ANDROLOGY

ISSN: 2047-2919

ANDROLOGY

ORIGINAL ARTICLE

Correspondence:
Michael L. Eisenberg, Department of Urology, Stanford Hospital and Clinics, 300 Pasteur Drive, Stanford, CA 94305-5118, USA.
E-mail: eisenberg@stanford.edu

Keywords:
cardiac disease, infertility, metabolic disease, varicocoele/varicocele, vascular disease

Received: 11-Jun-2017
Revised: 18-Sep-2017
Accepted: 28-Sep-2017

doi: 10.1111/andr.12437

The association between varicocoeles and vascular disease: an analysis of U.S. claims data

[1]N. N. Wang, [1]K. Dallas, [2]S. Li, [3]L. Baker and [4]M. L. Eisenberg

[1]Department of Urology, Stanford Hospital and Clinics, Stanford, CA, USA, [2]Department of Urology, Stanford University School of Medicine, Palo Alto, CA, USA, [3]Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA, USA, and [4]Department of Urology, Obstetrics and Gynecology, Stanford University School of Medicine, Stanford, CA, USA

SUMMARY

Studies have suggested an association between varicocele, hypogonadism, and elevated oxidative stress markers, but no other health risks have been associated with varicoceles. We sought to determine the association between varicocele and incident medical comorbidities. Using the Truven Health MarketScan® claims database from 2001 to 2009, we identified 4459 men with varicoceles, and 100,066 controls based on ICD-9 and CPT codes, with an average follow-up of 3.1 person years. Men with varicoceles were classified as symptomatic or asymptomatic based on co-existing diagnoses. Men with medical comorbidities present before or within 1 year of index diagnosis were excluded. Metabolic and cardiovascular outcome variables were identified via ICD-9 codes. A Cox regression analysis was used to assess incident risk of metabolic and cardiovascular disease amongst the different groups. Men with varicoceles had a higher incidence of heart disease compared to men who underwent infertility testing (HR 1.22, 95% CI: 1.03–1.45), and men who underwent vasectomy (HR 1.32, 95% CI 1.13–1.54). The varicoceles group also had a higher risk of diabetes (HR 1.73, 95% CI: 1.37–2.18) and hyperlipidemia (HR 1.15, 95% CI: 1.03–1.28) compared to the vasectomy group. Furthermore, men with symptomatic varicoceles (n = 3442) had a higher risk of heart disease, diabetes, and hyperlipidemia following diagnosis, while men with asymptomatic varicoceles (n = 1017) did not. Given the prevalence of varicoceles, further research is needed to understand the implications of a varicocele to a man's overall health.

INTRODUCTION

Varicocoeles occur in 15% of men and have been associated with testicular atrophy, scrotal pain, and alternations in the hypothalamic-pituitary-gonadal axis including hypogonadism or decreased spermatozoa or testosterone production with elevated gonadotropins (Tanrikut *et al.*, 2011a; Damsgaard *et al.*, 2016). While the pathophysiology of varicocoeles has not been completely determined, it is assumed that a combination of increased oxidative stress, scrotal temperatures, pressures, and an accumulation of toxins (e.g. metabolites) contributes to the symptoms experienced in some men (Naughton *et al.*, 2001; Eisenberg & Lipshults, 2011).

Treatment recommendations regarding the management of a varicocoele generally address symptoms and bother. While some men are offered treatment, others are managed expectedly especially in men beyond reproductive years (Movassaghi & Turek, 2008). As varicocoeles are thought to be a progressive lesion, treatment may also be offered to avoid further decline in testicular function (World Health Organization, 1992). While impaired sperm production is the most common reason for repair, some have advocated varicocoelectomy to improve testosterone production given the association between varicocoeles and low serum testosterone (Younes, 2000; Tanrikut *et al.*, 2011b). Hypogonadism has been associated with metabolic risk factors including obesity, hyperglycemia, hypertension, dyslipidemia, and insulin resistance (Wang *et al.*, 2011) as well as cardiovascular disease events (English *et al.*, 2000; Jones, 2010) and increased all-cause mortality (Khaw *et al.*, 2007; Haring *et al.*, 2010). In addition, varicocoeles are associated with oxidative stress which has also been linked to heart and metabolic disease (Cervellione *et al.*, 2006).

