The Association Between Male Infertility and Cardiometabolic Disturbances: A Population Based Study

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Abstract

**Aim:** Studies focusing of male infertility and cardio-metabolic disorders is insufficient and controversial. The aim of this study was to evaluate the association between male infertility and cardiometabolic disturbances in a population based Tehran lipid and glucose study.

**Material and methods:** For the purpose of the present study, we used data collected in 3rd follow up visit of Tehran Lipid and Glucose Study, which included comprehensive data on reproductive status of participants. All those who were never married, were unwillingness to have a child, had documented female infertility were excluded from the study. A total of 1611 remaining participants were further classified as two groups: men who had documented male infertility as infertile group (n = 88) and those had at least one live birth and did not have a history of primary infertility as the fertile group (n = 1523). Generalized Linear Regression model (GLM) with logit link were applied to assess the association between male infertility and cardiometabolic disturbances including diabetes mellitus, pre-diabetes, hypertension, metabolic syndrome, dyslipidemia, obesity, central obesity and chronic kidney disease after further adjustment for age and BMI.

**Results:** Compared to fertile controls, infertile men were more likely to be older, [58 (13.3) versus 53 (10.2) years (P = 0.003)]. The results of unadjusted model revealed that infertility were significantly associated with hypertension and CKD, OR = 1.8 (95%CI: 1.2, 2.9, P-value = 0.006) and OR = 1.9 (95%CI: 1.1, 3.6, P-value = 0.033), respectively. However, the significant association, which were found in crude analyses, were disappeared after adjusting for potential confounders of age and BMI. Moreover, infertility did not have any association with other cardiometabolic disturbances including diabetes and pre-diabetes, metabolic syndrome, dyslipidemia, obesity and central obesity in unadjusted and adjusted analysis.

**Conclusion:** Our study revealed that there were not any association between male infertility and cardiometabolic disturbances in a population based setting. This study is an incentive to initiate more explicit surveys concerning this topic in order to provide more accurate data on male infertility. More population-based studies with large sample size are still warranted to confirm these findings.

Introduction

Male-factor infertility as one of the most common cause of infertility are solely responsible for 10–30% of infertility cases and contribute to 50% of cases overall [1–4]. The experience of male infertility is still a major public health problem represents a negative psychological burden, health costs and ostracism and social discrimination in some contexts with a strong emphasis on child-bearing. While there has been extensive focus on the female infertility, the growing body of literature suggests an correlation between male infertility and some other chronic disorders, ranging from cardiometabolic, oncologic and autoimmune disorders to increased mortality rate later in life [5–9]. The exact underlying pathophysiology of these associations remains unclear, although it is suggested that genetic, intrauterine environment and lifestyle factors may play a role [8, 10–12].
However, studies focusing on male infertility and cardio-metabolic disorders is insufficient and controversial. Moreover, most of those studies had some important limitations including using the surrogate marker of infertility such as varicocele or childless situation of men, non-population bases setting of study which could not be representative of infertile men's population, lack of suitable adjusting for potential confounders such as age and BMI, thus limiting the interpretability of those findings. In this respect, Eisenberg et al. (2011) evaluated the relationship between the fatherhood and the risk of cardiovascular death among the US men in average of 10.2 years and found that childless men had elevated risk of cardiovascular mortality after the age of 50 compared to men with two or more children [13]. However, since the childless men may not necessarily be infertile, the results of this study should be interpreted with caution. In another epidemiological study, Wang et al. reported that men with varicoceles have a higher incidence of heart disease, diabetes and hyperlipidemia compared to men with vasectomy [14]. Another retrospective cohort study using national insurance database reported that men diagnosed with male factor infertility had a significantly higher risk of developing diabetes and ischemic heart disease in the years after an infertility evaluation compared to men receiving only fertility testing [15]. However, although varicoceles may contribute to male infertility, the presence of a varicocele does not necessarily imply infertility, thus limiting the interpretability of the data.

Due to lack of data available, the aim of this study was to evaluate the association between male infertility and cardiometabolic disturbances in a population based Tehran lipid and glucose study.

