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ORIGINAL ARTICLE

Testicular volume discrepancy is associated with decreased semen quality in infertile Japanese males with varicoceles

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Abstract
Purpose We retrospectively reviewed infertile Japanese males for testicular volume discrepancies (D) and semen parameters to evaluate whether left grade II–III varicoceles (V) cause testicular damage.
Methods Seventy-seven patients who had idiopathic male infertility and 88 who had V without other causes of infertility were examined. We excluded cases of azoospermia. Testicular volume was measured using a punched-out orchidometer. D was defined as a size difference of at least 3 ml. The frequency of D was compared between the patients with and without V. The semen parameters were reviewed in association with D and V.
Results The mean left and right testicular volumes were 19.4 and 20.1 ml, respectively ($p < 0.001$). D with a smaller left testis was more common in V+ cases than in V− cases (26.1 vs. 13.0%, $p = 0.0351$). The sperm count and motility were also significantly lower ($p = 0.0213$ and $p = 0.0217$, respectively) in the D+ patients with a smaller left testicular volume.
Conclusions In the patients with V, D was more common than in those without V. The semen parameters were worse if D was present in the patients with V. These results indicated that V could induce testicular atrophy and negatively affect semen quality. Therefore, the ipsilateral reduced testicular volume is considered to be a sign of persisting testicular damage by V.

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Introduction

Varicoceles have been considered to be a reversible cause of male subfertility for more than 40 years [1]. Varicoceles are present in approximately 15% of the general population, in 19–41% of males with primary infertility and in 45–81% of those with secondary infertility [1–4]. It is generally accepted that male patients with varicoceles are at risk for an accelerated, progressive decrease in fertility with time if the varicocele is left unrepaired [5].

The infertile male patients often experience ipsilateral testicular atrophy in the presence of a varicocele. This is believed to be due to continuous damage by the existing varicocele. Testicular hypotrophy associated with a varicocele is the most common indication for prophylactic varicocele repair in adolescents. After varicocele repair, the majority of adolescents and adults have catch-up growth of the affected testis [6–8]. The recommendation to perform varicocele repair in adolescents and young adults is based on the assumption that patients with varicocele-associated testicular hypotrophy are more likely to have impaired semen parameters and fertility in adulthood [9]. In this context, Sigman and Jarow [9] reported that infertile patients with testicular hypotrophy associated with unilateral varicoceles have worse semen parameters than those without hypotrophy, which supports the development of testicular damage due to varicoceles.

The objective of this study was to evaluate the testicular volume discrepancy, which represents atrophy in the affected testis, in the patients with or without left grade II-III varicoceles, and to determine the impact of testicular

volume discrepancy on the semen parameters. To our knowledge, this is the first such study in a Japanese population.

Materials and methods

Patients

After obtaining institutional review board approval, we retrospectively reviewed the records of patients who visited the Male Infertility Clinic of Toyama University Hospital from April 2006 to March 2011 with availability of a medical history, physical examination and the results of at least two semen analyses. The present study included 165 patients; 77 had idiopathic male infertility and 88 had grade II–III unilateral left varicoceles without other possible causes of their infertility. The definition of male infertility is the failure to conceive following 12 months of unprotected intercourse by possible male factors. The patients were excluded from the study if they had bilateral or right varicoceles, or a history of cryptorchidism, vasectomy, varicocelectomy or orchiectomy. Patients with azoospermia were excluded from the study because of the significant potential of a pathological condition other than a varicocele causing their infertility. This work was undertaken under the provisions of the Declaration of Helsinki.

Patient evaluation

Varicoceles were diagnosed during a scrotal examination with the patient in a standing position and were graded according to Suzuki's study [10]. Patients with left grade II–III varicoceles were included in this study. Those with a grade I varicoceles were not included because their impact on testicular function was thought to be minimal, and such patients are not appropriate candidates for varicocele repair.

The testicular volume was measured using an orchidometer consisting of 14 punched-out elliptical rings with graded volumes, 1–26 ml (1 to 6, 8, 10, 12, 14, 16, 19, 22 and 26 ml) [11]. A difference in testicular volume of 3 ml or more was considered to be a significant volume discrepancy [9, 12]. The semen analyses were performed according to the WHO guidelines [13, 14]. Semen samples were obtained by masturbation after at least 5 days of abstinence. Samples were collected into sterile containers and allowed to liquefy at 37°C for 30 min, and then analyzed for the sperm concentration, percent motility according to the WHO criteria and morphology according to Tygerberg's strict criteria [15]. At least two centrifuged semen samples were carefully examined for each patient. According to the Guidebook for Reproductive Medicine 2010 edited by the Japan Society of Reproductive Medicine, if semen analysis was performed twice, the mean values were used. If semen analysis was performed more than twice, the median values were used for analyses [16]. We chose the data from the cases with left grade II–III varicoceles and a right testicular volume $\geq$19 ml for subclass analyses. We judged the size $\geq$19 ml as an adequate testicular volume according to the studies by Sigman [9] and Iwamoto [17].