Given the association between varicocoeles, hypogonadism, and oxidative stress as well as hypogonadism, oxidative stress, and metabolic diseases, we sought to determine if varicocoeles

are associated with increased risk for incident metabolic and vascular disease.

MATERIALS AND METHODS

Patients

We analyzed subjects with claims data contained within the Truven Health Marketscan™ Commercial Claims and Encounters database. This database provides information from adjudicated and paid insurance claims filed for the care of privately insured individuals with employment-based insurance through a participating employer. Marketscan provides claims data on 77 million covered lives since 1996. This study used data from 2001 to 2009. The number of individuals represented in the database varies over time; the more recent years of the data contain more than 30 million covered lives. Institutional Review Board approval was obtained.

Men with a history of varicocoeles were identified using diagnosis (ICD-9) and treatment codes (CPT). ICD-9 coding used was 456.4. CPT varicocoele treatment codes included 55530, 55535, 55540, 55550. Men undergoing infertility testing were identified using ICD9 V26.21 and CPT semen analysis codes 89300, 89310, 89320, 89322. Next, we identified men who underwent vasectomy, implying fertility, using ICD9 V25.09, V25.2, V26.52 and CPT 55250, 55450, 55400, 54900, 54901. All groups were mutually exclusive. In each group, each man was assigned an 'index date' as the first date on which a varicocoele diagnosis or treatment code, an infertility testing code, or a vasectomy code, respectively, was observed in the data.

For all groups, men were required to be enrolled in a plan covered by the database for at least 1 year before and 1 year after the index date. Men observed before the index date, or within 1 year after, to have other prevalent comorbidities included in the outcome analysis (i.e., hypertension, diabetes, hyperlipidemia, renal disease, pulmonary disease, liver disease, depression, peripheral vascular disease, cerebrovascular disease, heart disease [ischemic and other], injury, alcohol abuse, drug abuse, anxiety disorders, and bipolar disorder) were also excluded. Subjects were required to be between the ages of 18 and 50 years at the time of the first database entry.

For each man in the cohort, the number of outpatient visits after the index date was ascertained with CPT codes indicating new and follow-up office visits, consultations, or preventative medicine encounters. Medical comorbidities were determined based on ICD9 codes on any claim and included obesity (278.0) and smoking (305.1, V1582).

Patients with varicocoeles were further classified as symptomatic or asymptomatic based on the presence or absence of any of the co-existing diagnoses: male infertility (ICD9 606.x), testicular hypofunction (ICD9 257.2), testicular atrophy (ICD9 608.3), and scrotal pain (ICD9 608.89, 608.9).

Outcome measures

We identified incident metabolic and vascular diseases based on diagnosis codes: hypertension (401–405), diabetes (250), hyperlipidemia (272), renal disease (403, 404, 580–588 and v42, 45.1 and 56.x), peripheral vascular disease (433–434), cerebrovascular disease (430, 434), and heart disease (ischemic 410–414, other heart diseases 420–429 e.g. cardiomyopathy, dysrhythmias, etc.) which includes both ischemic and non-ischemic heart disease.

Statistical analysis

Men accrued at-risk time beginning 1 year after their index dates until medical diagnosis or their final day of the final year of enrollment in a health plan included in the MarketScan database. The first year was excluded as a queried medical diagnosis within this time period was an exclusion criterion.

We calculated incidence rates in our cohorts per 1000 person-years. We then compared the risk of health outcomes in men diagnosed with varicocoele to men who only underwent fertility testing and men utilizing vasectomy using a Cox proportional hazard regression model that adjusted for age, index year, obesity, smoking, number of outpatient visits, and follow-up time.

