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Varicocele Is Associated with Impaired Semen Quality and Reproductive Hormone Levels: A Study of 7035 Healthy Young Men from Six European Countries

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Abstract

Background: Present knowledge on the impact of varicoceles on testicular function is largely based on studies of subfertile and infertile men, making it difficult to extrapolate the impact of varicocele on the general population.
Objective: To describe associations between varicocele and testicular function assessed by semen analysis and reproductive hormones in men from the general population.
Design, setting, and participants: A cross-sectional multicentre study of 7035 young men, median age 19 yr, from the general population in six European countries (Denmark, Finland, Germany, Estonia, Latvia, and Lithuania) were investigated from 1996 to 2010.
Outcome measurements and statistical analysis: We analysed results from physical examination, conventional semen variables, and serum reproductive hormones using multivariable regression analyses.
Results and limitations: A total of 1102 (15.7%) had grade 1–3 varicocele. Increasing varicocele grade was associated with poorer semen quality, even in grade 1 varicocele. In grade 3 varicocele, sperm concentration was less than half of that in men with no varicocele. Presence of varicocele was also associated with higher serum levels of follicle-stimulating hormone, lower inhibin B, and higher levels of luteinising hormone; testosterone and free testosterone were not significantly different between men with and without varicocele. This study cannot draw a conclusion on the progressiveness of varicocele or the effect of treatment.
Conclusions: We demonstrated an adverse effect of increasing grade of varicocele on testicular function in men not selected due to fertility status.
Patient summary: The presence and increasing grade of varicocele is adversely associated with semen quality and reproductive hormone levels in young men from the general population.

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1. Introduction

Varicocele is the medical term for dilated, tortuous spermatic veins in the pampiniform plexus. In the adult general population, the prevalence is approximately 15% [1–3]. It is 35–44% in men with primary infertility and 45–81% in men with secondary infertility [4,5]. The association between the presence of a varicocele and poorer semen quality is well documented in men presenting to fertility clinics [6] and in small-scale studies of patients not selected on fertility criteria [7,8]. Several meta-analyses report improvements in semen quality following varicocelectomy in infertile men [9,10]. However, far from all men with a varicocele are infertile [11].

Varicocele is most commonly observed on the left side, although some men are affected bilaterally. The isolated right-sided varicocele is rare [12]. The right testicular vein drains obliquely into the vena cava, whereas the left drains perpendicularly into the left renal vein, resulting in higher hydrostatic pressure on the left compared with the right side. Also believed to increase left-sided hydrostatic pressure is the so-called nutcracker effect with compression of the left renal vein between the aorta and the superior mesenteric artery [13,14]. The exact pathophysiology behind the adverse effect of varicocele on semen quality remains uncertain. A number of proposed mechanisms have been examined including scrotal hyperthermia, altered testicular blood flow, increased venous pressure, hypoxia, testicular hormonal dysfunction, accumulation of toxic substances, and catecholamine reflux [13,14].

Studies comparing reproductive hormones in infertile men with varicoceles with unaffected infertile men have reported conflicting results. Some reported higher follicle-stimulating hormone (FSH) among infertile men with varicoceles compared with controls but no difference in fertile men [15], whereas others detected no difference among infertile men with varicocele compared with controls [16]. Serum inhibin B was lower in men with varicocele compared with controls in some studies [16,17] but not all [18]. Serum testosterone has been reported lower [16], unchanged [15], or higher in grade 3 varicocele patients compared with grade 1 [19].

Our present knowledge on the potential impact of varicoceles on semen quality and reproductive hormones is largely based on studies of subfertile and infertile men, as well as observations of increased prevalence in groups of men referred to fertility and urology clinics where the cause of infertility might not be limited to the varicocele. Even in cases where varicocele is the only discernible cause of infertility, preselection of infertile patients will include only the severely affected cases. The lack of large-scale population-based studies makes it difficult to extrapolate the impact of the varicocele on reproductive health to the general population. We therefore describe associations between varicocele and hormonal and semen variables in a large number of young men from general populations in Europe who were not selected due to fertility status, semen quality, or presence of varicocele to evaluate the potential impact of the varicocele on testicular function.

2. Materials and methods

The current study is based on a large cross-sectional investigation of semen quality in unselected young men from the general population, standardised and coordinated between six European countries. The local Science Ethics Committees approved the studies, and participants gave written informed consent before participation. Information about inclusion and assessment procedures were previously described in detail [20,21]. We offer a very brief overview, with expanded details in Supplement 1.

2.1. Study population

In total, 7035 young European men were included from 1996 to 2010 in the current study when attending a compulsory medical examination before being considered for military service. Men from the Copenhagen area (Denmark), the Hamburg area (Germany), the Turku area (Finland), the Riga area (Latvia), Kaunas area (Lithuania), and the Tartu area (Estonia) were asked to participate in the semen quality study, regardless of whether they were deemed fit for military service. The only further inclusion criteria for the current study were complete data on the presence and grade of varicocele, diagnosed by a trained physician according to a standardised protocol for physical examination (flowchart in Supplementary Fig. 1). The Estonian men were divided into ethnically Estonian and Russian men. The regional distribution of men is shown in Supplementary Table 1. Men who gave consent participated in the local research unit and answered a questionnaire on previous and current diseases and conditions and lifestyle factors, delivered a semen sample and a blood sample, and underwent a physical examination. All procedures were performed on the same day. Participants were instructed to abstain from ejaculation for at least 48 h before the study visit.

The presence of varicocele, hydrocele, changes in the epididymis, and the location and size of the testes were evaluated by inspection and palpation only by trained physicians according to a standardised protocol for physical examination. For the assessment of testicular size, all examiners used the same type of wooden orchidometer. Varicocele was graded with the men in standing position: grade 0: no varicocele present, grade 1: only palpable during the Valsalva procedure, grade 2: palpable in the resting state, and grade 3: plainly visible [22].

All examiners were medical doctors employed at departments of andrology and performed andrologic physical examinations as part of their daily clinical practice. Twelve examiners performed the physical examination for 90% of the men; seven others performed the remaining 10% of the physical examinations. Supplementary Table 2 shows the specifics of the examining physicians and their diagnostic rates.

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