Does Type 1 Diabetes Affect Male Infertility: Type 1 Diabetes Exchange Registry-Based Analysis

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Abstract

Introduction The prevalence of type 1 diabetes (T1D) has been increasing over the last few decades and is commonly believed to negatively impact male fertility. We aimed to estimate the prevalence of infertility among men with T1D and to characterize potential clinical predictors for male infertility among men with T1D.

Methods We used data collected from the T1D Exchange Registry from 2012 to 2017. Men with T1D completed an infertility questionnaire indicating whether they had ever had problems conceiving a child or had ever received abnormal results from infertility testing. Collected data included age at questionnaire, age at diagnosis of T1D, duration of T1D, race/ethnicity, insurance status, education level, annual household income, hemoglobin A1c (HbA1c), low density lipoprotein (LDL), diabetic retinopathy, micro/macroalbuminuria, and renal failure.

Results The survey was completed by 2171 registry members, 33 (1.5%) of whom reported male infertility. Mean age at questionnaire was 38 and 56 years in the fertile and infertile groups, respectively ($P < 0.001$). There was no statistically significant difference in the mean age at T1D diagnosis (16 and 27 years), mean duration of T1D at questionnaire (22 and 30 years), white non-Hispanic ethnicity (1906/2138, 89% versus 30/33, 91%), private insurance (1509/2138, 79% versus 30/33, 91%), and annual household income in US dollars ≥ $100 000 (757/2138, 45% versus 16/33, 55%) in the fertile and infertile men, respectively. On multivariate analysis, for each year of advancing age, men were 5% more likely to experience infertility. Age at questionnaire was the only significant predictor of infertility (OR 1.05; 95%CI 1.03 to 1.08). Age at T1D diagnosis (OR 1.01; 95%CI 0.99 to 1.04), duration of T1D (OR 0.99; 95%CI 0.96 to 1.01), mean HbA1C (OR 1.03; 95%CI 0.77 to 1.37), diabetic retinopathy (OR 1.04; 95%CI 0.50 to 2.15), and mean LDL (OR 1.01; 95%CI 0.99 to 1.02) failed to independently predict infertility; however, presence of renal failure (OR 3.38; 95%CI 0.94 to 12.13) and micro/macroalbuminuria (OR 1.27; 95%CI 0.42 to 3.82) trended toward increased odds of infertility.

Conclusions This study highlights the prevalence of male infertility among men with T1D. Beyond age, there were no independent clinical predictors for male infertility among men with T1D; however, men with clinical evidence of diabetes-associated renal compromise trended toward greater odds of infertility. Further studies of fertility in this growing, at-risk population are warranted.

Key Words

Type 1 diabetes, male infertility, clinical predictors

Competing Interests

Dr Hehemann is a consultant for Boston Scientific Corporation. The remaining authors declare no competing interests.

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Introduction

The prevalence of type 1 diabetes (T1D) has been increasing worldwide and in the United States over last few decades and commonly manifests during childhood. T1D is an autoimmune destruction of the pancreatic beta-cells that ultimately leads to failure of insulin production. Several important risk factors for T1D have been identified and include obesity, family history, and genetic polymorphisms[1,2]. More importantly, T1D is associated with an increased risk of cardiovascular disease and mortality, and clinical prognosis worsens if T1D is left untreated[3].

It has been suggested that male infertility is not a unique disease of the reproductive axis, but rather a clinical marker underpinning overall health and well-being in men[4,5]. While research has focused on the relationship between metabolic syndrome, obesity, dyslipidemia, hypertension, and insulin resistance or genitourinary malignancies on male infertility, there is paucity of contemporary literature specifically addressing the detrimental effects of T1D on male fertility[6,7].

In this study, we sought to characterize the prevalence of infertility among men with T1D. We hypothesized that the rate of infertility among men with T1D would be higher than rate reported in the general population. Additionally, we sought to identify clinical predictors of infertility among men with T1D.

Materials and Methods

Study population and design

The study was conducted using the large dataset collected from the T1D Exchange Registry[8]. The protocol was approved by the University of Washington Institutional Review Board, and study participants provided written informed consent. The T1D Exchange Registry provides demographic and clinical information on individuals diagnosed with T1D in the United States, offering a broad representation of pediatric and adult patients with T1D. Data are collected for the registry database at enrollment and then once a year. Data are obtained through (1) completion of a questionnaire by the participant or parent of the participant and (2) retrieval of information collected from the medical records[8].

Fertility was determined using 2 questions on male infertility in the T1D Exchange Registry questionnaire: (1) Have you ever had problems conceiving a child? Yes/No (2) Have you ever received infertility testing? Yes/No; if yes, (2a) were the test results normal? Yes/No (Appendix 1). Men were considered infertile if they indicated they had previously had problems conceiving a child and/or if they had abnormal test results on infertility testing. Otherwise, men were assigned to the

TABLE 1.