**Material And Methods**

The participants in current study were selected from the Tehran Lipid and Glucose Study (TLGS). The TLGS is an ongoing, long-term, population-based prospective study initiated in 1998 to assess the prevalence and risk factors of noncommunicable diseases in a representative population sample of men and women in Tehran, Iran; eventually a total of 15005 individuals, aged ≥ 3 years, were followed every 3 years follow-up, to document data on demographic, anthropometric, reproductive and metabolic characteristics, general physical examinations as well as laboratory measurements. Detailed descriptions of the TLGS have been published elsewhere [16, 17]. Our study proposal was approved by the ethics committee of Research Institute for Endocrine Sciences, and written, informed consent was obtained from all participants after explaining to them of the purpose of the study.

**Study Population**

For the purpose of the present study, we used data collected in 3rd follow up visit of TLGS which included comprehensive data on reproductive status of participants [16]. All those who were never married, were unwillingness to have a child, had documented female infertility were excluded from the study. Finally, 1611 remaining participants fulfilled the eligibility criteria for the study and were classified as two groups: men who had documented male infertility were included in the infertile group (n = 88) and who had at
least one live birth and did not have a history of primary infertility were classified as the fertile group (n = 1523).

**Measurements**

In face-to-face interviews by trained staff the participants completed a standard questionnaire that included information on variables, with emphasis on fertility and metabolic history. All clinical, anthropometric, and biochemical parameters were measured by general practitioner; detailed descriptions of the measurements in TLGS have been published elsewhere [18, 19]. In brief, body mass index (BMI) was calculated based on the formula [weight in kilograms (kg) divided by height squared (m^2)]. Waist circumference (WC) was measured with an unstretched tape measure at the level of the umbilicus, without any pressure to the body surface. Hip circumference (HC) was measured at the level of the anterior superior iliac spine without any pressure to body surface. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice on the right arm in a seated position using a standard mercury sphygmomanometer after 15 mines of rest and the mean of these measurements was recorded. Blood samples were taken from participants after 12 h of overnight fasting and all blood analyses were performed at the TLGS research laboratory on the day of blood collection. Triglyceride (TG) levels were assayed using glycerol phosphate. Total cholesterol (TC) was assayed using the enzymatic colorimetric method with cholesterol esterase and cholesterol oxidase. Levels of high-density lipoprotein cholesterol (HDL-C) were measured after precipitation of the apolipoprotein B (apo B)-containing lipoproteins with phosphotungstic acid; we used a modified Friedewald to calculate LDL-C. All metabolic analyses were performed using related kits (Pars Azmon Inc., Tehran, Iran) and a Selecta 2 autoanalyzer (Vital Scientific, Spankeren, Netherlands). Intra-assay and inter-assay coefficients of variations for TG, TC, HDL-C, and LDL-C were less than 2.1, 1.9, 3, and 3%, respectively. Serum creatinine (Cr) levels were assayed by kinetic colorimetric Jaffe; sensitivity of the assay was 0.2 mg/dL (range, 18–1330 µmol/L (0.2–15 mg/dL). Reference intervals based on the manufacturer's recommendation was 53–97 µmol/L (0.6–1.1 mg/dL) in men. Intra-assay and inter-assay CVs < 3.1% in both baseline and follow-up phases. All biochemical assays were performed using commercial kits (Pars Azmoon Inc., Tehran, Iran) using a Selecta 2 autoanalyzer (Vital Scientific, Spankeren, The Netherlands). Assay performance was monitored after every 25 tests using lyophilized serum controls in normal and pathologic ranges and all samples were analyzed only when the internal quality control met the standard acceptable criteria.

