

# Reducing the Burden of Diabetes Mellitus: Is It Achievable?

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## ABSTRACT

Diabetes mellitus is rapidly on the rise globally, particularly in low- and middle-income countries. Pakistan has emerged with the highest prevalence of diabetes by percentage according to recent estimates. Evidence is available for different strategies to reduce this burden. Screening high-risk individuals can reduce burden of undiagnosed diabetes and improve outcomes. Although prediabetes can progress to type 2 diabetes, it has the potential to regress to normoglycaemia as well. Interventions like lifestyle modifications and metformin in high-risk individuals can reduce the risk of progression to diabetes. Furthermore, there is a potential to reverse diabetes in some individuals in the early years after diagnosis with a low-calorie diet, carbohydrate restriction or bariatric surgery.

**Keywords:** *Diabetes mellitus, prediabetes, prevalence, prevention, remission.*

## INTRODUCTION

Diabetes mellitus is a global public health problem associated with disabling and life-threatening complications, reducing life expectancy and having a significant economic impact. Although the incidence has either stabilized or started to decrease in some countries, the prevalence has increased in most other countries in recent decades [1]. This rising prevalence is a result of complex interaction between genetic, environmental, socioeconomic and demographic factors.

The majority (>95%) have type 2 diabetes mellitus (T2DM), accounting mostly for the rising burden [2]. The main driving factors include an epidemic of obesity associated with reduced physical activity, a demographic shift towards an older population and urbanization [3]. An estimated 2.2 billion adults (42% of the adult population) had high BMI (overweight and obesity) in 2020. Of the 1.47 million deaths due to diabetes globally in 2019, 42% were attributed to high BMI [4]. The prevalence of diabetes has increased significantly from an estimated 108 million (4.7%) in 1980 to 537 million (10.5%) in 2021 globally. Almost one in two individuals is undiagnosed (44.7%). The increase in diabetes prevalence has been faster in low- and middle-income countries (LMIC) in contrast to high-income countries; three out of four adults with diabetes live in LMIC. Additionally, the proportion of people with undiagnosed diabetes is higher in LMIC [5].

Pakistan is the fifth most populous country in the world, with an estimated population of over 225 million [6]. Following the global trend, there has been a remarkable rise in prevalence of diabetes in Pakistan as well. In 1980, it ranked 13<sup>th</sup> in diabetes prevalence worldwide, with 1.7 million adults affected. The diabetes prevalence survey of Pakistan reported the prevalence of T2DM at

around 17% with another 11% having pre-diabetes in 2017 [7]. The prevalence was reported much higher at 26.3% in the National Diabetes Survey of Pakistan 2016-17 [8]. However, according to the International Diabetes Federation (IDF), Pakistan had the highest estimated prevalence rate of diabetes at 30.8% in 2021 which is alarming. The number of adults affected has gone up from 19.4 million in 2019 to 33 million in 2021, ranking third in the world, above the United States of America which has a population of 332 million [5].

Since the rising prevalence of this costly disease has disproportionately affected countries with limited resources, it is important to utilize cost-effective strategies to lessen the impact of the rising burden of diabetes in our countries.

## LITERATURE SEARCH STRATEGY

We searched PubMed database for studies published between 2002 and 2022 using the terms diabetes mellitus, prediabetes, prevalence, prevention and remission. We prioritized search results based on quality (systematic reviews and meta-analyses, randomized controlled trials) and relevance to the topic. We also included relevant international professional guidelines. In addition, we performed a targeted search for data from Pakistan.

## SCREENING & EARLY DIAGNOSIS

The longer diabetes remains undiagnosed and untreated, the worse the outcomes are likely to be [9]. Screening for T2DM can reduce the burden of undiagnosed diabetes. This can lead to early diagnosis and treatment, with a potential for improvement in the outcomes. In a trial which recruited patients from general practices in Denmark, the Netherlands and the UK, early intensive multifactorial treatment of screen-detected diabetes, achieved a modest but significant reduction in glycaemia and other cardiovascular risk factors at 5 years. Although non-significant, there was a reduction in cardiovascular

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events, microvascular complications and mortality over 5-10 years as well [10]. Screening can also detect pre-diabetes, providing an opportunity to offer evidence based preventive interventions.

