for those who were at the highest risk of developing diabetes after less than 4 months of follow-up. About 34.9% of control individuals and 25.7% of intervention participants acquired diabetes over the 3-year follow-up period ($p = 0.014$); the relative risk decrease was 32% (95% CI: 7–50) (Fig. 9). According to the type of prediabetes (IFG + IGT, 36%; IGT, 31%; and IFG, 12%; $p = 0.77$), the relative risk reduction varied.[57]

Although there was variation by type of prediabetes (IFG, 76.5%; IFG + IGT, 83.0%; and IGT, 51.3%), the majority of patients (72.0%) needed metformin in addition to a healthy lifestyle. The D-CLIP trial demonstrated that adding metformin gradually to lifestyle counseling is a successful strategy for avoiding or delaying the onset of diabetes in persons with prediabetes.[57]

In the IDPP trial, metformin was effective in reducing the progression rate of IGT to diabetes in the Asian Indian population at a much smaller dose (500 mg/day) as compared to DPP (1700 mg/day). As per ADA 2022, metformin therapy for the prevention of T2D should be considered in those with prediabetes, especially for those with BMI ≥35 kg/m^2, those aged <60 years, and women with prior gestational diabetes mellitus.[49,55]

Current Guideline Recommendations on the Use of Metformin in Diabetes Prevention (Table 4)

Place of metformin in Prediabetes[55]

- Metformin therapy for the prevention of T2D should be considered in those with prediabetes, especially with
- BMI >35 kg/m^2
- Age 60 years
- Women with prior gestational diabetes mellitus
- Metformin may reduce the risk of T2D in subjects with IGT
- Use metformin 250–850 mg/day where lifestyle intervention is insufficiently effective in reducing body weight and improving glucose tolerance

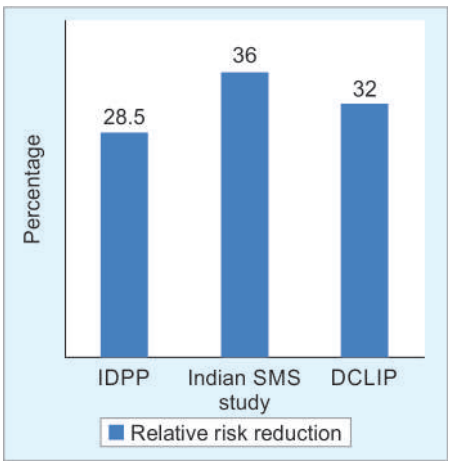

Fig. 8: Relative risk reduction for incidence of diabetes in major diabetes prevention trials[49,50,57]

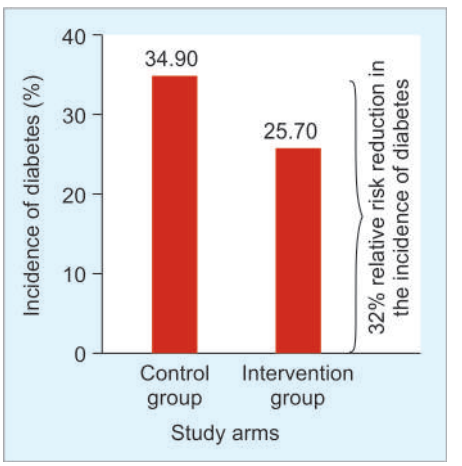

Fig. 9: Cumulative incidence of diabetes by study arm in the D-CLIP trial from baseline to year 3[57]

Table 4: Overview of recommendations relating to the use of metformin for the prevention or delay of T2D from selected guidelines with international influence