Patient demographics and characteristics

Variable	Fertile N = 2138 n (%)	Infertile N = 33 n (%)
Age at questionnaire years (mean)[a]	38	56
18–25	872 (41)	0
26–34	239 (11)	0
35–49	407 (19)	13 (39)
≥ 50	620 (29)	20 (61)
Age at diagnosis years (mean)	16	27
<6	340 (16)	4 (12)
6–12	784 (37)	6 (18)
13–17	345 (16)	4 (12)
18–25	231 (11)	5 (15)
26–49	396 (19)	8 (24)
≥ 50	42 (2)	6 (18)
Duration of T1D at questionnaire years (mean)	22	30
1–9	400 (19)	2 (6)
10–19	818 (38)	7 (21)
20–49	817 (38)	23 (70)
≥ 50	103 (5)	1 (3)
Race/Ethnicity		
White non-Hispanic	1906 (89)	30 (91)
Black non-Hispanic	46 (2)	1 (3)
Hispanic or Latino	118 (6)	2 (6)
Others	68 (3)	0
Insurance status		
Private insurance	1509 (79)	30 (91)
Other insurance	381 (20)	3 (9)
No insurance	11 (<1)	0
Education level		
<High school	95 (5)	0
High school/associates	981 (46)	10 (30)
Bachelors	660 (31)	11 (33)
Masters	239 (11)	6 (18)
Professional/doctorate	136 (6)	6 (18)
Annual household income (US$)		
< 35 000	285 (17)	3 (10)
35 000–< 50 000	133 (8)	2 (7)
50 000–< 75 000	232 (14)	3 (10)
75 000–< 100 000	263 (16)	5 (17)
≥ 100 000	757 (45)	16 (55)

[a] *P* < 0.001

fertile group.

Collected data included age at questionnaire, age at diagnosis of T1D, duration of T1D, race/ethnicity, insurance status, education level, annual household income, hemoglobin A1c (HbA1c), low density lipoprotein (LDL), diabetic retinopathy, micro/macroalbuminuria, and renal failure. Linear regression multivariate models were performed to assess the clinical predictors of T1D patients associated with male infertility.

We sought to determine the prevalence of infertility in males with T1D. Secondarily, we sought to identify the clinical predictors of infertility among T1D men.

Statistical analysis

We used the Mann-Whitney U test and chi-square test for continuous and categorical variables, comparing the fertile and infertile groups. Multivariable analysis was also performed to identify these clinical factors associated with male fertility. Statistical significance was defined by P-value < 0.05. All data analysis was performed using statistical software R version 3.3.2.

Results

In this study, a total of 2171 out 3955 men completed the infertility portion of the year 5 questionnaire within the T1D Exchange Registry from 2012 to 2017. This database includes 18 743 participants from 79 clinic sites. T1D Exchange Clinic Network is coordinated by the Jaeb Center for Health Research, a nonprofit clinical research coordinating center in Tampa, Florida.

Thirty-three men (1.5%) reported male infertility. Mean age at questionnaire was 38 and 56 years in the fertile and infertile groups, respectively (P < 0.001). There was no statistically significant difference in the mean age at T1D diagnosis (16 versus 27 years), mean duration of T1D at questionnaire (22 versus 30 years), white non-Hispanic ethnicity (1906/2138, 89% versus 30/33, 91%), private insurance (1509/2138, 79% versus 30/33, 91%), and annual household income in US dollars ≥ $100 000 (757/2138, 45% versus 16/33, 55%) in the fertile and infertile men, respectively (Table 1).

On multivariate analysis, for each year of advancing age men were 5% more likely to experience infertility. Age at questionnaire was the only significant predictor of infertility (OR 1.05; 95%CI 1.03 to 1.08). Age at T1D

TABLE 2.

Multivariate analysis for clinical predictors of T1D patients associated with male infertility

Variables/Predictors	Fertile N (%)	Infertile N (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age at diagnosis, years (mean)	16	27	1.05 (1.03–1.07)	1.01 (0.99–1.04)
Duration of T1D at questionnaire, years (mean)	22	30	1.04 (1.01–1.06)	0.99 (0.96–1.01)
Hemoglobin A1c (HbA1c) mg/dL (mean)	8.0	7.7	0.84 (0.64–1.10)	1.03 (0.77–1.37)
Diabetic retinopathy	566 (28)	14 (42)	0.54 (0.27–1.08)	1.04 (0.50–2.15)
Renal status				
Renal failure	32 (2)	3 (10)	7.69 (2.20–26.93)	3.38 (0.94–12.13)
Micro/macroalbuminuria	156 (8)	4 (13)	2.10 (0.72–6.16)	1.27 (0.42–3.82)
No albuminuria	1887 (91)	23 (77)	Ref	Ref
Low density lipoprotein level, mg/dL (mean)	90.5	88.4	1.00 (0.98–1.01)	1.01 (0.99–1.02)

