

Type 1 Diabetes Mellitus and the Risk of Male Infertility: A Mendelian Randomization Study

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Abstract

Multiple studies have indicated that type 1 diabetes mellitus (T1DM) disrupts male reproductive function and contributes to infertility. In contrast, type 2 diabetes mellitus (T2DM) has been demonstrated to exert a direct causal influence on male infertility, as validated by Mendelian randomization (MR) analysis. The magnitude and direction of the causal association between T1DM and male infertility, however, remain uncertain. To clarify this potential relationship, a two-sample MR (2SMR) analysis was conducted. Data related to male infertility and T1DM in European populations were retrieved from the publicly available Integrated Epidemiology Unit (IEU) Open genome-wide association studies (GWAS) database. The outcome dataset included 680 male infertility cases and 72,799 controls. Five MR approaches—MR-Egger, weighted median estimation (WME), simple mode, weighted mode (WM), and inverse-variance weighted (IVW)—were applied to assess the causal association between T1DM and male infertility. Among these, the IVW method served as the primary analytical strategy. To assess the potential causal association between T1DM and male infertility, a multivariable MR analysis was conducted. The 2SMR results indicated that T1DM was linked to an increased genetic predisposition to male infertility among Europeans (IVW, odds ratio (OR): 0.914, 95% confidence interval (CI): 0.849–0.985, $P = 0.019$; MR-Egger, OR: 0.870, 95% CI: 0.778–0.972, $P = 0.018$; WME, OR: 0.908, 95% CI: 0.818–1.008, $P = 0.071$; WM, OR: 0.918, 95% CI: 0.838–1.005, $P = 0.072$; simple mode, OR: 1.004, 95% CI: 0.803–1.254, $P = 0.974$). Heterogeneity tests yielded P -values of 0.866 and 0.851, indicating the absence of significant heterogeneity. The Egger-intercept ($P = 0.240$) revealed no evidence of horizontal pleiotropy. A leave-one-out analysis further confirmed the stability of the results. These findings provide statistical support for a causal link between T1DM and male infertility based on data from 680 European cases. However, given that the ORs approximate unity, the directionality of the association remains unclear. Considering existing literature and known diabetic pathophysiological impacts on the reproductive system, the results suggest that T1DM contributes to an elevated risk of male infertility among Europeans. Further research is warranted to clarify the underlying biological mechanisms connecting T1DM and male infertility, which may inform preventive strategies for affected male populations.

Keywords

Mendelian Randomization, Type 1 Diabetes Mellitus, Male Infertility, GWAS