Prospective Cohort Study on Modifiable Risk Factors and Long-Term Risk of T2 DM among Individuals with a History of Gestational Diabetes Mellitus

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Abstract

Objectives: This prospective cohort study aimed to assess how five modifiable risk factors individually and collectively influenced the risk of T2 DM in women with a history of gestational diabetes mellitus (GDM) and whether these effects varied based on obesity and genetic predisposition to T2 DM.

Methods: In the Department of Medicine, NSMCH, Patna we examined 4,275 women with a history of GDM from 2021 to 2022. Self-reported clinically diagnosed T2 DM case were identified. Five modifiable risk factors were evaluated: not being overweight or obese (BMI < 25.0), following a high-quality diet (top 40% of the modified Alternate Healthy Eating Index), engaging in regular exercise (≥150 min/week of moderate or ≥75 min/week of vigorous intensity), moderate alcohol consumption (5.0-14.9 g/day), and non-smoking status. Genetic susceptibility was assessed with a risk score based on 59 diabetes-associated single nucleotide polymorphisms in a subset (n=1372).

Results: In a 27.9-year follow-up, 924 women developed T2 DM. Having all five risk factors at optimal levels reduced the risk by over 90% compared to those with suboptimal levels. Hazard ratios for one, two, three, four, and five optimal factors versus none were 0.94, 0.61, 0.32, 0.15, and 0.08, respectively. This trend persisted in overweight/obese and genetically susceptible participants. Among women with a BMI ≥25 (n=2227), having four optimal factors resulted in a hazard ratio of 0.40. In those with higher genetic susceptibility, four optimal factors had a hazard ratio of 0.11, while all five optimal factors showed no cases of T2 DM.

Conclusions: In women with a history of gestational diabetes mellitus, each additional optimal modifiable risk factor was linked to a progressively reduced risk of T2 DM. These associations remained significant for individuals who were overweight/obese or had a higher genetic predisposition to T2 DM.

Keywords: Risk Factors, T2 DM, Gestational Diabetes Mellitus

Introduction

T2 DM mellitus (T2 DM) arises as a consequence of a complex interplay between lifestyle and genetic determinants, wherein lifestyle modifications exhibit encouraging potential in the realm of disease prevention. The empirical evidence suggests that a substantial proportion, up to 90%, of instances can be postponed or prevented by means of prudent weight control and adoption of healthy lifestyle behaviors [1]. Furthermore, the implementation of a salubrious lifestyle may serve to ameliorate the augmented susceptibility linked to hereditary inclination towards T2 DM. Notwithstanding the substantiated evidence affirming the advantageous outcomes associated with a salubrious way of life, the prevalence of T2 DM continues to pose a substantial public health quandary. This predicament is primarily attributable to elevated rates of obesity and suboptimal compliance with health-promoting behaviors.

Based on the findings presented in the 2020 National Diabetes Statistics Report, it has been determined that a notable proportion of the adult population in the United States [2], specifically 14.7%, corresponding to a staggering 37.1 million individuals, are afflicted with diabetes. It is noteworthy that the vast majority of these cases, approximately 90-95%, are classified as T2 DM. The diagnosis of metabolic issues frequently experiences a delay, wherein the manifestations of said issues become apparent approximately 4-6 years prior to the actual diagnosis [3, 4]. This delay in diagnosis has the potential to result in irreversible damage to the cardiovascular, renal, and neurological systems. Therefore, the timely detection of populations at elevated risk is imperative in the prevention of T2 DM and its corresponding complications.

Females who have encountered gestational diabetes mellitus (GDM) constitute a notable subset of individuals at elevated risk. GDM is a pregnancy complication that exhibits a prevalence of approximately 8% among pregnancies in the United

States [5]. This prevalence is on the rise, primarily attributed to factors such as maternal age and obesity. In contrast to the overall populace, females with a previous diagnosis of GDM encounter a substantially elevated risk, potentially up to ten times greater, of developing T2 DM [6]. GDM reveals an inherent disturbance or vulnerability in cardiometabolic regulation during its initial phases, presenting a chance for timely intervention to impede the advancement towards T2 DM.

The association between specific dietary and lifestyle factors and the risk of developing T2 DM in high-risk women with GDM has been established. However, there is a dearth of comprehensive knowledge regarding the collective influence of these modifiable factors on long-term risk [7]. Furthermore, the potential impact of maintaining optimal levels of these factors on the reduction of T2 DM risk remains uncertain, particularly in individuals who exhibit overweight or obesity or possess a genetic predisposition to this ailment [8]. The examination of this correlation is of utmost importance, considering the elevated occurrence of obesity and genetic predisposition toT2 DM in females diagnosed with GDM in comparison to the overall populace. In order to address the existing gaps in research, a prospective study was undertaken to evaluate the impact of adherence to optimal levels of five modifiable risk factors on the risk of developing T2 DM in women with a history of GDM. The modifiable risk factors considered in this study included maintaining a healthy body mass index, following a high-quality diet, engaging in regular physical activity, consuming alcohol in moderation, and refraining from smoking. The data utilized for this study was obtained from Patna. Additionally, the study investigated the potential impact of obesity status or inherent genetic predisposition to T2 DM on the aforementioned associations.