Guideline	*Summary of recommendations relating to metformin*
ICMR (India, 2018)[58]	When lifestyle alone is not sufficient and especially in those with combined IFG and IGT where progression to T2D appears imminent, use of metformin in addition to lifestyle measures may be considered especially in Indians who progress rapidly to diabetes from the prediabetes stage
RSSDI (India, 2020)[59]	People with prediabetes failing to achieve any benefit on lifestyle modifications after 6 months may be initiated on oral antidiabetic agents (OADs): • Metformin: in younger individuals with one or more additional risk factors for diabetes regardless of BMI, if overweight/obese and having IFG + IGT or IFG + HbA1c >5.7%, addition of metformin (500 mg, twice daily) after 6 months of follow-up is recommended
ADA (USA 2022)[55]	Metformin therapy for prevention of T2D should be considered in adults with prediabetes, as typified by the Diabetes Prevention Program, especially those aged 25–59 years with BMI ≥35 kg/m^2, higher fasting plasma glucose (e.g., ≥110 mg/dL), and higher A1C (e.g., ≥6.0%), and in women with prior gestational diabetes mellitus Monitor vitamin B12 periodically, especially where anemia or peripheral neuropathy is present
ALAD (Latin America, 2011)[60]	First step is lifestyle management; if not sufficient and/or in additional risk factors, pharmacological treatment (e.g., metformin) is recommended
CDA (Canada, 2013)[61]	Implement intensive lifestyle intervention to prevent T2D; metformin may reduce the risk of T2D in subjects with IGT
IDF (Global, 2006)[62]	Use metformin 250–850 mg/day where lifestyle intervention is insufficiently effective in reducing body weight and improving glucose tolerance
Malaysian Endocrine & Metabolic Society (MEMS guidelines 2009)[63]	Metformin to be considered in patients with additional risk factors or if lifestyle change alone is not sufficient

Table 5: Summary of T2D prevention trials with other antidiabetic drugs

Study	*Interventions*	*Duration*	*Results*
STOP-NIDDM[64]	Acarbose (100 mg TID) vs placebo	3.3 years	Incidence of T2D was 32% in the therapy group and 42% in the placebo group. Acarbose caused increased flatulence and diarrhea
Voglibose for prevention of DM[65]	Voglibose (0.2 mg TID) vs placebo	48 weeks	5.6% T2D incidence in treatment group vs 12.0% in placebo
CANOE trial[66]	Rosiglitazone (2 mg) + metformin (500 mg) twice daily vs placebo	Median 3.9 years	In patients with IGT, rosiglitazone plus metformin at half the recommended dose were very successful in preventing diabetes and restoring NGT
IDPP-2[67]	Pioglitazone (30 mg) vs placebo	3 years	The cumulative incidence of diabetes was 29.8% with pioglitazone and 31.6% with placebo
Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication[68]	15 mg/day ramipril vs placebo and 8 mg/day. Rosiglitazone vs placebo	3 years	Neither ramipril (15.7 vs 16.0%) nor rosiglitazone (15.0 vs 16.8%) decreased the risk of the cardiorenal composite outcome in comparison to placebo. The prevention of the renal component was independently linked to the prevention of diabetes

CANOE: Canadian Normoglycemia Outcomes Evaluation; IGT: Impaired glucose tolerance; T2D: Type 2 diabetes

Other drugs like inhibitors of pancreatic lipase (orlistat), peroxisome proliferator-activated receptor-g agonists (pioglitazone), α-glucosidase inhibitors (acarbose), meglitinides (nateglinide), and GLP-1 receptor agonists (liraglutide) have also demonstrated benefits.[64–66] The results of important landmark trials are summarized in Table 5.

Surgical Intervention

Another efficient method of treating prediabetes is bariatric surgery. It is recommended for individuals whose BMI is greater than 32.5 kg/m^2 with comorbidity or greater than 37.5 kg/m^2 without comorbidity and who are unable to reduce weight under medical supervision. Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding, sleeve gastrectomy, and duodenal switch with biliopancreatic diversion are among the frequently performed procedures.[46]

Bariatric surgery is linked to sustained weight loss and a significant drop in the incidence of diabetes at the 2- and 10-year mark in patients who are morbidly obese. Additionally, the research that is now available suggests that bariatric surgery offers more long-lasting glycemic control than rigorous medication therapy. Additionally, gastric bypass has been shown to reduce visceral fat, including hepatic and pancreatic fat, and to specifically restore pancreatic cell activity, curing the primary abnormalities in diabetes.[47]

Creating a Holistic Prediabetes Management Plan

The management of prediabetes should be multidimensional. It should not only include lifestyle interventions and pharmacotherapy but also psychological support and education programs.[69] A population-based study in urban India reported an increasing prevalence of depression with increasing grades of glucose intolerance which highlights the need for early assessment of psychological factors influencing prediabetics.[70] Education programs can be an efficient way of providing education and support to individuals with prediabetes. It could bring significant improvement in knowledge, attitude, and practice. These programs can also help in increasing psychological strength and motivating

people to change their behavior, and improving quality of life and self-management skills.[71]

However, in India, prediabetes education is an underused tool for the prevention of diabetes. Thus, the need of the hour is nationwide prediabetes education and dissemination of knowledge and action plan.

