



Varicocele repair for low testosterone

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Purpose of review

Several recent clinical studies have added to the existing literature on the impact of varicocelectomy on serum testosterone levels. These studies were not included in the most recent previous review of this topic and strengthen considerably the evidence base supporting the claim that varicocele repair can reliably restore below-normal testosterone levels.

Recent findings

Three studies were published in 2011 on the effect of varicocele repair on testosterone levels. These studies were all adequately powered to detect statistically significant changes in testosterone preprocedure and postprocedure, and all demonstrated significant increases in testosterone levels in patients who had low preprocedure testosterone levels.

Summary

Varicocele repair can restore testosterone to the eugonadal range in hypogonadal patients with either unilateral or bilateral varicocele.

Keywords

hypogonadism, low testosterone, microsurgical repair, testosterone, varicocele, varicocelectomy

INTRODUCTION

Varicocele is an abnormal enlargement of the internal spermatic vein and pampiniform plexus of the testis. Most urologists believe that varicoceles arise from incompetent or absence of valves within the major veins of the testis, although other etiological factors no doubt play a role [1]. Varicocele typically occurs on the left side, but bilateral varicoceles occur in more than 50% of patients [2]. In the general male population, the prevalence of varicocele is between 10 and 15%, but is as high as 40% among men with infertility [3]. It is likely that the pathophysiological processes that promote varicocele begin as early as puberty because the incidence of varicocele in adolescents is similar to that of adults [4].

The association of varicocele and male infertility has been known for more than a century [5] and varicocele is now regarded as the leading cause of male infertility [6^{***}]. The effect of varicocele on testosterone levels, however, has not been as well studied or defined. The studies conducted prior to 2011 have yielded results that are difficult to interpret, which has led to equivocal statements about the utility of varicocele repair for correcting hypogonadal levels of testosterone. Several recent studies, however, have produced consistent evidence for both the harmful effects of varicocele on testosterone production and for the restoration of normal

testosterone levels following varicocele repair in men with below-normal testosterone levels. This article reviews the totality of evidence to date and makes recommendations based on that evidence.

PATHOPHYSIOLOGICAL EFFECTS OF VARICOCELE

The harmful effects of varicocele on both fertility and testosterone production are likely caused by a combination of factors that include testicular hyperthermia, hormonal dysfunction, increased or decreased testicular blood flow, reflux of toxic metabolites, and/or seminiferous tubular hypoxia [7]. Testosterone levels are maintained by the Leydig cells in the testes, and there are several hypotheses about how varicocele could impair Leydig cell functioning. The hyperthermia produced by varicocele, for example, may

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KEY POINTS

- Varicocele is the leading cause of male infertility and has been suspected of impairing testosterone biosynthesis.
- Several recent studies have added high-quality data to an existing base of research clearly demonstrating that varicocele can impair testosterone production and that varicocele repair can restore testosterone to the eugonadal range in hypogonadal male patients of all ages with either unilateral or bilateral varicocele.
- Varicocele repair in men with normal or above-normal testosterone levels may not have a significant effect on testosterone, although repair may nonetheless be warranted for other reasons, such as a desire for increased fertility.

inhibit 17 α -hydroxyprogesterone aldolase, an enzyme responsible for the conversion of 17 α -hydroxyprogesterone to testosterone [8]. Another theory suggests that varicocele indirectly creates conditions of oxidative stress in the seminiferous tubules [9]. Ishikawa *et al.* [9] found that the expression of 8-hydroxy-2-deoxyguanosine in the seminiferous tubules was more prevalent in patients with varicocele, and that this expression was linked to the release of reactive oxygen species.

That varicocele is, indeed, capable of impairing androgen synthesis has been demonstrated in both animal studies and those in humans. For example, two studies with rats demonstrated that surgical creation of varicocele resulted in lower testosterone levels, and that these reductions were fully corrected by surgical repair of the varicocele. [10,11]. Several studies have observed below-normal mean testosterone levels in men with palpable varicoceles [6^{••},12^{••},13^{••}].

EARLIER STUDIES OF VARICOCELE REPAIR AND TESTOSTERONE LEVELS

Until recently, the evidence on the effect of varicocele repair on testosterone levels has been relatively mixed, with some studies showing a rise in testosterone levels following repair, and others finding no statistically significant rise (see Table 1).