The serum follicle-stimulating hormone (FSH) level was measured by chemiluminescent immunoassays. The serum total testosterone concentration was also measured by radioimmunoassay.

Statistical analyses

A paired t test was performed to evaluate the volume differences between the right and left testes. The chi-square test was used to analyze the incidence of volume discrepancies between the right and left testes. A one-way analysis of variance (ANOVA) was used to analyze the differences between groups. A p value <0.05 was considered to be statistically significant. The JMP software program version 8.0.1 (SAS institute JAPAN) was used for the data analyses.

Results

Background of the patients

The mean age of the patients was 35 years old, and the duration of infertility was an average of 46 months. No statistical difference was observed in the clinical factors, including hormone levels and semen quality, between the patients with idiopathic male infertility and those with left grade II–III varicoceles (Table 1).

Volume differences between the right and left testes

The testicular volumes were smaller in the left than in the right testis among the whole cohort of patients ($p < 0.0001$). In the patients with left grade II–III varicoceles, the testicular volume difference was significant ($p = 0.0001$), with smaller left testes. Within the group of patients with idiopathic male infertility, the left testes were also smaller; however, the difference did not reach significance (Table 2).

The relationship between a testicular volume discrepancy and the presence of left grade II–III varicoceles

A testicular volume discrepancy was significantly more common (26.1%) in the patients with left grade II–III varicoceles than in those with idiopathic male infertility

Table 1 The background of the patients

Patient characteristics	Patient group			p value (ANOVA, a vs. b)
	Whole cohort ($n = 165$, mean ± SD)	Idiopathic male infertility ($n = 77$, mean ± SD)[a]	Left grade II-III varicoceles ($n = 88$, mean ± SD)[b]	
Age (years old)	34.7 ± 5.8	35.0 ± 6.2	34.3 ± 5.4	0.4805
Duration of infertility (months)	46.1 ± 32.3	41.7 ± 29.9	49.8 ± 33.9	0.1264
Serum FSH level (mIU/ml)	7.14 ± 5.90	6.75 ± 5.29	7.5 ± 5.84	0.3999
Serum total testosterone level (ng/ml)	4.08 ± 1.26	3.89 ± 0.15	4.26 ± 0.14	0.0708
Semen volume (ml)	2.66 ± 1.12	2.64 ± 1.56	2.67 ± 1.29	0.8868
Sperm count ($\times 10^6$/ml)	44.5 ± 55.0	51.3 ± 56.8	38.5 ± 52.9	0.1367
Sperm motility (%)	32.8 ± 18.9	32.8 ± 19.2	32.7 ± 18.6	0.9578
Sperm normal morphology (%)	26.4 ± 17.6	25.5 ± 15.6	27.3 ± 19.3	0.5115

Table 2 A comparison of the volumes between the right and left testes

Patient group	Testicular volume (ml)		p value (Paired t test)
	Right	Left	
Whole cohort ($n = 165$)	20.1 ± 4.7	19.4 ± 4.8	<0.0001*
Idiopathic male infertility ($n = 77$)	20.4 ± 4.8	19.9 ± 5.0	0.0743
Left grade II–III varicoceles ($n = 88$)	19.9 ± 4.6	18.9 ± 4.6	0.0001*

* Statistically significant

Table 3 The association of a testicular volume discrepancy and the presence of left grade II–III varicoceles

Patient group	Presence of testicular volume discrepancy (right > left)		Chi-square test	Presence of testicular volume discrepancy (right > left, right testis ≥ 19 ml)		Chi-square test
	(+) $n = 33$	(−) $n = 132$		(+) $n = 33$	(−) $n = 81$	
Idiopathic male infertility	10 (13.0%)	67	$p = 0.0351$*	10 (17.5%)	47	$p = 0.0073$*
Left grade II–III varicoceles	23 (26.1%)	65		23 (40.4%)	34	

* Statistically significant

(13.1%, Table 3). The incidence of discrepancy was much higher (40.4%) in the patients with left grade II–III varicoceles than in those with idiopathic male infertility (26.3%) among those with a right testicular volume ≥19 ml [9, 17].

The association between testicular volume discrepancies and semen parameters

In 57 cases with left grade II–III varicoceles and a right testicular volume ≥19 ml, a testicular volume discrepancy was associated with poorer semen quality. The sperm count, sperm motility and total motile sperm count were significantly lower in the patients with testicular volume discrepancies than in those without any difference. The sperm morphology was not significantly different between the two groups (Table 4).

On the other hand, if the same analysis was performed among the 56 patients with idiopathic male infertility and a right testicular volume ≥19 ml, no relationship was observed between the semen parameters and volume discrepancy status (Table 5).