**Terms Definition**

Infertility was defined as failure of a ‘couple’ to become pregnant despite 12 or more months of unprotected intercourse [20] and male infertility was defined as any infertility that attributed to male factor diagnosed by sperm parameters below the WHO normal values [21]. In present study, information about male infertility was obtained by history of infertility, using a self-reporting questionnaire and was further confirmed by medical documentation. Hypertension was defined according to criteria of the
Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [22] as a mean systolic blood pressure ≥ 140 mm Hg, mean diastolic blood pressure ≥ 90 mmHg, or undergoing treatment for hypertension. We defined MetS according to the Joint Interim Statement criteria [23] as the presence of any three or more of the following five risk factors: fasting triglycerides (TG) level of ≥ 150 mg/dL or specific treatment; fasting high-density lipoprotein (HDL) ≤ 40 mg/dL or specific treatment; raised systolic blood pressure ≥ 130 mmHg, or raised diastolic blood pressure ≥ 85 mm Hg, or receiving treatment; fasting plasma glucose of ≥ 100 mg/dL or treatment; and high waist circumference using waist-circumference cutoff points of ≥ 90 cm for men according to the population and the country-specific cutoff point for Iranians. Based on the National Cholesterol Education Program Adult Treatment Panel III criteria, dyslipidemia was defined as a TG level of 240 mg/dL, or low-density lipoprotein (LDL) 160 mg/dL, or TG 200 mg/dL, or HDL < 40 mg/dL, or receiving lipid-lowering therapy [24]. Obesity was defined as a body mass index (BMI) ≥ 30 kg/m2 and central obesity was defined as a waist circumference ≥ 90 cm [25]. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m² (26). In this study, GFR was estimated using the abbreviated prediction equation, provided by the Modification of Diet in Renal Disease (MDRD) study as follows: GFR = 186 × (Scr) ^{-1.154} × (Age) ^{-0.203}, in which eGFR (estimated GFR) is expressed as mL/min per 1.73 m² and serum creatinine (Scr) is expressed as mg/dL. Diabetes was defined as fasting plasma glucose (FPG) of ≥ 126 mg/dL or 2-h-post-challenge plasma glucose (2 h-PCPG) ≥ 200 mmol/L or taking anti-diabetic medication in all phases of study [27].

**Statistical Analyses**

All continuous variables were assessed for normality using the one-sample Kolmogorov–Smirnoff test and are expressed as mean (standard deviation), if variables had a normal distribution, or median with inter-quartile range (IQ25-75) for variables with skewed. As well, Categorical variables expressed as percentages. Baseline characteristics were compared between infertile and fertile groups using the Man-Whitney U test, t-student and Chi-squared tests, appropriately. Generalized Linear Regression model (GLM) with logit link was performed to explore the association between cardiometabolic disturbances and male infertility and odds ratio with 95% confidence-interval were estimated to show the association. Moreover, penalized logistic regression via data augmentation method was implemented to obtained unbiased estimates was used to reduce sparse data bias and increase the precision of the estimate. Statistical analyses were performed using STATA software package (version 14; STATA Inc., College Station, TX, USA), and Penlogit STATA package was applied to run data augmentation method. significance level was set at p < 0.05, and 95% confidence interval.

**Results**

Baseline characteristics of the subjects are presented in Table 1. Compared to fertile controls, infertile men were more likely to be older, [58 (13.3) versus 53 (10.2) years (P = 0.003)], and had significantly
higher SBP [120 (28.8) vs. 115 (18) mm Hg, P < 0.001], FBS [93 (10.3) vs. 91 (11) mg/dL, P = 0.011] and Bs-2hPG [115.5 (46) vs. 104 (45) mg/dL, P < 0.0014].

Table 1
Baseline characteristics of study population according to their history of male infertility

