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ANDROLOGY

Clinical and laboratory profiles of a large cohort of patients with different grades of varicocele

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Objective. In this retrospective study we attempted to report our own data on the different clinical parameters in association with the presence and severity of varicocele in a large group of Austrian men.
Methods. The records of 1,111 consecutive patients with clinical varicocele from 1993 to 2010 were evaluated. The presence, grade, and side of any varicocele were recorded. Semen samples, serum FSH, LH, and testosterone levels, and testicular volume were assessed.
Results. The mean age was 28.8 (±7.3) years. Three hundred seventeen (28.5%) patients presented with grade I varicocele, 427 (38.4%) with grade II varicocele, and 367 (33%) with grade III varicocele. Correlation between different grades of varicocele and semen quality indicated an over–representation of oligospermia and asthenoteratospermia in the group of grade III varicocele ($p < 0.05$), whereas other parameters of semen quality showed no significant difference between the three groups. Serum testosterone levels and BMI were significantly associated ($p < 0.05$) with the grade of varicocele, but no association was found with the other parameters analyzed.
Conclusions: Our analysis showed a significant relationship between the grade of varicocele and semen analysis. Moreover, higher testosterone levels and lower body mass index were associated with the higher grade of varicocele and decreased semen quality. More prospective studies are recommended.

Key Words: body mass index ‹› varicocele ‹› follicle stimulating hormone (FSH) ‹› luteinizing hormone (LH) ‹› testosterone (T)

INTRODUCTION

Varicocele, a common disease that affects men, is the elongation and tortuousity of the spermatic veins [1, 2]. It is estimated that 15% of men have varicocele of different grades. Moreover, 19% to 41% of men with primary infertility, and 45% to 81% of men with secondary infertility suffer from varicocele [3]. Although varicoceles have been known for a long time, the mechanisms underlying their detrimental effects on men's fertility are still largely unknown [4]. Nevertheless, many studies have outlined varicocele's effect on various sperm characteristics including count, motility, and morphology. In a recently published article by our group we reported data on 716 patients who presented with primary infertility and various grades of varicocele [5]. Our results showed that about 33.3% of patients presented with normospermia, followed by asthenospermia (17.9%), oligoasthenoteratospermia syndrome (14.2%), and oligospermia (13.2%). Sperm density significantly decreased with increasing grade of varicocele. Body mass index was inversely proportional to varicocele. Serum testosterone levels were higher in grade III varicoceles (5.7 +/– 0.2 ng/ml) compared with grade I (4.9 +/– 0.2 ng/ml) and grade II (5.0 +/– 0.1 ng/ml) varicoceles ($P < 0.001$; range, 0.4–16.6 ng/ml).
In this retrospective study we report our data on 1,111 consecutive patients presenting with varicocele and infertility between 1993 and 2010.

MATERIAL AND METHODS

This retrospective analysis included data from 1,111 consecutive patients with varicocele presenting for infertility evaluation at the Department of Urology at the Medical University of Graz, between 1993 and 2010. This retrospective study was approved by

the Ethics Committee of the Medical University of Graz, Austria. All clinical and laboratory data were retrieved from medical records, which included age, weight, height, body mass index, varicocele grade, semen analysis, as well as different serum based laboratory endocrine parameters: follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone (T), estradiol, and prolactin. The minimum duration of infertility required was defined as a failure to establish a pregnancy during the course of one year with unprotected intercourse. A basic infertility evaluation including a detailed history and a complete physical examination was undertaken. Testicular volumes and spermatic veins were evaluated in all patients. The presence, grade, and side of varicocele were recorded. Grade I (small) varicoceles were palpable only with the Valsalva maneuver, grade II (medium) were palpable on examination in a standing position, and grade III (large) were visible and palpable when the patient was standing. Semen samples were collected from all patients after at least 48 hours of sexual abstinence in sterile containers and allowed to liquefy at 37°C for 30 minutes and analyzed for sperm concentration and percentage motility according to World Health Organization (WHO) criteria. Serum FSH, LH, and T levels and testicular volume were assessed in all patients. Varicocele grade was assessed by clinical criteria and confirmed by Doppler sonography with the subjects standing in a room at room temperature. Semen analysis was done on sperms collected by masturbation within one hour after ejaculation and was performed according to WHO standards. Measurement of endocrine parameters was performed after serum sample collection within a time range between 9:00 and 10:00 am. The range of reference values for the analyzed endocrine parameters: FSH (1.312 ml U/ml), LH (0.8–8.5 ml U/ml), testosterone (2.2–11 ng/ml), prolactin (2.1–19.3 ng/ml), and estradiol (1–55 pg/ml).