Discussion

In this study, nearly half of Japanese male infertility patients with left varicoceles had a testicular size discrepancy, which was associated with worse semen quality. In the patients with left grade II–III varicoceles, a testicular volume discrepancy was significantly more common than in those without significant varicoceles. These findings are similar to the previous reports from Western countries [9, 18]. To our knowledge, this study is the first such

Table 4 The relationship between testicular volume discrepancies and semen parameters in 57 cases with left grade II-III varicoceles and a right testicular volume ≥19 ml

Semen parameter	The presence of testicular volume discrepancy (right > left)		*p* value (one-way ANOVA)
	(+) (n = 23, mean ± SD)	(−) (n = 34, mean ± SD)	
Semen volume (ml)	2.9 ± 1.1	2.2 ± 1.2	0.0194*
Sperm count ($\times 10^6$/ml)	57.9 ± 28.1	65.0 ± 71.3	0.0213*
Sperm motility (%)	28.4 ± 18.3	40.7 ± 19.6	0.0217*
Sperm normal morphology (%)	24.4 ± 16.6	30.4 ± 21.4	0.2659
Total motile sperm count ($\times 10^6$)	26.2 ± 33.6	66.2 ± 77.2	0.0235*

* Statistically significant

Table 5 The relationship between testicular volume discrepancies and semen parameters in 56 cases without left grade II–III varicoceles (right testicular volume ≥19 ml)

Semen parameter	The presence of testicular volume discrepancy (right > left)		*p* value (one-way ANOVA)
	(+) (n = 14, mean ± SD)	(−) (n = 42, mean ± SD)	
Semen volume (ml)	2.6 ± 1.3	2.7 ± 1.7	0.8775
Sperm count ($\times 10^6$/ml)	49.2 ± 50.4	64.7 ± 61.8	0.4819
Sperm motility (%)	27.6 ± 28.30	34.9 ± 17.8	0.3151
Sperm normal morphology (%)	19.2 ± 14.3	28.3 ± 16.3	0.1281
Total motile sperm count ($\times 10^6$)	47.3 ± 72.5	73.4 ± 119.5	0.5301

investigation in a Japanese population. The results of this study indicate that the existence of testicular volume hypotrophy with ipsilateral grade II–III varicoceles is evidence of persisting testicular damage by the varicocele. Therefore, this finding can encourage physicians to perform varicocele repair.

Sigman and Jarow identified 611 male infertility patients with unilateral clinical left varicoceles, including 305 (50%) with ipsilateral testicular hypotrophy (a volume decrease of 3 ml or more, including right testicular volume >19 ml). Infertile patients with testicular hypotrophy associated with unilateral varicoceles showed worse semen parameters than those without hypotrophy [9]. These data support the idea that varicocele repair is indicated for adolescents with varicocele-associated testicular growth retardation [9]. The present study demonstrated results consistent with this report.

In addition, Ku et al. [19] reported in a community-based study that varicoceles negatively influenced the testicular volume on the affected side in young Korean males and that the subjects with higher grades of varicoceles had an enlarged testis on the contralateral side. Sakamoto et al. [20] reported that left clinical testicular varicoceles were associated with relative ipsilateral testicular hypotrophy in infertile Japanese patients. However, the semen quality was not evaluated in these Asian study series.

Male infertility due to a varicocele may be caused by several mechanisms [21]. Varicoceles are more commonly (90%) found on the left side. It has also long been recognized that left-sided varicoceles can have bilateral effects [22, 23]. Left venous distension is involved in the mechanism leading to the contralateral response to a unilateral varicocele [24, 25]. In the present study, the semen quality was worse in patients with a testicular volume discrepancy, even if the contralateral testicular size was considered to be large enough. This finding supports the fact that a unilateral varicocele has bilateral effects.

Previous studies have reported that the improvements in semen parameters after varicocele repair were positively related to the varicocele size; the sperm concentration and motility improved significantly in males with higher grade varicoceles after microsurgical ligation of the varicocele. On the other hand, it has been reported that testicular atrophy in an infertile patient indicated a decreased potential for seminal improvement and pregnancy after varicocele repair [24, 26]. In our clinical experience, the semen parameters improved after varicocele repair in the patients with left grade II–III varicoceles, regardless of the presence of a testicular volume discrepancy (data not shown). In addition, it was reported that a bilateral testicular volume increase was observed with improvement of semen parameters after varicocele repairs in Japanese male infertility patients [27].

There are some limitations to this study. First, the study sample size was relatively small compared to the previous studies. In addition, the design of the present study was

retrospective. It is possible that the results might be different if the study were to be performed in a larger cohort of patients and with a prospective design. The control population in the present study also comprised infertile males, although the patients' backgrounds were not significantly different between the two groups.

In conclusion, the presence of a testicular volume discrepancy was observed two times more often in patients with left grade II–III varicoceles than in those without. The semen parameters were significantly lower in the patients with a testicular volume discrepancy with left grade II–III varicoceles, even if the contralateral testis was of normal size. These results indicate that the presence of left grade II–III varicoceles can have a significant negative impact on spermatogenesis in Japanese patients with infertility. The reduced testicular volume with ipsilateral grade II–III varicoceles is a sign of persisting testicular damage by the varicocele. Further studies are needed to confirm these findings.

Conflict of interest The authors have nothing to disclose.

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