Role of Telemedicine in Prediabetes

Successful lifestyle intervention programs require intensive involvement with the patients. An inexpensive style of delivering educational advice about lifestyle modification is mobile phone messaging.[72]

In a study from Southeast Asia, researchers looked at whether T2D in Indian Asian men with IGT could be reduced *via* mobile messaging. According to this study of 8,741 individuals, those who got text messages with advice and encouragement to change their lifestyles had a lower overall incidence of T2D than the controls.[72]

The Ministry of Health and Family Welfare, Government of India, has also initiated and executed a mDiabetes program called mHealth Project, a commissioned study to test the feasibility of using mobile technology to reach a large number of people to improve their lifestyle and health-seeking behavior. This evidence positively exhibited the acceptability and feasibility of mHealth in a large population to improve health-seeking behavior by disseminating knowledge regarding diabetes and a healthy lifestyle.[73]

Diabetes digital health offers an effective solution for changing the Indian primary health care environment. It interconnects multiple contributors of diabetes care including clinicians, patients, diabetes educators, nurses, and caregivers *via* smartphones and other communication devices.[74]

Telemedicine is one such platform that utilizes information and communication technologies for the delivery of health care services where distance is a very important issue. In India, it has been widely used to create awareness about diabetes prevention among urban and rural populations.[74]

An excellent example of how telemedicine may be used effectively to bring diabetes health care and prevention to neglected rural communities in India is the Chunampet Rural Diabetes Prevention Project.[75] In Trivandrum, South India, at the Jothydev's Diabetes Research Center, a telemedicine-based follow-up program known as the Diabetes Tele Management System was first established in 1998. It gives patients and the multidisciplinary diabetes team a live, interactive platform for two-way contact over the phone, the internet, or a secure website at predetermined intervals for an indefinite amount of time.[76]

Bridging the Gap

All general practitioners, physicians, and specialists are aware of prediabetes. However, there seems to be a gap between awareness and adoption of prevention strategies due to a lack of communication. The only solution to bridge the gap is to communicate, share the information, sensitize the stakeholders, and support sensible, rational, and pragmatic action. This is possible through shared decision-making, that is, information should be shared between the person living with diabetes and the physician and caregiver. The purpose of this is to identify reasonable options that best fit and address the situation of the patient. Physicians should be empowered to give the right advice. Peer-to-peer shared decision-making is also needed.

Conclusion

Prediabetes is rising at an alarming rate in the Indian population. Thus, the time is right to develop a proactive approach to prediabetes. Keeping this in view, a consensus was developed on prevalence, risk factors, biomarkers, and interventions for prediabetes. This consensus on early detection and management will help in reducing the progression of prediabetes to diabetes and associated complications. It will also help in increasing awareness for screening and risk stratification of individuals with prediabetes which may guide physicians to understand potential interventions.

Summary

- Prediabetes is a precursor of T2D.
- The conversion rate from prediabetes to T2D is very high among Asian Indians.
- Individuals with clinical risk factors for prediabetes can be screened using the IDRS screening tool.
- The risk for macrovascular disease starts at the stage of prediabetes as it increases the risk of CVD events, myocardial infarction, stroke, and CV death.
- Prediabetes has been also linked with retinopathy, neuropathy, and nephropathy.
- Biomarkers help in identifying people with a high risk of developing diabetes.
- Identification and aggressive treatment of prediabetes are mandatory.
- Lifestyle intervention is the key to the management of prediabetes.
- Metformin is the only pharmacologic agent recommended for the prevention or postponement of T2D.
- Large, randomized clinical trials have provided evidence that metformin is effective in preventing diabetes, particularly in younger and obese patients.
- The pleiotropic benefits of metformin beyond glycemic control play an important role in the long-term management of dysglycemia.
- Bariatric surgery is another effective way of treating prediabetes, but this is recommended for those with morbid obesity.
- Future requirements:
  - Development of structured prediabetes education programs.
  - Bridging the gap between awareness and adoption of lifestyle and pharmacological treatment when indicated.
- Telemedicine can be an effective tool.

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Compliance with Ethics Guidelines

This article is based on available literature and previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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