We conducted subgroup analyses restricting the analysis to include only men with specific diagnosis of symptomatic varicocoeles (e.g. men who also had ICD 606.x, ICD 257.2, ICD 608.3 and ICD 608.89, 608.9) compared to men who were diagnosed with varicocoeles without any associated symptoms. All p values were two-sided with $p < 0.05$ considered statistically significant. Analyses were performed using SAS (version 9.3, SAS Institute, Inc., Cary, NC, USA).

RESULTS

In all, we identified 4459 men with varicocoeles, 21,840 men who underwent infertility testing without concurrent varicocoeles, and 78,226 men who underwent vasectomy. The average ages of men in the three groups were 32.2 years old for the varicocoele group, 32.9 for those seeking infertility testing without varicocoeles, and 35 years old for men who underwent vasectomy. The average number of annual visits per patient was also comparable between groups (Table 1).

Men with varicocoeles had a higher incidence of overall heart disease (HR 1.22, 95% CI: 1.03–1.44) in the years following the diagnosis when compared to men who underwent infertility testing. A similar result was identified when comparing men with varicocoeles to those utilizing vasectomy (HR 1.31, 95% CI 1.13–1.53). Similar results were seen when examining either ischemic heart disease (HR 1.36, 95% CI: 1.02–1.82) or other heart diseases (HR 1.27; 95% CI: 1.07–1.51, Table 2). In addition, men with varicocoeles had a higher risk of diabetes (HR 1.71, 95% CI: 1.35–2.16) and hyperlipidemia (HR 1.15, 95% CI: 1.03–1.28) when compared to men who underwent vasectomy (Table 2). There were no significant differences between the

Table 1 Characteristics of study participants

		Infertility Testing	Varicocoele	Vasectomy
N		21,840	4459	78,226
Age	Mean (SD)	32.9 (5.8)	32.2 (5.9)	35.0 (5.9)
Follow-up time (y)	Mean (SD)	3.0 (1.6)	3.2 (1.8)	3.3 (1.8)
Obesity		493 (2.26)	107 (2.40)	1575 (2.01)
Smoking		523 (2.39)	158 (3.54)	2703 (3.46)
Index Year	2001	734 (3.36)	176 (3.95)	3121 (3.99)
	2002	1219 (5.58)	314 (7.04)	5835 (7.46)
	2003	1689 (7.73)	447 (10.02)	7551 (9.65)
	2004	2709 (12.40)	594 (13.32)	10,684 (13.66)
	2005	2766 (12.66)	573 (12.85)	10,240 (13.09)
	2006	4617 (22.51)	993 (22.27)	16,561 (21.17)
	2007	4690 (21.47)	817 (18.32)	14,597 (18.66)
	2008	3116 (14.27)	545 (12.22)	9637 (12.32)
Visits per person year	Mean (SD)	2.2 (2.4)	3.4 (2.6)	2.5 (2.3)

Table 2 Hazard ratios (95% Confidence intervals) of comorbid disease in patients with varicocoeles compared to men who underwent infertility testing and men who underwent vasectomy

Disease	Varicocoele			
	n (%)	Events/1K person years	vs. inf testing HR (95% CI)	vs. vasectomy HR (95% CI)
Heart disease	173 (3.89)	12.30	1.22 (1.03–1.44)	1.31 (1.13–1.53)
Ischemic Heart Disease	49 (1.10)	3.49	1.33 (0.97–1.84)	1.36 (1.02–1.82)
Non-ischemic Heart Disease	137 (3.08)	9.74	1.19 (0.98–1.44)	1.27 (1.07–1.51)
Diabetes	76 (1.71)	5.41	1.16 (0.90–1.50)	1.71 (1.35–2.16)
Hyperlipidemia	359 (8.06)	25.53	0.96 (0.85–1.07)	1.15 (1.03–1.28)
Hypertension	266 (5.97)	18.92	0.87 (0.77–0.997)	0.96 (0.85–1.09)
Renal disease	12 (0.27)	0.85	1.17 (0.61–2.24)	1.36 (0.76–2.46)
Peripheral Vascular Disorders	8 (0.18)	0.57	0.51 (0.24–1.06)	0.76 (0.37–1.53)
Cerebrovascular Disease	22 (0.49)	1.56	0.94 (0.59–1.50)	1.15 (0.75–1.77)