[a]*Adjusted for age at questionnaire*

diagnosis (OR 1.01; 95%CI 0.99 to 1.04), duration of T1D (OR 0.99; 95%CI 0.96 to 1.01), mean HbA1C (OR 1.03; 95%CI 0.77 to 1.37), diabetic retinopathy (OR 1.04; 95%CI 0.50 to 2.15), and mean LDL (OR 1.01; 95%CI 0.99 to 1.02) failed to independently predict infertility; however, presence of renal failure (OR 3.38; 95%CI 0.94 to 12.13) and micro/macroalbuminuria (OR 1.27; 95%CI 0.42 to 3.82) trended toward increased odds of infertility (**Table 2**).

Discussion

Recent studies have linked diabetes mellitus (DM) (type 1 or 2) and infertility with an increased risk of developing DM among infertile men which can reach as high as 30%[9]. This association has been reproduced in a large prospective Danish in vitro fertilization registry by Glazer et al. of 39 516 men who had undergone fertility treatment with their female partner with a median follow-up time of 5.6 years. This study found 651 (1.6%) cases of type 1 or 2 DM among men with infertility (eg, oligospermia, azoospermia) with the risk being related to the severity of the underlying fertility problem[10]. In our study, 33 men out of 2171 (1.5%) with T1D reported infertility, which supports the findings of Glazer et al.[10].

Furthermore, several previous studies have suggested DM has a mild impact on semen quality. For example, DM may have its effects on male reproductive function by endocrine control of spermatogenesis, sperm maturation, and impairment of ejaculation[11].

The prevalence of abnormalities such as azoospermia, oligospermia, and aspermia may be higher in patients with DM and in elderly men[12-14]. In our study, men who were older at the time of the questionnaire were more likely to have experienced infertility, suggesting that the longer the duration of T1D, the greater likelihood of infertility in these men. Moreover, this study highlighted some common DM sequalae such as renal failure and micro/macroalbuminuria, which were found to be significantly more prevalent among infertile men. It is worth mentioning that this study did not report specific sperm abnormalities as it is questionnaire-based study (**Appendix 1**).

The findings of this study reinforce the importance of understanding the common metabolic pathway linking DM and male infertility. Cross-sectional studies have shown that even at the time of a fertility evaluation, men with reduced fertility already present with more medical comorbidities than their fertile peers[15,16]. The observation of a higher baseline prevalence of DM among men with infertility is concordant with this evidence. However, the relationship between male infertility and overall health is rather complex as several confounders may affect both. For example, as both age and smoking are known to affect semen quality[14] and diabetes risk[17], the results of this study must be interpreted with caution. Furthermore, a genetic link between DM and male infertility may exist as a recent study identified over 100 genes associated with both male infertility and several disease mechanisms, including metabolic disease pathways[18]. Further, as many genes are expressed during male germline cell differentiation, it seems plausible that possible mutations in this process could lead to both male infertility and risk of DM[19].

Our study does have some limitations that should be noted. Our questionnaire did not ask specific questions about when these patients experienced infertility, so it is difficult to interpret whether men in the infertile group experienced infertility in their 20s and 30s, or at an older age. However, we did find that men with advancing age were more likely to experience infertility, which we believe suggests that a greater duration with T1D might increase the likelihood of infertility. Secondly, our study questionnaire does not specify whether the difficulty conceiving a child was due solely to male factors or also female factors. Finally, this study asked patients with T1D to identify whether they had experienced trouble conceiving and whether they had undergone fertility testing, but did not report specific abnormalities, which would have been of interest. We believe more research should be conducted in the future to look at specific fertility abnormalities associated with DM, while our study attempted to address the overall prevalence of infertility in this population.

Conclusions

This study highlights the prevalence of male infertility among men with T1D. Beyond age, there were no independent clinical predictors for male infertility among men with T1D; however, men with clinical evidence of diabetes-associated renal compromise were more likely to be infertile. Further studies of fertility in this growing, at-risk population are warranted.

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APPENDIX 1.

Participating research centres

Infertility

The next questions are about infertility history
This will be shown to participants ≥ 18 years old.

☐ Do not wish to answer the following questions

1. Have you ever had problems conceiving a child?
   ☐ Yes ☐ No
2. Have you ever received infertility testing?
   ☐ Yes ☐ No

   If you answered yes to question 2, please answer 2a.

   2a. Were the test results normal?
   ☐ Yes ☐ No