The results of earlier studies that did not find a statistically significant rise in testosterone following varicocele repair are difficult to interpret. For example, participants in the studies by Di Bisceglie *et al.* [18], Zheng *et al.* [21], and Rodriguez *et al.* [20] appear to have had normal-to-above-normal baseline testosterone levels, which may have limited the ability of these studies to detect a rise in testosterone level after varicocelectomy [18,20,21]. Methodological differences in the way testosterone levels

Table 1. Major studies of the relationship between varicocelectomy and testosterone

Paper, year	Study type	N	Mean prevaricocelectomy TT, ng/dl ^a	Mean postvaricocelectomy TT, ng/dl ^a
Su <i>et al.</i> [14]	Retrospective	35	319 ± 12	409 ± 23 (<i>P</i> < 0.0004)
Cayan, <i>et al.</i> [15]	Retrospective	78	563 ± 140	837 ± 220 (<i>P</i> < 0.01)
Gat, <i>et al.</i> [16]	Retrospective	83	348 ± 175	496 ± 243 (<i>P</i> < 0.001)
Lee, <i>et al.</i> [17]	Retrospective	12	348 ± 202	416 ± 358 (<i>P</i> = 0.25)
Di Bisceglie <i>et al.</i> [18]	Retrospective	38	650 ± 50	660 ± 50 (<i>P</i> = 0.97)
Hurtado de Catalfo <i>et al.</i> [19]	Prospective	36	298 ± 17	398 ± 20 (<i>P</i> = NA)
Rodriguez <i>et al.</i> [20]	Prospective	202	648 ± 156	709 ± 232 (<i>P</i> > 0.05)
Zheng <i>et al.</i> [21]	Prospective			
LV group		53	599 ± 157	619 ± 160 (<i>P</i> > 0.05)
BV group		51	615 ± 159	627 ± 162 (<i>P</i> > 0.05)
Hsiao <i>et al.</i> [22 ^{••}]	Retrospective			
Baseline T < 400 ng/dl		49	309 ± 7	431 ± 16 (<i>P</i> < 0.001)
Baseline T > 400 ng/dl		57	498 ± 17	463 ± 31 (<i>P</i> = 0.29)
Sathya Srini <i>et al.</i> [12 ^{••}]	Prospective	100	177 ± 18	301 ± 43 (<i>P</i> < 0.001)
Tanrikut <i>et al.</i> [6 ^{••}]	Retrospective	325	358 ± 126	454 ± 168 (<i>P</i> < 0.001)
Zohdy <i>et al.</i> [13 ^{••}]	Prospective	103	379 ± 206	450 ± 170 (<i>P</i> < 0.001)

BV, bilateral varicocelectomy; LV, left-side only varicocelectomy; TT, serum total testosterone.

^aTestosterone results originally reported in other units of measurement (i.e. ng/ml or nmol/l) have been converted to the more standard ng/dl for ease of comparison.

were obtained and measured between these studies make interpretation of the reported high baseline testosterone levels difficult to interpret as well.

A 2007 study by Lee *et al.* [17] showed a post-varicocelectomy rise in testosterone compared to baseline, but the change did not reach statistical significance. This likely resulted from the relatively small numbers of individuals (12) and the very wide range of testosterone values recorded after varicocelectomy (416 ± 358 ng/dl).

Despite these difficulties of interpretation, a meta-analysis of studies published up until May 2011 concluded that a varicocele causes a disturbance of Leydig cell function resulting in decreased testosterone biosynthesis (and) surgical repair significantly increasing testosterone levels in men with varicocele [23[■]]. Nonetheless, this meta-analysis did not include three more recent articles, all of which found statistically significant increases in testosterone levels following varicocelectomy in men with below-normal baseline levels [12[■],13[■],22[■]]. These studies strengthen considerably the evidence base about the positive relationship between varicocele repair and testosterone levels.

RECENT STUDIES

Three studies were published in 2011 with results that shed valuable light on the issue of varicocele repair and testosterone levels. Hsiao *et al.* [22[■]] retrospectively reviewed the records of men who underwent microsurgical subinguinal varicocelectomy. The primary goal of the study was to determine if older age is associated with similar improvements in semen parameters and testosterone after subinguinal microsurgical varicocelectomy compared to younger men.