groups when examining renal disease, peripheral vascular disorders, or cerebrovascular disease. Men with varicocoeles showed a lower risk of developing incident hypertension compared to men who underwent infertility testing (HR 0.87, 95% CI 0.77–0.997).

To identify men most at risk, we stratified our data into men with symptomatic or asymptomatic varicocoeles (e.g. none of the associated diagnoses). Men with symptomatic varicocoeles (n = 3442) had similar elevations in risk of heart disease and hyperlipidemia as seen in the whole cohort. Specifically, men with symptomatic varicocoeles had an increased incidence of heart disease compared to men with infertility testing (HR 1.26, 95% CI 1.05–1.52) and when compared to men who had a vasectomy (HR 1.38, 95% CI 1.16–1.63). Similarly, when compared to men with vasectomies, men with symptomatic varicocoeles also had higher incidence of diabetes (HR 1.91, 95% CI 1.49–2.46) and hyperlipidemia (HR 1.17, 95% CI 1.04–1.32) (Table 3).

In contrast, men with asymptomatic varicocoeles (n = 1017) did not have an increased risk of heart disease (HR 1.08, 95% CI 0.76–1.54), diabetes (HR 0.81, 95% CI 0.44–1.48), hyperlipidemia (HR 0.93, 95% CI 0.74–1.17), or other comorbid disease when compared to the group who underwent infertility testing. Similarly, men with asymptomatic varicocoeles also did not have an increased risk of disease compared to men who underwent vasectomy in regard to heart disease (HR 1.11, 95% CI 0.79–1.57), diabetes (HR 1.11, 95% CI 0.61–2.01), hyperlipidemia (HR 1.07, 95% CI 0.86–1.35), and other comorbid diseases (Table 3).

The symptomatic varicocoeles group was further subdivided into each specific symptom (i.e. male infertility (606.x), scrotal pain/disorder (608.89, 608.9), testicular hypofunction (257.2), and atrophy of testis (608.3). As shown in Table 4, men with a varicocoele and male infertility had an increased risk of diabetes (HR 1.46; 95% CI 1.1–1.95) as well as heart disease (HR 1.26; 95% CI 1.03–1.55). Similar trends for varicocoeles-bearing men with scrotal pain or testis atrophy were also seen among other metabolic outcomes although the number of individuals in the subgroups was small (Table 4). Associations with men with varicocoele and testicular failure were not identified.

DISCUSSION

This study identified a higher risk of incident metabolic and vascular disease in men with varicocoeles in the years following a diagnosis. Moreover, the current data suggest that most of the risk occurs in men with symptomatic varicocoeles. When further stratified, it was noted that similar risk seemed to be present whether varicocoele symptomatology was male infertility or scrotal pain. To our knowledge, this is the first study to demonstrate a higher risk of incident metabolic and vascular disease among men with varicocoeles.

The current surgical management of varicocoeles is largely focused on preventing or treating male infertility (Schlegel, 2012; Choi & Kim, 2013), with treatment of refractory orchialgia as a less common indication (Abrol *et al.*, 2014). However for men without future reproductive intent, the absence of pain often leads to expectant management of varicocoeles rather than surgical repair although varicocoeles are recognized as progressive lesions (World Health Organization, 1992; Witt & Lipshultz, 1993).