### Screening Recommendations

Several screening tools are available to identify high-risk individuals for testing. Risk Assessment of Pakistani Individuals with Diabetes (RAPID) tool was effective in identifying people at high risk for diabetes and prediabetes in Second National Diabetes Survey of Pakistan (NDSP) 2016-2017 [11]. However, the American Diabetic Association (ADA) guideline may be simpler to use in practice, which recommends screening adults who are overweight and obese, with additional risk factors. Since people in South Asia have a higher risk of developing type 2 diabetes, all adults in Pakistan with a BMI of  $\geq 23$  kg/m<sup>2</sup>, should be screened [12]. Family history of T2DM in first degree relatives is another important risk factor to consider. It is prudent to encourage adult family members of individuals with diabetes to be screened if they have a BMI of  $\geq 23$  kg/m<sup>2</sup>. Individuals with other high-risk conditions should be screened opportunistically as well, including hypertension, dyslipidemia, cardiovascular disease (CVD), polycystic ovary syndrome (PCOS) and other insulin resistant states (e.g. acanthosis nigricans). Non-alcoholic fatty liver disease is another high-risk condition for type 2 diabetes. Detailed screening recommendations are provided in ADA guidelines [12]. The current ADA guideline has lowered the screening age for individuals not falling in the above high-risk categories. Whereas the previous editions recommended screening all individuals from the age of 45 years, the 2022 edition recommends starting screening from 35 years. This is in keeping with a declining trend in age at the time of diagnosis of T2DM and could further reduce the burden of undiagnosed disease [13].

Children and young people at high risk should be screened for type 2 diabetes as well. The incidence of obesity has increased in this age group, which is a major risk factor for type 2 diabetes. An estimated 22% of children aged 5 to 19 years had high BMI (overweight and obesity) which is projected to increase to 28% by 2025. Obesity contributed to 18 million cases of hyperglycaemia in this age group [4]. Similarly, there has been a rise in obesity in children and adolescents in Pakistan [14]. The prevalence of high BMI in Pakistan was estimated to be 13% in 2020 in children, which is projected to increase to 30% by 2035 [4].

The ADA recommends screening children and adolescents, starting from puberty or 10 years of age (whichever is earlier), who are overweight or obese (BMI  $\geq 85^{\text{th}}$  centile) with one more risk factor. Again, being in a high-risk ethnic group, all children in Pakistan who fall in this category should be screened for type 2 diabetes. Additional risk factors include diabetes in the mother, including during the child's gestation, family history of

type 2 diabetes (1<sup>st</sup> or 2<sup>nd</sup> degree relatives) and conditions associated with insulin resistance [12].

Lifelong screening is recommended every 3 years in women who had gestational diabetes mellitus (GDM). In both adults and children, if initial screening is normal, repeat test should be offered every 3 years, testing more frequently depending on initial results and risk factors. People who are found to have pre-diabetes, should be tested at least annually [12].

### Infections and Diabetes Mellitus

Diabetes mellitus increases the risk of infections due to different pathophysiological mechanisms. Several infections are associated with diabetes mellitus and these infections may be the first manifestation of diabetes. These include fungal infections, recurrent skin infections, tuberculosis, hepatitis B & C and HIV etc. Patients presenting with these infections should provide an opportunity to screen for diabetes mellitus [15].

## PREDIABETES

The prevalence of prediabetes was 14.4%, according to the 2<sup>nd</sup> National Diabetes Survey of Pakistan 2016-17 [8]. Prediabetes is a high risk condition for progressing to type 2 diabetes and developing vascular complications [16]. Around 5-10% of individuals with prediabetes will progress to diabetes annually, with around three quarters progressing over a lifetime [17]. The risk factors for this progression are listed in Table 1 [16, 17].