Methods

Study Population:

The research focused on women with a history of gestational diabetes mellitus (GDM) within the Department of Medicine, NSMCH, Patna. Patients initially enrolled 6,429 registered female nurses aged 24-44 years. They were followed up biennially. Ethical approval was obtained, and questionnaire completion indicated consent. The study began in 2021 when detailed dietary information was collected.

Inclusion criteria encompassed women with a history of GDM before 2021 or an incident GDM report between 2021-2022.

Exclusions involved multiple gestation pregnancies, T2 DM history, cardiovascular diseases, or cancer before the first GDM-related questionnaire. The final sample included 4,275 women, with an 88% follow-up rate as of June 2022.

Risk Factor Assessment:

The study examined five modifiable risk factors: body mass index (BMI), diet quality, physical activity, alcohol consumption, and smoking. Participants reported height and weight every two years, validated against measured weight. Dietary data were collected every four years. Physical activity was reported every 2-6 years. Smoking status and alcohol consumption were assessed biennially. Cumulative averages represented long-term behavior.

Outcome Assessment:

Physician-diagnosed T2 DM was confirmed through supplemental questionnaires. Self-reported diagnoses were validated against medical records.

Covariate Assessment:

Participants reported personal, lifestyle, and reproductive details. Genetic data were available for some participants through genome-wide association studies. An unweighted genetic risk score was constructed based on 59 associated SNPs.

Statistical Analysis:

Cox proportional hazards models calculated adjusted hazard ratios. The study examined individual risk factors, combined risk factors, and their interaction with obesity, family history, and genetic susceptibility. Sensitivity analyses accounted for reverse causality, proportional hazards assumptions, and changes in risk factor levels over time.

Results

Study Duration and Diabetes Cases: The study identified 924 new cases of T2 DM among 4,275 women with a history of gestational diabetes mellitus (GDM).

Baseline Characteristics: Women with optimal levels of four or more modifiable risk factors were generally older at first birth, had longer breastfeeding durations, were more likely to be pre-menopausal, but were less likely to have a family history of diabetes.

Individual Modifiable Risk Factors:

- Higher body mass index (BMI) was strongly associated with increased T2 DM risk. The risk escalated significantly with higher BMI categories.
- Physical activity was inversely related to T2 DM risk in a dose-dependent manner.
- The Alternate Healthy Eating Index (AHEI) score showed an inverse association with T2 DM risk, but this association diminished when adjusted for BMI.

- Alcohol consumption had a U-shaped association, with the lowest risk observed in moderate drinkers (5.0-14.9 g/day).
- Smoking was not significantly related to T2 DM risk.

Combined Modifiable Risk Factors:

- The number of optimal levels of modifiable risk factors was inversely related to T2 DM risk. Having more optimal factors was associated with significantly lower risk.

- Even after removing the BMI component and adjusting separately for it, the inverse association remained significant.

Modifiable Risk Factors and BMI Status: BMI status (<25.0 vs. ≥25.0) did not significantly modify the associations. The inverse relationship between optimal modifiable risk factors and T2 DM risk persisted even among overweight or obese women.
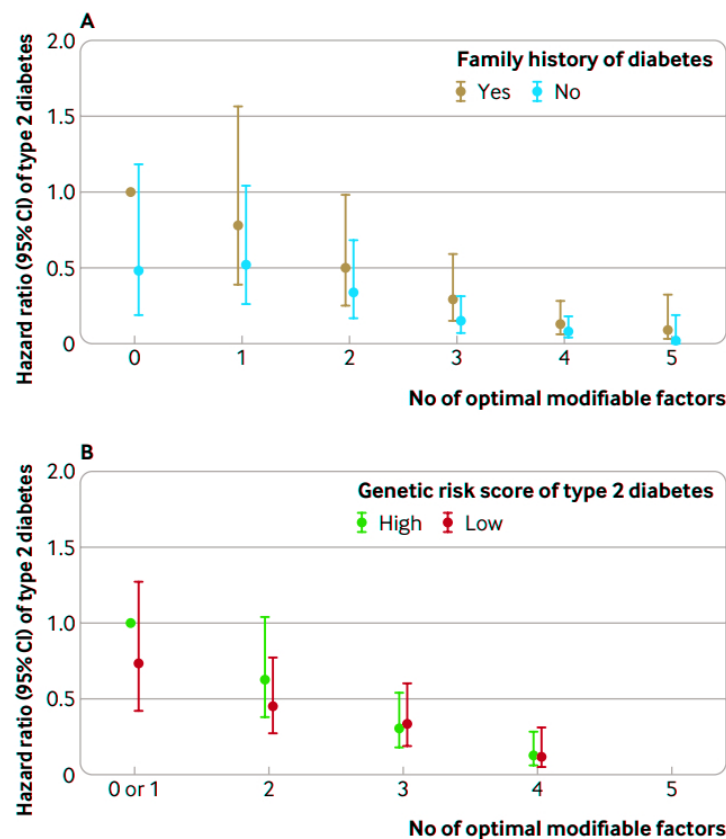