However, varicocoeles have been associated with conditions that can impair health. The association between varicocoeles and low testosterone levels has been shown in both rat and human studies (Tanrikut *et al.*, 2011b). Many meta-analysis and prospective studies on human patients have also shown that treatment of varicocoeles has resulted in increase in testosterone

Table 3 Hazard ratios (95% Confidence intervals) of comorbid disease in patients with symptomatic versus asymptomatic varicocoeles compared to men who underwent infertility testing and men who underwent vasectomy

Disease	Symptomatic Varicocoele				Asymptomatic Varicocoele			
	n (%)	Events/1K person years	vs. inf testing HR (95% CI)	vs. vasectomy HR (95% CI)	*n* (%)	Events/1K person years	vs. inf testing HR (95% CI)	vs. vasectomy HR (95% CI)
Heart disease	141 (4.10)	12.99	1.26 (1.05–1.52)	1.38 (1.16–1.63)	33 (3.24)	10.21	1.08 (0.76–1.54)	1.11 (0.79–1.57)
Diabetes	66 (1.92)	6.08	1.28 (0.98–1.68)	1.91 (1.49–2.46)	11 (1.08)	3.40	0.81 (0.44–1.48)	1.11 (0.61–2.01)
Hyperlipidemia	284 (8.25)	26.17	0.97 (0.85–1.10)	1.17 (1.04–1.32)	76 (7.47)	23.52	0.93 (0.74–1.17)	1.07 (0.86–1.35)
Hypertension	210 (6.10)	19.35	0.88 (0.76–1.02)	0.98 (0.85–1.13)	58 (5.70)	17.95	0.87 (0.67–1.13)	0.93 (0.72–1.20)
Renal disease	9 (0.26)	0.83	1.12 (0.54–2.31)	1.30 (0.66–2.54)	3 (0.29)	0.93	1.39 (0.43–4.50)	1.61 (0.51–5.04)
Peripheral Vascular Disorders	8 (0.23)	0.74	0.64 (0.31–1.34)	0.98 (0.48–1.98)	1 (0.10)	0.31	0.30 (0.04–2.19)	0.42 (0.06–2.96)
Cerebrovascular Disease	19 (0.55)	1.75	1.03 (0.62–1.69)	1.29 (0.81–2.05)	3 (0.29)	0.93	0.60 (0.19–1.91)	0.69 (0.22–2.15)

Table 4 Hazard ratios (95% Confidence intervals) of comorbid disease in patients with symptomatic varicocoeles stratified by associated symptoms compared to men who underwent infertility testing and men who underwent vasectomy

