

Prediabetes and cardiovascular diseases: a serious but overlooked issue

Abstract

The elevated risk of cardiovascular diseases and prediabetes is a practical area of concern although there is dearth of data coming from across the globe despite epidemiological studies connecting the duo. Recent meta-analysis in BMJ reported relative risk of 1.15 for a composite of cardiovascular disease and 1.16 for ischaemic heart disease in the prediabetic population as opposed to that in the population with normal sugar levels. A recent research placed a 25% elevated risk of myocardial infarction in the prediabetic population along with greater chances of undergoing various forms of revascularization. Prediabetes although defined by numbers and classified as IFG (Impaired fasting glucose) and IGT (Impaired glucose tolerance), debates still exist on the cutoffs to be used and also on use of HbA1C to define prediabetes. Recent Chinese study looked at age specific cut offs for the interplay between prediabetes and elevated cardiovascular disease risk and found family history as an important pointer in the younger age group and life style factors to be of importance in older age group. More research and studies encompassing the global population at large needs to be done to eliminate the population bias involved in a nationwide studies, with insights into the Sirtuin proteins SIRT1- 7 and its modulators, whose impact on cardiovascular disease is well established.

Keywords: prediabetes, cardiovascular disease, sirtuin

Volume 12 Issue 4 - 2024

Soumyabrata Roy Chaudhuri, Debmalya Sanyal, Anirban Mazumdar

University of New Castle, Australia & KPC Medical College
Kolkata, India

Correspondence: Debmalya Sanyal, University of New Castle, Australia & KPC Medical College Kolkata, India, Email drdebmalysanyal@gmail.com

Received: August 28, 2024 | **Published:** November 05, 2024

Introduction

In the realm of public health, the intricate relationship between prediabetes and cardiovascular diseases (CVD) has emerged as a serious concern, often underestimated and overlooked. It seems to be the need of the hour because in the countries like India, which house a large number of diabetic individuals without a structured health care targeting diabetes; the number of prediabetics by far exceed the number of diabetics as seen in the national cross sectional ICMR INDIAB 17 study where the number of diabetics were estimated to be 101.3 million and the number of prediabetics were estimated to be 136 million.

Discussion

Epidemiological studies such as those conducted by the DECODE (Diabetes Epidemiology: collaborative analysis of diagnostic criteria in Europe) and Funagata Diabetes study have consistently highlighted prediabetes as a potent predictor of CVD.^{1,2} The San Antonio Heart Study, further reinforces this notion, providing evidence that the risk of CVD increases well before the clinical onset of diabetes.³ Supporting this evidence, a recent meta-analysis led by Xiaoyan Cai and colleagues and published in BMJ in 2020 reported a relative risk of 1.15 for composite cardiovascular disease and 1.16 for coronary heart disease in individuals with prediabetes, underscoring the seriousness of the issue.⁴ In concrete terms, these findings equate to 7 additional deaths per 10,000 person-years and nearly 9 extra cases of cardiovascular disease per 10,000 person-years in the prediabetes population compared to those with normal blood sugar levels.

The alarmingly high stakes associated with prediabetes become even more evident in the context of a presentation at ENDO 2022 in Atlanta.⁵ Researchers presented data from 1.79 million patients hospitalized with myocardial infarction, indicating that 1% of them were prediabetic. After accounting for non-modifiable risk factors such as age, sex, and family history, along with modifiable risk factors

like blood pressure, cholesterol, smoking, and obesity, the research findings indicated that individuals with prediabetes faced a 25% higher likelihood of experiencing a myocardial infarction. Moreover prediabetes subjects, faced 45% increased odds of percutaneous intervention and double the risk of undergoing coronary artery bypass surgery compared to normoglycemic subjects.⁶

The term “prediabetes” itself has a history marked by debate. Initially discarded by the World Health Organization (WHO) in 1980 due to concerns about unnecessary alarm, it resurfaced in 2005 through the American diabetes Association (ADA) to encompass reduced fasting glucose (IFG) and reduced glucose tolerance (IGT).⁷ The adoption of HbA1C as an alternative to plasma glucose for identifying prediabetes, suggested by an ADA committee in 2009, faced resistance from WHO due to insufficient evidence.⁸

The controversy extends to the classification of IFG, with shifting cutoffs and ongoing debates. A paper by Xie S et al., focusing on age, prediabetes, and CVD, considered IFG cutoffs as 110-125 mg/dl (6.1-7 mmol/L).⁹ The unresolved question of whether elevated glucose levels directly cause atherosclerosis is central to this discussion. Meta-analyses, such as the one conducted by Ford et al, have provided mixed evidence, with varying risks associated with IFG and IGT.^{10,11}

In a recent study from China, researchers delved into the age-specific nuances of prediabetes and cardiovascular disease.¹² Stratifying participants into age groups (20- < 40yrs and > 40yrs), the study utilized the Framingham risk score and the China PAR model. Notably, they found differing patterns in cardiovascular disease prevalence and risk factors between the two age groups. CVD prevalence of was significantly higher (2.85%) in the older group compared to the younger group (0.29%). In the study, 11.11% of the younger cohort and 29.59% of the older group exhibited an intermediate/high risk of cardiovascular disease (CVD) as per the ASCVD Risk prediction equation for a ten-year span. It's noteworthy that despite this heightened risk, these individuals did not currently

have the disease. Furthermore, the study linked the 10-year CVD risk in the younger group more closely to a family history of CVD rather than their lifestyle choices. In contrast, for the older prediabetic demographic, both men and women, lifestyle factors and the living environment emerged as the primary contributors to the risk of CVD.

However due country specific risk equations, the universal applicability of these findings have to be evaluated in a global study. With internationally accepted CVD risk engines having varying lower age limits, the challenge lies in risk assessment for those under 25 years old. Furthermore, defining lipid targets to mitigate CVD risks in prediabetes remains elusive, necessitating large-scale studies across different races to formulate effective management protocols. These data, not only reaffirms the association between prediabetes and CVD but also unveils age-specific nuances that should guide tailored interventions for this high-risk population.

Prediabetes leads to the vascular inflammation and oxidative stress that is a key pathophysiological process in the evolution of cardiovascular disease. In this context the sirtuin family of proteins (SIRT) seven in number have gained importance in cellular biology. Till date seven proteins of this family (SIRT 1-7) have been identified which play numerous important roles in cell biology such as inflammation oxidative stress, apoptotic process and also in metabolism. Modulators of SIRT proteins are being looked into to address different kinds of pathologies including arthritis, cancer, respiratory illnesses and also cardiovascular disease and can in future become a key to reduce the cardiovascular disease burden in diabetes.¹³

Conclusion

It is the need of the hour to address the ever-increasing burden of cardio metabolic disease. We need to be more proactive with an upstream approach with early detection and risk factor modification at the prediabetes stage, independent of age to arrest the epidemic of cardiovascular disease and this is a clarion call for increased awareness, research, and targeted strategies like modulation of Sirtuin proteins in this high risk population to reduce cardiovascular disease burden.

Acknowledgments

None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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