**Table 1:** Risk factors for progression of prediabetes to diabetes.

High BMI
Sedentary lifestyle
PCOS
History of GDM
High risk ethnicity (e.g. South Asian)
Family history of T2DM

The conversion to type 2 diabetes from impaired glucose tolerance (IGT) was much higher in the control group of the Indian Diabetes Prevention Programme (IDPP) study [18]; the cumulative incidence was 55% over three years (18.3% per year).

Prediabetes is associated with a higher risk of CVD and individuals with prediabetes should be screened and treated for other CVD risk factors like smoking, hypertension and dyslipidemia [19]. Importantly, prediabetes can regress to normoglycaemia with a reduction in risk of CVD and mortality as well [20].

## PREVENTION OF TYPE 2 DIABETES

Evidence from large randomized controlled trials has shown that T2DM can be delayed or even prevented in high-risk individuals. The diabetes prevention programme (DPP) study included a multiethnic American cohort with intervention over 3 years. The lifestyle intervention reduced the incidence of T2DM by 58%,

with a number needed to treat (NNT) of 6.9. In contrast, metformin reduced the incidence by 31% with an NNT of 13.9 [21]. The participants didn't have diabetes but had raised fasting or 2-hour plasma glucose concentration with high BMI (overweight or obese). The goal for the participants in the intensive lifestyle group was to lose at least 7% of body weight. This was achieved with moderate intensity exercise, like brisk walking, for 150 minutes per week, and a healthy diet with low-calorie and low-fat content. The Diabetes Prevention Program Outcomes Study (DPPOS) was a follow-up of DPP which showed a sustained effect of intervention with reduced incidence of type 2 diabetes by 34% at 10-year and 27% at 15-year [22].

The effectiveness of intensive lifestyle intervention to reduce the risk of T2DM was demonstrated in the Finnish Diabetes Prevention Study (DPS) as well. The study included high-risk individuals, who were overweight and having IGT. The intervention included a low-fat, high-fiber diet with moderate intensity physical activity for 30 minutes/day, delivered over a median of 4 years. At 7-year follow-up, the lifestyle intervention reduced the risk of progression to diabetes by 43%. Importantly, both the lifestyle changes and reduced incidence of T2DM were sustained post-intervention [23].

The Da Qing diabetes prevention outcome study reported long-term outcomes after 6-year of intervention in Chinese participants with impaired glucose tolerance. The combined intervention with diet and exercise reduced progression to T2DM by 39% at 30-year follow-up. In addition, there was a reduction in long-term complications including cardiovascular events, reduced mortality and microvascular disease [24]. This trial has shown a legacy effect as well, with the benefits of intervention sustaining years after the intervention period.

The above data is from multi-ethnic American, Finnish and Chinese populations, demonstrating that lifestyle interventions can reduce the risk of progression to type 2 diabetes in high-risk individuals. The IDPP investigated the effect of lifestyle modification and metformin on reducing the risk of type 2 diabetes in the Asian Indian population. In high-risk individuals with raised BMI and impaired glucose tolerance, there was a significant reduction in the incidence of T2DM over 3 years with both lifestyle modification and metformin; combining the two interventions did not have an added benefit. Although both interventions were significantly beneficial, the effect was less in comparison to DPP. Several factors in intervention design can explain this. While assessing physical activity, mode of transport to work, occupation, and leisure activities were considered. Participants already engaged in regular physical activity for >30 minutes/day, including physical labour and walking or cycling to work, were encouraged to continue. Participants who were physically inactive or performing light physical activity were advised and motivated to

undertake regular brisk walk for 30 minutes a day. Unlike DPP, the weight of the participants didn't change significantly in IDPP. In addition, in IDPP, metformin was used at a much lower dose of 250 to 500mg twice a day, compared to 850 mg twice a day in DPP [18].

In the context of Pakistan, a trial from Karachi, demonstrated a reduced risk of progression of IGT to type 2 diabetes with lifestyle intervention over 18 months, with an absolute risk reduction of 10.7% and NNT of 9. The addition of metformin at a dose of 500mg twice a day, didn't affect the progression to diabetes significantly [25].