| Variables          | Infertile (n=88) | Fertile (n=1523) | P-value |
|--------------------|------------------|------------------|---------|
| Age, (years) €     | 58(13.3)         | 53(10.2)         | 0.003   |
| BMI, (kg/m²) €     | 26.2(4.2)        | 26.2(3.95)       | 0.513   |
| WHR €              | 0.93(0.08)       | 0.93(0.08)       | 0.789   |
| SBP, (mm Hg) €     | 120(28.8)        | 115(18)          | 0.001   |
| DBP, (mm Hg) €     | 78(14.5)         | 78(14)           | 0.155   |
| TC (mg/dL) €       | 181(59)          | 191(47)          | 0.307   |
| TG (mg/dL) €       | 157.5(100.5)     | 161(109)         | 0.841   |
| HDL-C, (mg/dL) €   | 41(11)           | 42(12)           | 0.883   |
| LDL-C, (mg/dL) €   | 116(32)          | 117(32)          | 0.640   |
| FBS, (mg/dL) €     | 93(10.3)         | 91(11)           | 0.011   |
| Bs-2hPG (mg/dL) €  | 115.5(46)        | 104(45)          | 0.014   |
| Educational level  |                  |                  |         |
| Academic           | 9(14.5)          | 171(14.2)        | 0.584   |
| Non-academic       | 53(85.5)         | 1037(85.5)       |         |
| Smoking history, Yes (%) | 18(20.4)     | 257(20.5)        | 0.539   |

Bold value is statistically significant; € mean (±standard deviation), £ median (interquartile range); BMI: body mass index; WHR: waist to hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein; LDL-C: low-density lipoprotein cholesterol; FBS: fasting plasma glucose; Bs-2hPG: 2-hour plasma glucose.

The crude as well as age and BMI adjusted relationships between cardio-metabolic disorders and male fertility status are provided in Table 2. The results of unadjusted model revealed that infertility were significantly associated with hypertension and CKD, OR = 1.8 (95% CI: 1.2, 2.9, P-value = 0.006) and OR = 1.9 (95% CI: 1.1, 3.6, P-value = 0.033), respectively. However, the significant association, which were found in crude analyses, were disappeared after adjusting for potential confounders of age and BMI. Moreover, infertility did not have any association with other cardiometabolic disturbances including diabetes and
pre-diabetes, metabolic syndrome, dyslipidemia, obesity and central obesity in unadjusted and adjusted analysis.

Table 2
Association of cardiometabolic disorders with male infertility status

| Outcomes                        | Infertile (n=88) | fertile (n=1523) | Unadjusted OR (95%CI) * | Age-BMI adjusted OR (95%CI) |
|---------------------------------|------------------|------------------|-------------------------|----------------------------|
| Diabetes mellitus, Yes (%)      | 21 (31.8)        | 300 (25.4)       | 1.3 (0.8, 2.3)          | 1.1 (0.6, 2.0)             |
| Pre-diabetes, Yes (%)           | 26 (29.5)        | 368 (24.2)       | 1.3 (0.8, 2.1)          | 1.1 (0.7, 1.8)             |
| Hypertension, Yes (%)           | 34 (38.6)        | 389 (25.5)       | 1.8 (1.2, 2.9)          | 1.4 (0.8, 2.3)             |
| Metabolic syndrome, Yes (%)     | 48 (54.5)        | 731 (48.0)       | 1.3 (0.8, 2.0)          | 1.1 (0.7, 1.9)             |
| Dyslipidemia, Yes (%)           | 47 (53.4)        | 822 (54)         | 0.9 (0.6, 1.5)          | 1 (0.6, 1.7)               |
| Obesity, Yes (%)                | 23 (26)          | 366 (24)         | 1.1 (0.7, 1.9)          | 1.5 (0.4, 5.7)             |
| Central Obesity, Yes (%)        | 32 (36.4)        | 503 (33)         | 1.1 (0.7, 1.9)          | 1.1 (0.6, 2.1)             |
| CKD, Yes (%)                    | 13 (14.8)        | 125 (8.2)        | 1.9 (1.1, 3.6)          | 1.3 (0.6, 3.5)             |

*Bold value is statistically significant (P-value < 0.05)

Discussion

Our population-based cross-sectional study demonstrated that there were not any association between history of male infertility and cardio-metabolic disturbances in infertile men compared to healthy fertile ones.