Associated conditions	Male infertility			Testicular failure			Testis atrophy			Scrotal pain		
	n (%)	vs. inf testing HR (95% CI)	vs. vasectomy HR (95% CI)	*n* (%)	vs. inf testing HR (95% CI)	vs. vasectomy HR (95% CI)	*n* (%)	vs. inf testing HR (95% CI)	vs. vasectomy HR (95% CI)	*n* (%)	vs. inf testing HR (95% CI)	vs. vasectomy HR (95% CI)
Hypertension	165 (6.07)	0.9 (0.77–1.06)	0.99 (0.85–1.16)	46 (7.58)	0.98 (0.73–1.31)	1.13 (0.85–1.52)	8 (7.14)	1.01 (0.51–2.03)	1.13 (0.57–2.27)	71 (6.40)	0.87 (0.69–1.11)	1.02 (0.81–1.29)
Diabetes	57 (2.10)	1.46 (1.1–1.95)	2.17 (1.66–2.84)	10 (1.65)	0.98 (0.52–1.85)	1.49 (0.8–2.77)	1 (0.89)	0.6 (0.08–4.29)	0.93 (0.13–6.61)	19 (1.71)	1.03 (0.65–1.65)	1.61 (1.02–2.54)
Hyperlipidemia	219 (8.06)	0.98 (0.85–1.13)	1.18 (1.03–1.35)	54 (8.90)	0.93 (0.71–1.22)	1.17 (0.89–1.53)	9 (8.04)	0.92 (0.48–1.78)	1.11 (0.58–2.13)	97 (8.74)	0.96 (0.78–1.18)	1.21 (0.99–1.48)
Renal disease	3 (0.11)	0.47 (0.15–1.53)	0.56 (0.18–1.77)	3 (0.49)	2.02 (0.62–6.57)	2.14 (0.68–6.7)	0	NA	NA	5 (0.45)	1.87 (0.73–4.8)	2.07 (0.85–5.07)
Peripheral Vascular Disorders	4 (0.15)	0.44 (0.16–1.2)	0.65 (0.24–1.75)	3 (0.49)	1.14 (0.36–3.65)	1.81 (0.58–5.67)	0	NA	NA	6 (0.54)	1.29 (0.56–2.99)	2.12 (0.94–4.78)
Cerebrovascular Disease	16 (0.59)	1.13 (0.66–1.93)	1.42 (0.86–2.35)	1 (0.16)	0.27 (0.04–1.94)	0.35 (0.05–2.49)	1 (0.89)	1.84 (0.26–3.27)	2.11 (0.3–5)	10 (0.90)	1.5 (0.78–2.91)	2.02 (1.07–3.78)
Heart disease	108 (3.97)	1.26 (1.03–1.55)	1.36 (1.12–1.66)	18 (2.97)	0.79 (0.5–1.27)	0.9 (0.56–1.43)	5 (4.46)	1.37 (0.57–3.31)	1.54 (0.64–3.71)	52 (4.68)	1.34 (1.01–1.78)	1.55 (1.18–2.04)

levels (Fish & Hyun, 2012; Abdel-Meguid *et al.*, 2014). Furthermore, the literature suggests that the effect is more pronounced among hypogonadal men and even among older men (defined as > 40 years) (Hsiao *et al.*, 2011; Abdel-Meguid *et al.*, 2014). There is also a growing body of literature that demonstrates the relationship between low testosterone and increased comorbidity including cardiovascular events such as myocardial infarction, angina, or coronary heart disease (Araujo *et al.*, 2011; Corona *et al.*, 2011) as well as metabolic disorders including obesity and metabolic syndrome (Kelly & Jones, 2015; Wickramatilake, 2015). While the etiology of the observed association between varicocoele and metabolic and vascular disease could plausibly be mediated by testosterone, the current data do not allow such analyses. It is important to note that men with a varicocoele and testicular failure (a common code used to indicate low testosterone levels) did not show higher risk of incident metabolic syndrome. Importantly, studies have consistently demonstrated that BMI is inversely related to varicocoele prevalence (Rais *et al.*, 2013). Thus, obesity would be unlikely to mediate the observed effect.

In addition, varicocoeles are associated with elevated levels of oxidative stress. While the effects of reactive oxygen species can impair sperm production, it is conceivable that systemic effects may also exist. Indeed, elevated levels of oxidative stress have been associated with cardiovascular risk (Ridker, 2016).

Several limitations warrant mention. As the data are based on diagnosis and treatment codes, it is unclear how many patients were screened for varicocoeles or how varicocoeles were diagnosed. It is possible that only a limited portion of the population underwent screening which may introduce some bias toward patients with symptomatic varicocoeles. Additionally, while it is reasonable to expect that most varicocoeles were diagnosed based on physical exam, which is the gold standard, there are no codes that explicitly designate how they were diagnosed or their clinical grade.

As previously mentioned, laboratory measurements were not available, so we cannot determine the causal etiology of the identified associations. However, the association between varicocoeles, hypogonadism, oxidative stress, and metabolic diseases may be a possible etiology for the findings of our study. Another limitation to our study is the limited follow-up time. Although the number of total patient years is high, the average follow-up for each individual was limited. Given that the average age of the participants in the three groups was in the fourth decade of life, it is possible that the study may underestimate the incident risk of the comorbid diseases as many of disorders may not have been diagnosed during the short follow-up window where the risk of such metabolic diseases is relatively low.