### Metformin

The above trial data has shown clear benefits of lifestyle interventions in reducing the risk of developing diabetes in high-risk individuals. Although, metformin significantly lowered the risk of T2DM, it was less effective than lifestyle intervention in DPP. On the other hand, both metformin and lifestyle modification showed similar effects in IDPP. Combining the two interventions didn't seem to have an added benefit, as shown in IDPP and a diabetes prevention study from Pakistan [18, 25]. However, metformin should be recommended as an option in subgroups that benefited the most from it in DPP as listed in Table 2 [21, 26].

**Table 2:** Metformin for prevention of diabetes.

Age: 25-59 years
History of GDM
BMI $\geq$ 35kg/m <sup>2</sup>
FBS $\geq$ 110mg/dl or HbA1C $\geq$ 6.0%

Other factors that may be considered include high triglycerides and low high-density lipoprotein (HDL), which are independent predictors of diabetes [27]. Metformin can be prescribed to high-risk individuals, especially if glycaemia worsens even with lifestyle modification. The dose should be titrated, starting at 500mg once daily and increasing as tolerated up to 1500 to 2000 mg daily. Fasting plasma glucose or HbA1c should be checked at a 3-month follow-up. Metformin should be stopped if it is of no benefit over 6-12 months [28].

Pioglitazone,  $\alpha$ -glucosidase inhibitor, angiotensin converting enzyme inhibitors and angiotensin receptor blockers are among other drugs that have demonstrated benefits in reducing the risk of developing type 2 diabetes in high risk individuals [29].

### Medicines for Weight Loss

Being overweight or obese is a risk factor for developing T2DM. Weight reduction is the primary factor in decreasing progression from prediabetes to diabetes. Both DPP and Finnish DPS have demonstrated that modest weight loss of 5 to 7% with lifestyle modification in high-risk individuals reduced the risk of developing T2DM. Medications, if used as a part of an overall weight-

management plan, may help in weight reduction in some high-risk individuals [30]. The XENical in the prevention of diabetes in obese subjects (XENDOS) study, looked at the effect of orlistat plus lifestyle modification in reducing the risk of T2DM in participants with obesity and impaired glucose tolerance over 4 years. The combination not only achieved a greater weight loss but also reduced the incidence of T2DM by 37.3%, compared to lifestyle modification alone [31]. Other weight-loss medications that have shown promise in reducing the progression to diabetes from prediabetes in overweight or obese individuals include, an extended-release combination of phentermine and topiramate and glucagon-like peptide 1 analogues [32, 33]. Weight loss after bariatric surgery can also reduce the risk of progression from prediabetes to diabetes [34].

### Cost-Effectiveness of Diabetes Prevention

Diabetes mellitus is an expensive disease to manage with total diabetes-related health expenditure estimated to be 966 billion United States dollars (USD) in 2021 and 1,838.4 USD per person, globally for adults aged 20 to 74 years [35]. A study from four provinces of Pakistan has reported the annual direct cost of diabetes management as 646.7 USD in 2021-22. Out of this, 42% of the cost was for the medicines and 49% for hospitalization. The total cost of diabetes management was 62% of per capita gross domestic product (GDP) of Pakistan. According to this study, the total burden of diabetes management was estimated to be 1.67% of Pakistan's total GDP [36]. This represents a significant economic burden both for the individual with diabetes and the country.

According to IDF, comprehensive lifestyle programmes and metformin, an inexpensive drug, are cost-effective strategies to prevent T2DM in high-risk individuals [37]. A meta-analysis of studies from South Asia has reported lifestyle modification and metformin to be cost-effective in preventing T2DM [38].