Male infertility is a multi-dimensional problem, with the increasing anticipation over the next 20 years [28]. Emerging evidence suggests an intertwined link between male infertility and the overall health status of men [6, 29]. However, in the last two decades several studies investigated the prevalence and incidence of some cardio-metabolic comorbidities in populations of patients with male infertility, in contrast to our findings, most data from these series supported the association between infertility and those disturbances [6, 30–33]. In this respect, Lawlor et al. (2003) assessed the relationship between prevalence of coronary heart disease (CHD) with number of offspring in a British population; they showed that men with ≤ 1 child had a higher risk of CHD compared to those with more children [34]. In another study, Ringbäck Weitoft analyzed Swedish data about mortality from different causes among 682919 lone
fathers and among childless men. Their results suggest that the risk of ischemic heart disease were increased among lone childless men face [35]. Likewise, Eisenberg et al. investigated the relationship between semen production and medical comorbidity in a cohort of 9387 men with available semen analysis in fertility clinic, revealed that cardiovascular disease including hypertension, peripheral vascular diseases, cerebrovascular diseases and non-ischemic heart diseases were associated with a significantly higher rate of any type of semen abnormality [30]. In another recently published study, Helene Glazer et al. in a Danish national IVF register-based cohort study on 39516 men, who had undergone fertility treatment, reported that male factor infertility may predict later occurrence of diabetes mellitus with the risk being related to the severity of the underlying fertility problem [36].

The results of our population-based study did not support previous association reported between cardiometabolic disturbances and male infertility. Disparate findings may be due to the different methodologies that were used to measure fertility. Unlike female infertility, the addressing the of male infertility is one of the important challenging issues and is not well reported in general [1] which may potentially lead to conflicting results of the associated studies. In this respect, male infertility has not been defined as an independent disease [1]. In the lack of unique definition, most of studies used the various criteria, such as infertility associated disorders or childless situation of men. However, although those may contribute to male infertility, however does not necessarily imply male infertility, thus limiting the interpretability of the data. Moreover, most of studies evaluated men infertility did not have population-based design and were performed in the tertiary setting mainly infertility clinics which potentially included severe form of the infertility that could not be a representative of the larger population of infertile men. This may importantly bias the data. In addition, in some context, men disclaim infertility help-seeking traditionally and do not usually agree to undergo fertility evaluation, resulting in underestimating the male infertility. However, different populations vary by age range, ethnicity, unit of measurement as well as other risk factors which could affected the results.

However, this study is limited by investigating only an Iranian population and cannot be extrapolated to other population, which emphasizes the need for more studies in other ethnic populations. Furthermore, infertility diagnosis was self-reported, which may be limited by recall bias, however, the diagnosis were further confirmed by medical records. In addition, previous studies found a negligible relationship between self-reported and confirmed infertility [37, 38]. However, since our study was cross-sectional, we did not identify the causality association between infertility and cardiometabolic disturbances. Long-term prospective studies are needed to show those causality effect.

Conclusions

In conclusion, our study revealed that there were not any association between male infertility and cardiometabolic disturbances. By focusing solely on men in a population-based setting, we tried to fill the gaps in knowledge in the male infertile population. This study is thus an incentive to initiate more explicit surveys concerning this topic in order to provide more accurate data on infertile men’s health. More population-based studies with large sample size are still warranted to confirm these findings.
Abbreviations

OR
odds ratio; TLGS:Tehran Lipid and Glucose Study; BMI:body mass index; WC:Waist circumference; HC:Hip circumference; SBP:Systolic blood pressure; DBP:diastolic blood pressure; TG:Triglyceride; TC:Total cholesterol; LDL:low-density lipoprotein; HDL:High-density lipoprotein; CKD:Chronic kidney disease; GFR:glomerular filtration rate; MDRD:Modification of Diet in Renal Disease; FPG:fasting plasma glucose; 2 h-PCPG:2-hpost-challenge plasma glucose;

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the Research Institute for Endocrine Sciences and a written informed consent was obtained from all subjects before initiation of the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors’ contributions

SBG: Conceptualized the study, Project development, Data analysis, Manuscript writing

RBY: Data analysis, Manuscript writing

MRD: Project development, Critical discussion
FRT: Conceptualized the study, project development, Data analysis, Critical discussion, Manuscript writing

All authors read and approved the final manuscript.

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