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PREDIABETES DESERVES MORE ATTENTION: A REVIEW

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ABSTRACT

Aim & Objectives:
This review aims to describe the epidemiology of prediabetes and discusses current challenges in the field.

Materials And Methods:
We performed a systematic review of the literature consisting of observational or cross-sectional studies, which reported the risk factors of pre-diabetes

Conclusion:
At present there is no concrete evidence to formulate clinical guidelines for the treatment of prediabetes. Lifestyle interventions remain an essential part of the management of prediabetes.

INTRODUCTION

Prediabetes refers to an intermediate stage of dysglycemia along the continuum from normoglycemia to diabetes (1). Prediabetes is identified by laboratory measurement of fasting blood glucose (FBG), glycosylated hemoglobin (HbA1C), or 2-h postload blood glucose (2hBG) (1). The term prediabetes is used to identify those individuals who are at risk for future diabetes, but prediabetes is also associated with a high burden of cardiometabolic risk factors and is associated with poor outcomes (2). The increasing prevalence of prediabetes globally is a major public health concern and does not bode well for the growing epidemic of diabetes and its complications. The natural history of the condition is well documented, its detection can be straightforward, and evidence for its effective treatment has accumulated over the past two decades (3, 4, 5, 6).

However, there is controversy regarding the optimal definition of prediabetes and active recognition and treatment of prediabetes has lagged, as clinicians may fail to see it as a disease state that needs addressing.

This review aims to describe the epidemiology of prediabetes and discusses current challenges in the field. We focus on evidence from surveys investigating the prevalence of prediabetes, observational studies of the association of prediabetes with major clinical outcomes, and intervention studies including randomized clinical trials of therapies for prediabetes and discuss current approaches to prediabetes in clinical practice. This summary should help inform the process of translating the current evidence into public health and clinical policies for diabetes prevention.

MATERIALS AND METHODS

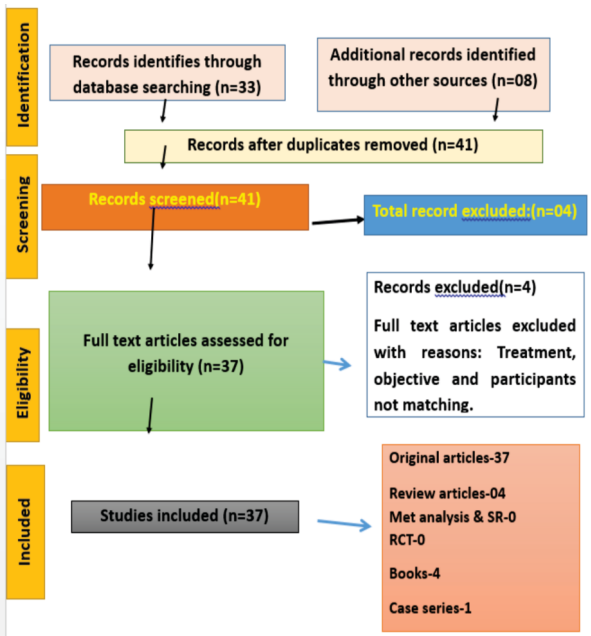
We performed a systematic review of the literature consisting of observational or cross-sectional studies, which reported the risk factors of pre-diabetes among adolescents by following the preferred reporting items for systematic reviews and meta-analysis (PRISMA) 2020 guidelines (Page et al., 2021).

Information sources and search strategy

We performed a literature search through PubMed, ScienceDirect, Scopus, and Web of Science databases in the time frame of 2001 to 2022. A careful manual search of reference lists of identified papers was also done by all authors to identify studies that were not detected by the database search. All the retrieved articles were then sent to Mendeley to remove duplicates. Screening of titles and abstract based on the pre-defined inclusion and exclusion criteria was done to get relevant citations that were included in the present review.