A total of 272 men met the study inclusion criteria. Patients were divided into three groups based on age at surgery: less than 30 years, 30–39 years and 40 years or older. After varicocelectomy, when analysis was restricted to men with baseline testosterone of 400 ng/dl or less, there was a mean increase in testosterone of 136 ng/dl in men younger than 30 years; a mean increase of 133 ng/dl in men 30–39 years old; and a mean increase of 110 ng/dl in men 40 years or older. Men with normal testosterone (defined as >400 ng/dl) did not show a statistically significant postsurgical rise in testosterone, however, leading the authors to the conclusion that ‘varicocelectomy is unlikely to improve testosterone production in men with normal testosterone.’ Nonetheless, the study concluded that microsurgical varicocelectomy resulted in significant increases in sperm concentration, total sperm count and testosterone in all age groups studied, including

men in the fifth and sixth decades of life, and that the surgery ‘should be offered to older men for infertility and/or hypogonadism.’

Sathya Srinani and Belur Veerachari [12[■]] analyzed 200 heterosexual infertile men diagnosed with clinical varicocele. The men were divided into two groups: 100 men had microsurgical varicocelectomy; the other 100 men underwent assisted reproduction procedures. All participants had semen analysis, serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, and total testosterone, measured both at recruitment time and 6 months later. In the varicocelectomy group, the mean total testosterone level increased significantly after varicocelectomy, from 177 ± 18 ng/dl at baseline to 301 ± 43 ng/dl ($P < 0.0001$). Testicular size correlated with the mean change in total testosterone ($P = 0.001$). No similar change was found in the group assigned to assisted reproduction procedures. In addition, of the 100 patients in the varicocelectomy group, 78 had postoperative normalization of total testosterone, compared to only 16 men in the assisted reproduction group. The authors concluded that varicocelectomy significantly improves serum testosterone level in men with hypogonadism and infertility and also improves symptoms of erectile dysfunction in men with hypogonadism.

Finally, Zohdy *et al.* [13[■]] sought to determine the impact of varicocelectomy on serum total testosterone level and erectile function in men with infertility and clinical varicocele. This study included 141 heterosexual infertile men with varicocele. They were divided into two groups: 103 men had microsurgical varicocelectomy and 38 men who decided to pursue assisted reproduction procedures. All participants completed the International Index of Erectile Function (IIEF)-5 questionnaire and underwent semen analysis. Serum levels of FSH, LH, prolactin, and total testosterone were measured both at recruitment time and 6 months later.

Mean total testosterone level increased from 379.1 ng/dl ± 205.8 at baseline to 450.1 ± 170.2 ng/dl after varicocelectomy ($P < 0.0001$). No similar change was found in the group who chose assisted reproduction procedures. Of the 49 patients in group 1 with hypogonadism at baseline assessment (defined as total testosterone <300 ng/dl), 37 (75.5%) exhibited a postoperative normalization of total testosterone. In contrast, only three of 15 hypogonadal men (20%) in group 2 had normal testosterone levels at the second visit. IIEF-5 scores improved significantly postoperatively in patients with hypogonadism (17.1 ± 2.6 to 19.7 ± 1.8 , $P < 0.001$).

The authors concluded that varicocele is associated with hypogonadism in some infertile patients, and that varicocelectomy significantly improves serum testosterone in infertile men, especially those with hypogonadism. This improvement in total testosterone level may be reflected in elevated IIEF scores.

CONCLUSION

Varicocele is the leading cause of male infertility and has been suspected of impairing testosterone biosynthesis. The effects on testosterone levels of varicocele and varicocele repair have, until recently, been equivocal. Several recent studies have added high-quality data to an existing base of research that, when combined, produce a consistent body of evidence for both the harmful effects of varicocele on testosterone production and the restoration of normal testosterone levels following varicocele repair in men with below-normal testosterone levels. The potential utility of varicocele repair for older men with androgen deficiency, in particular, has now been more fully characterized.

Although varicocele repair may not have a significant effect on testosterone in men with normal or above-normal testosterone levels, varicocelectomies may be warranted for other reasons, such as a desire for increased fertility. Potentially limiting the conclusions that can be drawn from both recent and former studies is the fact that they were conducted on subfertile or infertile men. Because testosterone levels have been seen to decline after varicocele repair in men with high testosterone levels and to increase after repair in men with low testosterone levels, the possibility cannot be excluded that researchers are observing a regression to the mean of a highly variable biological parameter. More research into these issues is clearly warranted.

The weight of available evidence, however, does strongly support the recommendation that varicocele repair can restore testosterone to the eugonadal range in hypogonadal male patients of all ages with a unilateral or bilateral varicocele.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

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- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 526).

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