Another limitation of using insurance claims database is that the information is affected by physician coding habits, which can vary widely in detail and specificity. A large portion of the men who were coded as having varicocoeles did not have associated symptoms that were coded; however, it is possible that not all of these men were indeed asymptomatic. Similarly, men who were listed as having associated symptoms may not have had all of their symptoms included in detail. The variety of symptoms associated with varicocoeles contributes to both smaller subgroup numbers (e.g. there are only 52 patients with varicocoeles and associated scrotal pain) and increased heterogeneity of the 'symptomatic varicocoele' group. Though this limits the strength

of these sub-group analyses, it is also possible that some of the trends that are not statistically significant may be stronger than they appear due to under-reporting.

Furthermore, the MarketScan Database, which is based on insurance claims data, draws from a selected group of patients who have access to health care and seek out specialist consultations which may not represent all US men.

Despite these limitations, MarketScan provides access to a large sample of US men. Moreover, the MarketScan Database has been previously validated and used to identify both increased risk of cancer and increase risk of incident chronic medical conditions among infertile men (Eisenberg *et al.*, 2015, 2016). Moreover, the number of patients included in the database along with the longitudinal follow-up provides a unique opportunity to identify important population-level associations among relatively rare conditions.

CONCLUSIONS

According to the 2010 US Census, there are 114 million men above age 18, suggesting that approximately 17 million (15%) or more men may have varicocoeles (United States Census Bureau, 2011). Although the associations between varicocoeles and infertility are well established, our findings suggest that varicocoeles may be a harbinger of lifelong metabolic disorders, though the pathophysiologic mechanism is still unclear. Nevertheless, given the prevalence of varicocoeles in the population, studies confirming and evaluating the etiology are needed to further identify the implications of a varicocoele on a man's overall health.

REFERENCES

Abdel-Meguid TA, Farsi HM, Al-Sayyad A, Tayib A, Mosli HA & Halawani AH. (2014) Effects of varicoceles on serum testosterone and changes of testosterone after varicocelectomy: a prospective controlled study. *Urology* 84, 1081–1087.

Abrol N, Panda A & Kekre NS. (2014) Painful varicoceles: role of varicocelectomy. *Indian J of Uro.* 30, 369–373.

Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT & Wittert GA. (2011) Clinical review: endogenous testosterone and mortality in men: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 96, 3007–3019.

Cervellione RM, Cervato G, Zampieri N, Corroppolo M, Camoglio F, Cestaro B & Ottolenghi A. (2006) Effect of varicocelectomy on the plasma oxidative stress parameters. *J Pediatr Surg* 41, 403–406.

Choi WS & Kim SW. (2013) Current issues in varicoceles management: a review. *World J Mens Health.* 31, 12–20.

Corona G, Rastrelli G, Monami M, Guay A, Buvat J, Sforza A, Forti G, Mannucci E & Maggi M. (2011) Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. *Eur J Endocrinol* 165, 687–701.

Damsgaard J, Joensen UN, Carlsen E, Erenpreiss J, Jensen MB, Matulevicius V, Zilaitiene B, Olesen IA, Perheentupa A, Punab M, Salzbrunn A, Toppari J, Virtanen HE, Juul A, Skakkebaek NE & Jorgensen N. (2016) Varicocele is Associated with Impaired Semen Quality and Reproductive Hormone Levels: a study of 7035 Healthy Young Men from Six European Countries. *Eur Urol* S0302–2838, 30396–30397.

Eisenberg ML & Lipshults LI. (2011) Varicocele-induced Infertility: newer insights into its pathophysiology. *Indian J Urol.* 27, 58–64.