Table 1. *Semen analysis in patients with different grades of varicocele (n = 1,111)*

Parameter	Grade I (n = 317)	Grade II (n = 427)	Grade III (n = 367)
Semen volume (ml)	3.9 (±1.7)	3.8 (±1.8)	3.6 (±1.8)
Progressive motility after 60 minutes (%)	23 (±9)	23 (±9)	23 (±9)
Normospermia	30.3%	31.6%	30.2%
Oligospermia	9.8%	8.9%	17.7%*
Oligoasthenospermia	8.8%	7.7%	9.8%
Asthenospermia	21.5%	16.6%	15.8%
Teratospermia	2.8%	2.3%	1.9%
Oligoteratospermia	2.2%	2.6%	2.5%
Asthenoteratospermia	9.1%	8.4%	3.8%*
Aspermia	2.8%	4.4%	2.7%
Oligoasthenoteratospermia	12.6%	17.3%	15.5%

Values represent mean values ± standard deviation
* indicates significant differences (p <0.05)

Statistical analysis

The relationship between different grades of varicocele and semen quality or other clinical and laboratory parameters was studied by non–parametric chi–square test and Kruskal–Wallis tests (when appropriate for categorical variables) or Student t–test (when appropriate for continuous variables); the data are presented either as number and proportions of patients or as means ± standard deviations. To test the independent influence of age, BMI, and endocrine factors on grade of varicocele, a multivariate regression analysis was performed. All statistical analyses were performed using the Statistical Package for Social Sciences version 17.0 (SPSS Inc., Chicago, IL, USA). A two–sided $p < 0.05$ was considered statistically significant.

RESULTS

A total of 1,111 patients with different grades of varicocele were included in this study. The mean age was 28.8 (±7.3) years. Three hundred seventeen (28.5%) patients presented with grade I varicocele, 427 (38.4%) patients with grade II varicocele, and 367 (33%) patients presented with grade III varicocele (Table 1). Mean age of grade I was 31.4 years, of grade II 28.8 years, and of grade III 26.6 years ($p < 0.01$). In the whole patient cohort, the mean volume of semen after masturbation was 3.77 ml (±1.78) and the percentage of progressive motility after 60 minutes was 23.2% (±8.9).

Normospermia was observed in 342 (30.8%) of patients, oligospermia in 134 (12.1%) of patients, oligoasthenospermia in 97 (8.7%) of patients, asthenospermia in 197 (7.7%) of patients, teratospermia in 26 (2.3%) of patients, oligoteratospermia in 27 (2.4%) of patients, asthenoteratospermia in 79 (7.1%) of patients, aspermia in 38 (3.4%) of patients, and oligoasthenoteratospermia in 171 (15.4%) of patients, respectively. The correlation between different grades of varicocele and semen quality indicated an overrepresentation of oligospermia and asthenoteratospermia in the group of grade III varicocele ($p < 0.05$), whereas other parameters of semen quality showed no significant difference between the three groups (Table 1).

The mean serum concentration of the analyzed endocrine parameters for the whole patient cohort was:

FSH 6.5 (±6.2); LH 4.2 (±2.9); testosterone 5.3 (±2.7); estradiol 23.5 (±41.8); and prolactin 13.1 (±17). From the five hormonal parameters, only testosterone concentration was significantly different in grade III varicocele compared to grade I or grade II varicocele (mean value 5.86 ±2.6 versus 5.03 ±3.13 versus 5.14 ±2.27, respectively; $p < 0.05$, Fig. 1). The mean height in the whole cohort was 1.8 (±0.07) meters, the mean weight was 78.8 (±11.8) kg and the mean body mass index was 24.2 (±3.2). A large height, a low body weight, and a low BMI were associated with grade III varicocele (for BMI: 25.1 ±3.3 for grade I, 24.2 ±3.1 for grade II and 23.2 ±2.9, respectively; $p < 0.05$). In a multivariate regression analysis, testosterone concentration and BMI were significantly associated ($p < 0.05$) with the grade of varicocele, but no association was found with the other parameters analyzed. We analyzed the relationship between age of patients and grade of varicocele, but this was not found to be significant since the age of our patients was similar.