### REMISSION OF DIABETES

Accumulation of fat in liver and pancreas causes glucose intolerance and reduced  $\beta$ -cell function in T2DM. Normoglycaemia may be restored if this fat accumulation can be reversed by losing enough weight in the initial years after diagnosis of T2DM [39]. The reversal of type 2 diabetes, although ambitious, may be achievable for at least some of the individuals with T2DM. Remission of T2DM may be defined if the following 3 criteria are met [40]:

1. Weight loss
2. Fasting glucose <126mg/dl or HbA1C <6.5% on two occasions at least 6 months apart
3. Cessation of all glucose-lowering medications

Evidence exists to support the reversal of T2DM with bariatric surgery, low-calorie diet or carbohydrate restriction. Bariatric surgery, also considered as metabolic surgery, is most effective for prolonged

remission of T2DM. In selected patients, this may not only improve glycemic control significantly but also cause remission of T2DM [41]. However, its cost, risk of surgical complications and commitment to lifestyle modification after surgery remain barriers to wider adoption [42].

Both low-calorie and low-carbohydrate diets can induce remission of diabetes in the short term but evidence on long-term remissions is lacking [43]. Additionally, adherence to these diets in the long run can be a challenge. In the Counterpoint study, a low-calorie diet helped participants with T2DM (less than 4-year duration) achieve 15kg weight loss at 8 weeks, resulting in reduced hepatic and pancreatic fat with normalization of hepatic insulin resistance,  $\beta$ -cell function and fasting glucose. However, this remission is less likely if diabetes duration is more than 10 years [44]. Diabetes Remission Clinical Trial (DiRECT) was a randomized controlled trial which recruited individuals with T2DM diagnosed in the previous 6 years, with a BMI of more than 27 kg/m<sup>2</sup>. Low-calorie diet of 825-853 kcal/day, with structured support, led to remission of diabetes in 46% of individuals at 12 months and 36% at 24 months, with remission rates increasing with increasing weight loss [45]. The initial results from ReTUNE trial (Reversal of type 2 diabetes Upon Normalization of Energy intake in non-obese people) have shown similar metabolic changes and remission of T2DM with weight loss using low-calorie diet in individuals with a BMI of <27kg/m<sup>2</sup> as well [46]. Although these trials demonstrate that weight loss and remission of diabetes are achievable, the use of a low-calorie diet, along with regular structured support may be difficult to achieve in real-life clinical settings.

### LIMITATIONS

There are a few limitations of this review, considering its application in the local population. The prevalence of diabetes described by IDF is based on estimates and there is a lack of data on true local prevalence. Most of the evidence about the prevention of diabetes comes from international studies, except for a small study of short duration from Karachi. Additionally, no local study was found on remission of diabetes.

### CONCLUSION

The prevalence of diabetes continues to rise, disproportionately affecting the countries which are less well-equipped to deal with it. The prevalence has risen dramatically in Pakistan, which now has the highest estimated global prevalence by percentage and 3<sup>rd</sup> in absolute numbers, above the USA. A significant proportion remains undiagnosed. Screening should be adopted widely to identify individuals with pre-diabetes and diabetes. Pre-diabetes increases the risk of future diabetes and CVD. There is plenty of evidence from long-term studies to support the benefit of lifestyle intervention in preventing diabetes in these high-risk individuals, with the addition of metformin for some.

Remission of diabetes may be an ambitious goal and can be achieved for some individuals with T2DM in the initial years after diagnosis and the need for weight loss should be emphasized. Although trials have shown a legacy effect, with reduced risk of diabetes persisting years after the intervention stage, weight loss achieved by lifestyle or other interventions needs to be sustained over a long period for continued benefit.

### TAKE HOME MESSAGES

- The prevalence of diabetes has increased globally, disproportionately affecting LMIC. Pakistan now ranks 3rd in global diabetes prevalence, an alarming situation requiring immediate attention and public health strategies to tackle it.
- Screening high-risk individuals provides an opportunity to diagnose and manage diabetes and pre-diabetes early with the potential to improve long-term outcomes.
- Evidence supports the use of cost-effective strategies of lifestyle modification and metformin in selected individuals to prevent progression to diabetes in high-risk individuals.
- Remission of T2DM is achievable in some individuals, especially in the initial years after diagnosis, provided weight loss can be achieved and maintained.

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None.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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### AUTHORS' CONTRIBUTION

RI conceived the study and wrote the manuscript.

RA and AA critically reviewed and revised the manuscript.

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