Prisma Chart

1. Systematic Review Of Literature (prisma Flow Diagram)



Diagnosis Of Prediabetes

Various organizations have defined prediabetes with criteria that

are not uniform. The World Health Organization (WHO) has defined prediabetes as a state of intermediate hyperglycemia using two specific parameters, impaired fasting glucose (IFG) defined as fasting plasma glucose (FPG) of 6.1-6.9 mmol/L (110 to 125 mg/dL) and impaired glucose tolerance (IGT) defined as 2 h plasma glucose of 7.8-11.0 mmol/L (140-200 mg/dL) after ingestion of 75 g of oral glucose load or a combination of the two based on a 2 h oral glucose tolerance test (OGTT)[7]. The American Diabetes Association (ADA), on the other hand has the same cut-off value for IGT (140-200 mg/dL) but has a lower cut-off value for IFG (100-125 mg/dL) and has additional hemoglobin A1c (HbA1c) based criteria of a level of 5.7% to 6.4% for the definition of prediabetes [8]. Several studies have shown poor correlation between HbA1c and IFG and IGT[9-11]. The usefulness of diagnosis of diabetes or prediabetes on basis of IFG and IGT have been challenged due to inability of these blood glucose cut points to capture pathology related to diabetes and probability of developing diabetes in future[12]. These cut-offs further loose their credibility due to poor reproducibility of these tests in adults and children[13,14]. Although, HbA1c is believed to represent an average blood sugar level and should ideally represent hyperglycemia more accurately, this may not be entirely true. HbA1c is substantially determined by genetic factors independent of blood glucose levels and may be an imprecise tool to measure average blood sugar[15,16]. While there are valid concerns about diagnostic criteria of prediabetes, prediabetes remains to have a lower reproducibility (approximately 50%) than diabetes (approximately 70%). Based on the available evidence, it appears that prediabetes defined by various alternative criterions consists of an overlapping group of individuals with one or more abnormalities in their glucose excursions. It is possible that presence of IFG and IGT identifies subjects with different pathological abnormalities in their glucose metabolism and presence of both of these signifies more advanced impairment in overall glucose homeostasis.

Table 1 Current Diagnostic Criteria For Prediabetes

TEST	ADA	WHO	IEC
FPG	100-125mg/dl	110-125mg/dl	NA
2hBG	140-199mg/dl	140-199mg/dl	NA
HbA1c	5.7-6.4%	NA	6.0-6.4%

Abbreviations:
2hBG - 2-hour postload blood glucose;
ADA- American Diabetes Association;
FPG- fasting plasma glucose;
HbA1C- hemoglobin A1C;
IEC- International Expert Committee;
NA-not applicable;
WHO- World Health Organization

Current criteria for IGT, IFG and HbA1C-based prediabetes will identify different people (17-19). The ADA guidelines for the diagnosis of diabetes explicitly recommend that any single elevation of fasting glucose, 2-h glucose, or HbA1C be confirmed with a second test (a different test in the same blood sample or second test at a different time point) (20). No such recommendations presently exist for confirming a diagnosis of prediabetes. The reliance on a single measurement to identify prediabetes will result in some false-positive diagnoses (21).

Other glycemic markers such as glycated albumin and fructosamine have a potential for identifying prediabetes. These markers strongly correlate with HbA1C and FBG (22,23), are associated with incident diabetes independent of HbA1C and FBG , predict macrovascular (24) and microvascular complications (25), and provide prognostic value similar to HbA1C with regard to the risk of cardiovascular disease, end-stage renal disease, and retinopathy . However, these biomarkers have not been incorporated into guidelines, and there is currently no consensus on the use of glycated albumin or fructosamine in clinical practice for defining glycemic status (26).

Heatlh Risks Associated With Prediabetes

A significant proportion of individuals with prediabetes will develop diabetes over time, though the magnitude of this risk depends substantially on the prediabetes definition used. The risk of diabetes among persons with prediabetes is a central question, but it is also somewhat tautological. Diabetes is defined by elevated fasting glucose, 2-h glucose, or HbA1C. Thus, those individuals with the highest fasting glucose, 2-h glucose, or HbA1C within the prediabetic range will, by definition, be at the highest risk for developing diabetes. Nonetheless, many individuals with prediabetes do not progress rapidly or do not progress at all to diabetes. Some individuals, especially those with glycemic values at the lower end of the prediabetes range, will revert to normal glucose tolerance or normal fasting glycemia.