Figure 1: According to (A) family history of diabetes (yes vs no) and (B) genetic risk score of type 2 diabetes (high vs low (above vs below median score of 68.0)) in the Nurses' Health Study II, the risk of T2 DM in women with a history of GDM is determined by the number of optimally modifiable factors. The number of risk factors and covariate status were combined to produce joint groups. Depending on the model, the high risk group was defined as having a high genetic risk score, a family history of diabetes, and an optimal level of zero or fewer factors as the reference group. Confidence interval, or CI

Modifiable Risk Factors, Family History, and Genetic Susceptibility: The inverse associations between the number of optimal modifiable factors and T2 DM risk held true regardless of family history of diabetes and genetic susceptibility. Women with a more favorable modifiable risk factor profile had a substantially reduced risk of T2 DM, even if they had a family history or higher genetic susceptibility.

Joint Categories of Modifiable Risk Factors and Family History/Genetic Susceptibility: Having a more favorable modifiable risk factor profile appeared to nearly eliminate the increased risk of T2 DM associated with family history of diabetes or greater genetic susceptibility.

Sensitivity Analyses: The conducted sensitivity analyses, encompassing appropriate adjustments for multiple factors and exclusions, provided further support for the primary findings. Temporal variations in the quantity of optimal risk factors have demonstrated a significant correlation with the risk of developing T2 DM.

The present study provides a comprehensive analysis of the considerable influence exerted by

modifiable risk factors, such as BMI, physical activity, dietary patterns, alcohol intake, and tobacco use, on the susceptibility to T2 DM in women with a previous diagnosis of gestational diabetes mellitus. The substantial reduction in risk is observed when optimal modifiable factors are present, irrespective of variables such as family history and genetic predisposition. The potential influence of obesity status or underlying genetic susceptibility to T2 DM on these associations was investigated.

Discussion

In a comprehensive longitudinal investigation involving women with a prior medical history of gestational diabetes, the adoption of a quintet of salubrious lifestyle practices exhibited a substantial reduction in the susceptibility to T2 DM, surpassing the 90% threshold. This noteworthy outcome persisted even upon meticulous consideration of additional risk factors associated with the development of diabetes. The aforementioned decrease was noted among women classified as overweight or obese, as well as those who possessed a genetic predisposition.

The findings of the study exhibited disparities in comparison to prior research, primarily attributable to the extended duration of follow-up, exceptional participant retention rates, and notable inclusion of individuals from diverse racial and ethnic backgrounds. The implementation of a wholesome lifestyle, even in the advanced stages of life, can serve as a preventive measure against the onset of T2 DM [9].

The augmentation of healthy lifestyle behaviors has been found to exhibit a negative correlation with the incidence of T2 DM, particularly in the demographic of women who are overweight or obese. The attainment of substantial weight loss poses a formidable challenge, thus necessitating the adoption of additional health-promoting behaviors as a crucial component [10].

Weight is a pivotal determinant in the susceptibility to diabetes, with certain lifestyle factors potentially influencing this risk by exerting an impact on body weight. The correlation between physical activity and a reduced incidence of T2 DM remains evident, even after adjusting for body weight [7].

The study revealed a lack of robust association between smoking and the risk of developing T2 DM in younger individuals. This finding may be attributed to the moderate smoking patterns observed and the heightened motivation to cease smoking as a result of gestational diabetes.

The consumption of alcohol within moderate limits has been observed to exhibit an inverse correlation with the risk of developing T2 DM [11]. However, it is imperative to acknowledge that even moderate alcohol intake may entail potential risks for the manifestation of various other health conditions. It is crucial to emphasize that individuals who are pregnant must abstain from alcohol consumption entirely in order to safeguard their well-being and that of the developing fetus.

The study underscores the significance of adopting a healthful lifestyle as a preventive measure against the onset of T2 DM, even among individuals deemed to be at a heightened risk.

Conclusion

In this prospective cohort study conducted among women who have a previous medical history of gestational diabetes mellitus, we have observed a duration of 28 years for the follow-up period. During this study, we have successfully identified a significant inverse association between the quantity of modifiable risk factors that are considered optimal and the subsequent risk of developing T2 DM. Individuals who exhibited optimal levels of all five modifiable factors subsequent to the index pregnancy demonstrated a risk reduction exceeding 90% in the development of T2 DM, in contrast to those who did not possess any of these factors. Significantly, the observed decrease in the likelihood of developing T2 DM in relation to optimal levels of modifiable risk factors was apparent, particularly among women at a heightened risk due to being overweight or obese, or possessing a higher genetic predisposition.

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