Eisenberg ML, Li S, Brooks JD, Cullen MR & Baker LC. (2015) Increased risk of cancer in infertile men: analysis of U.S. claims data. *J Urol* 193, 1596–1601.

Eisenberg ML, Li S, Cullen MR & Baker LC. (2016) Increased risk of incident chronic medical conditions in infertile men: analysis of United States claims data. *Fertil Steril* 105, 629–636.

English KM, Mandour O, Steeds RP, Diver MJ, Jones TH & Channer KS. (2000) Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms. *Eur Heart J* 11, 890–894.

Fish H & Hyun G. (2012) Varicocele repair for low testosterone. *Curr Opin Urol* 22, 495–498.

Haring R, Volzke H & Steveling A. (2010) Low serum testosterone levels are associated with increased risk of mortality in a population-based cohort of men aged 20-79. *Eur Heart J* 31, 1494–1501.

Hsiao W, Rosoff JS, Pale JR, Greenwood EA & Goldstein M. (2011) Older age is associated with similar improvements in semen parameters and testosterone after subinguinal microsurgical varicocelectomy. *J Urol* 185, 620–625.

Jones TH. (2010) Testosterone deficiency: a risk factor for cardiovascular disease? *Trends Endocrinol Metab* 21, 496–503.

Kelly DM & Jones TH. (2015) Testosterone and obesity. *Obes Rev* 16, 581–606.

Khaw KT, Dowsett M, Folkerd E, Bingham S, Wareham N, Luben R, Welch A & Day N. (2007) Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. *Circulation* 116, 2694–2701.

Movassaghi M & Turek PJ. (2008) The cost-effectiveness of treatments for male infertility. *Expert Rev Pharmacoecon Outcomes Res.* 8, 197–206.

Naughton CK, Nangia AK & Agarwal A. (2001) Pathophsiology of varicoceles in male infertility. *Hum Reprod Update.* 7, 473–481.

Rais A, Zarka S, Derazne E, Tzur D, Calderon-Margalit R, Davidovitch N, Afek A, Carel R & Levine H. (2013) Varicocele among 1 300 000 Israeli adolescent males: time trends and association with body mass index. *Andrology.* 1, 663–669.

Ridker PM. (2016) A test in context: high-sensitivity C-Reactive Protein. *J Am Coll Cardiol* 67, 712–723.

Schlegel PN. (2012) Contemporary issues in varicocele management. *Curr Opin Urol* 22, 487–488.

Tanrikut C, Goldstein M, Rosoff JS, Lee RK, Nelson CJ & Muhall JP. (2011a) Varicocele as a risk factor for androgen deficiency and effect of repair. *BJU In.* 108, 1480–1484.

Tanrikut C, McQuaid JW & Goldstein M. (2011b) The impact of varicoceles and varicoceles repair on serum testosterone. *Curr Opin Obstet Gynecol* 23, 227–231.

United States Census Bureau. "Age and sex composition: 2010." 2010 Census. Census Bureau May 2011.

Wang C, Jackson G, Jones TH, Matsumoto AM, Nehra A, Perelman MA, Swerdloff RS, Traish A, Zitzmann M & Cunningham G. (2011) Low testosterone associated with obesity and the metabolic syndrome contributes to sexual dysfunction and cardiovascular disease risk in men with type 2 diabetes. *Diabetes Care* 34, 1669–1675.

Wickramatilake CM. (2015) MOhideen MR and Pathirana C. Association of metabolic syndrome with testosterone and inflammation in men. *Ann Endocrinol* 76, 260–263.

Witt MA & Lipshultz LI. (1993) Varicocele: a progressive or static lesion? *Urology* 42, 541–543.

World Health Organization. (1992) The influence of varicoceles on parameters of fertility in a large group of men presenting to infertility clinics. *World Health Organization. Fertility and Sterility.* 57, 1289–1293.

Younes AK. (2000) Low plasma testosterone in varicoceles patients with impotence and male infertility. *Arch Androl* 45, 187–195.