A 2007 meta-analysis of community-based cohort studies reported an absolute annual incidence of diabetes among individuals with WHO-IFG or IGT of 5–10% (27), with a relative risk for diabetes versus normoglycemia of 6.35 [95% confidence interval (CI) 4.87–7.82] for IGT; 5.52 (3.13–7.91) for isolated IGT; 4.66 (2.47–6.85) for IFG; 7.54 (4.63–10.45) for isolated IFG; and 12.13 (4.27–20.00) for both IFG and IGT (27). In a 2010 meta-analysis, the IEC-HbA1C prediabetes state (6.0–6.5%) was associated with a relative risk for diabetes of approximately 20 compared with HbA1C <5%, with a 5-year cumulative incidence of diabetes ranging from 25% to 50% (28).

A large 2018 meta-analysis (103 prospective cohort studies with up to 24 years of follow-up) found relative risks for diabetes of 4.32 for ADA-IFG, 5.47 for WHO-IFG, 3.61 for IGT, 6.90 for IFG and IGT, 5.55 for HbA1C >5.7%, and 10.10 for HbA1C >6.0% (29). Regardless of the definition, prediabetes identifies individuals at high risk for progression to diabetes, although absolute and relative risks vary depending on the definition used. IFG and IGT definitions tend to be associated with similar risks of future diabetes (with a higher risk if IFG and IGT are combined), whereas HbA1C definitions have the highest risk. As mentioned earlier, HbA1C cut points for prediabetes are more specific than those for FBG or 2hBG. Thus, HbA1C-defined prediabetes identifies fewer but higher-risk individuals, as borne out in recent individual epidemiologic studies and meta-analyses. There are fewer data on rates of regression to normoglycemia among individuals with prediabetes. In a meta-analysis, the relative risk of regression from IGT to normoglycemia (compared with people who remained normoglycemic) was 0.33 (95% CI 0.23–0.43) over a 1-year follow-up period (27), suggesting low but not insubstantial rates of regression. In a different study of IFG, the reported cumulative proportion of individuals who reverted to normoglycemia by 10 years of follow-up was 55% (30). A meta-analysis of prospective studies (n = 18 studies involving 11,287 participants), which defined prediabetes by HbA1C using either the ADA (HbA1C of 5.7–6.4%) or the IEC (HbA1C 6.0–6.4%) definitions of prediabetes, reported cumulative incidence of regression ranging from 14% to 39% within 1–5 years of follow-up and from 17% to 31% for 6–11 years of follow-up (29). Some degree of regression might be expected in populations receiving lifestyle interventions to mitigate prediabetes risk; however, some of this regression undoubtedly reflects the known variability in tests of glycemia, which are highest for 2-h glucose, lowest for HbA1C, and intermediate for fasting glucose (31).

CONCLUSION

Prediabetes is common and a major public health issue globally. Individuals with prediabetes have a high risk of progression to diabetes and elevated risks of cardiovascular disease, kidney disease, and death. Lifestyle modification is the first-line therapeutic approach to prediabetes but is often difficult to sustain in practice. A lifestyle approach has a number of advantages, including potential cost-effectiveness and the adaptability to various settings worldwide. However, several challenges have limited cogent prediabetes treatment strategies, including the lack of a standardized clinical and public health approach for individuals with prediabetes as well as issues related to cost and reimbursement.

there remains a need for systematic evaluation of the health outcomes of prediabetes and the benefits if any of its early treatment. It is very important to choose the right outcomes for such a study. Moreover, the criteria used to define prediabetes needs to be refined in accordance with the long-term medical outcomes. While these studies seem essential, the length of duration needed to study the adverse outcomes of prediabetes and the low frequency of some of these outcomes may be a limiting factor for such studies. At present there is no concrete evidence to formulate clinical guidelines for the treatment of prediabetes. Lifestyle interventions remain an essential part of the management of prediabetes.

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