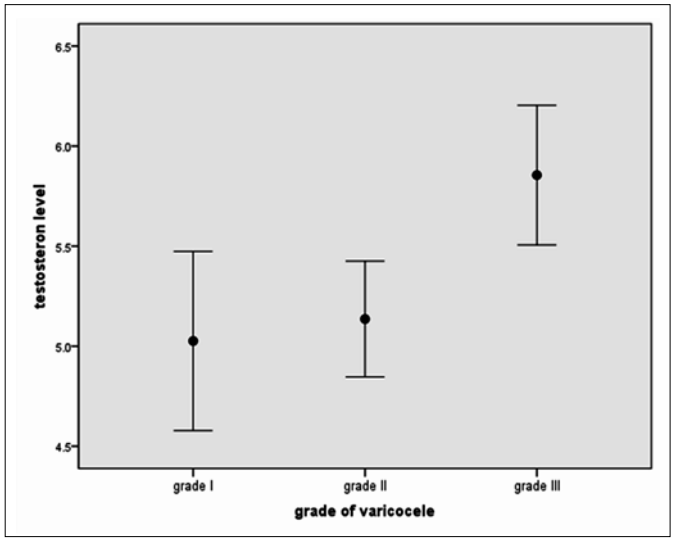

Figure 1. *Testosterone levels in ng/ml stratified to different grades of varicocele. Means (black dots) and corresponding 95% confidence intervals illustrates the higher the grade of varicocele, the higher the level of testosterone.*

DISCUSSION

The majority of the scientific evidence supports the concept that varicocele has a multitude of adverse effects on spermatogenesis [6, 7]. The exact pathophysiological mechanism underlying the hazardous effects of varicocele on spermatogenesis and male fertility is not completely understood. Moreover, the majority of scientific evidence supports that both venous reflux and testicular temperature elevation appear to play important roles in varicocele–induced testicular dysfunction [8].

The current American Urological Association recommendations advise offering of varicocelectomy to all adult men, seeking or not seeking conception, with any clinically palpable varicocele and abnormal semen parameters [8]. Moreover the biggest harmful effects observed on semen quality were with grade III varicocele [5]. In the current report a correlation between different grades of varicocele and semen quality indicated an overrepresentation of oligospermia and asthenoteratospermia in the group of grade III varicocele ($p < 0.05$), whereas other parameters of semen quality showed no significant difference between the three groups. Unfortunately, our current study does not include results of varicocelectomy on the fertility status of our patients so that any further comments on the relationship between varicocele grade and varicocelectomy outcome are impossible.

It is well known that testosterone performs its actions by interaction with its genomic androgen receptor [9]. Moreover, testosterone may have androgen–receptor independent actions such as smooth muscle relaxation and vasodilatation [10, 11, 12]. Several reports demonstrated that varicocele is associated with low serum testosterone that can significantly increase after successful varicocelectomy [13, 14, 15], according to these reports varicocele may lead to a decrease in specific enzymatic activity involved in testosterone synthesis. However, other studies could not demonstrate the reported decreased serum testosterone levels associated with varicocele [16]. These authors argued that testosterone levels may be significantly decreased with varicocele development; however, they are still within the normal range [17]. We observed higher testosterone levels in grade III varicoceles than varicoceles with lower grades. Although several hypotheses were introduced, but, to date, we still do not have a solid explanation for this interesting finding. Irkilata et al reported that, in vitro, testosterone's vasodilatory effects on the internal spermatic veins are significantly reduced in patients who have grade II and III varicocele than those who have grade I varicocele [18]. Our hypothesis "we think that the higher testosterone levels observed with grade III varicocele could be due to a testicular compensatory mechanism to resist the apparent hormonal dysfunction, i.e. the testes secrete more testosterone in order to compensate for impaired testosterone's functions" [5].

Obesity was identified as an important risk factor for many diseases [19]. Multiple pathophysiological mechanisms under which obesity adversely affects normal body functions are currently under extensive investigations [19]. Moreover, several studies conducted on the relationship between obesity and

varicocele acknowledged a rather protective effect of obesity. We found lower prevalence of varicocele, regardless of the grade, in patients with high BMI [5, 19]. In our current analysis we report that a large height, a low body weight, and a low BMI were associated with grade III varicocele (for BMI: 25.3 ±3.9 for grade I, 24.3 ±3 for grade II and 22.8 ±2.7, respectively; $p < 0.05$). Although we still do not have a solid explanation of these observations, but, a well known rationalization is that increased adipose tissue between the superior mesenteric artery and aorta in obese individuals may act as a barrier against the nutcracker mechanism responsible for compression of the left testicular vein and subsequent development of varicocele [19].

No study is without limitations, and our study is no exception. On the other hand, due to its retrospective nature we can present a robust data with a large number of patients.

Unfortunately, our current study does not include results of varicocelectomy on the fertility status of our patients so that any further comments on the relationship between varicocele grade and varicocelectomy outcome are impossible.

CONCLUSIONS

This analysis of 1,111 patients with varicocele showed a significant relationship between the grade of varicocele and semen analysis – semen quality deteriorated in patients with higher grades of varicoceles. Moreover, higher testosterone levels and lower BMI were associated with higher grades of varicoceles and decreased semen quality.

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