

Testosterone and Varicocele



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KEYWORDS

- Varicocele • Hypogonadism • Leydig cell • Erectile dysfunction • Testosterone • Steroidogenesis
- Androgen receptor • Varicocelectomy

KEY POINTS

- A multitude of studies suggests an adverse effect of varicocele on Leydig cell function.
- Men with lower preoperative serum testosterone levels have greater improvements in postvaricocelectomy testosterone levels as compared with eugonadal men.
- The pathophysiology of varicocele-mediated hypogonadism is poorly understood and remains an area of continued investigation.

INTRODUCTION

A varicocele is an aberrant dilation of the pampiniform plexus, the network of veins draining the testis. It is a common entity with a prevalence of 10% to 20% in the general population.^{1,2} Most varicoceles are asymptomatic and have an inconsequential impact on the individual's testicular function. However, a small subset of men will present with infertility, orchialgia, or ipsilateral testicular hypotrophy, which serve as common indications for varicocelectomy.^{3,4}

Traditionally, varicocele has been characterized by its impact on spermatogenesis via local effects on Sertoli and germ cells. It has become more evident, however, that varicocele presents a pantesticular insult. Leydig cell dysfunction is now a recognized potential consequence of varicocele and appears to be a reversible phenomenon with varicocelectomy.⁵ Multiple mechanisms for decreased androgen production have been proposed, likely reflecting a multifactorial process. Nevertheless, the pathophysiology of varicocele-mediated Leydig cell dysfunction, as with the cause of the varicocele's link to subfertility, remains an area of ongoing research.

CLINICAL DATA

Early Evidence

Initial reports exploring the possible impact of varicocele on testosterone production were limited by retrospective design, small cohorts, and selection bias.⁶⁻⁹ In addition, certain subsets of men will have worse Leydig cell function than others, an issue that may have limited studies that had permissive inclusion criteria. Comhaire and Vermeulen¹⁰ published one of the earliest reports documenting normalization of total testosterone levels in men undergoing varicocelectomy. In their small cohort of 33 men presenting with a clinical varicocele, 10 of the men had low serum testosterone levels (mean <400 ng/dL) and concomitant erectile dysfunction, both of which improved after varicocele repair. This initial account precipitated several other analyses of cohorts of men who presented with infertility and concurrent varicocele. In 1978, Rodriguez-Rigau and colleagues¹¹ expanded on Comhaire's work and analyzed a group with palpable varicoceles who also underwent testicular biopsy as part of their fertility evaluation. All subjects had serum testosterone levels in the normal range, albeit subjects with

Disclosures: None.

Funding: None.

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Urol Clin N Am 43 (2016) 223–232

<http://dx.doi.org/10.1016/j.ucl.2016.01.009>

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bilateral varicoceles typically had lower levels than those with unilateral varicoceles. Histopathologic assessment of the biopsy samples revealed diminished Leydig cell counts that were especially pronounced in men with concomitant oligospermia. In addition, they identified an abnormal testosterone-to-luteinizing hormone (LH) ratio in men with worse spermatogenesis. From these data, they postulated that varicocele affects all functions and cell lines of the testis.

Multiple small series followed that refuted the concept that varicoceles result in decreased testosterone synthesis.^{6,7,12-14} A study by Pirke and colleagues⁷ found normal testosterone levels among 21 subjects who presented with varicocele, a result mirrored by Weiss and colleagues,⁸ who reported on a cohort of 16 men with accompanying hypospermatogenesis. A contemporaneous analysis by Pasqualini and colleagues⁶ also documented normal testosterone levels in a group of 17 patients; however, their data did demonstrate elevated LH levels, leading to the conclusion that men with varicoceles can have normal androgen levels via compensated LH production.

These early conflicting accounts were offset by progressively larger cohorts that offered higher-quality evidence. In 1984, Ando and colleagues¹⁵ published their account of 108 infertile men with varicocele compared against 46 infertile men without varicocele. Those men with varicocele had significantly lower testosterone levels regardless of degree of oligospermia. The group also documented worse testosterone concentrations for those men who had their varicoceles for longer lengths of time. This finding suggested that varicocele imposes progressive negative impacts on both spermatogenesis and Leydig cell function.^{15,16} Subsequently, in 1995, Su and colleagues¹⁷ reviewed their experience in men undergoing varicocelectomy. In a group of 53 patients, they found a statistically significant increase of serum testosterone from a mean preoperative level of 319 ng/dL to a postoperative value of 409 ng/dL. Their analysis also demonstrated an inverse relationship between preoperative testosterone concentration and anticipated postoperative testosterone increase. This finding raised the possibility that some men, especially those with poorer preoperative Leydig cell function, may disproportionately be affected by their varicocele and may have meaningful improvements in testosterone after varicocelectomy.

Contemporary Evidence

The work of Su and colleagues¹⁷ was further bolstered by multiple studies that documented

improved testosterone levels following varicocele repair (**Table 1**). Cayan and colleagues¹⁸ followed 78 men who underwent varicocelectomy, quoting an improvement of mean serum testosterone from 563 to 837 ng/dL. In a similar cohort, Gat and colleagues¹⁹ found significant improvements of total and free testosterone following gonadal vein embolization, suggesting that the positive effect of varicocele repair may not be sensitive to mode of treatment.

Despite these compelling data, many investigators continued to find insignificant improvements of testosterone following varicocelectomy.²⁰⁻²² Rodriguez-Peña and colleagues²² reported a group of 202 patients with grade II or III varicoceles. Their results demonstrated a mean testosterone increase of 61 ng/dL, although the finding did not reach statistical significance. In another large series by Al-Ali colleagues²³ in which 1111 men had presented for infertility evaluation, the presence of grade III varicoceles was actually associated with higher testosterone levels. These conflicting reports were ultimately contextualized by Hsiao and colleagues²⁴ in 2011. In this series, 106 men underwent hormonal evaluation before and after varicocelectomy similar to previous study designs. However, Hsiao and colleagues stratified their cohort into men with eugonadal testosterone levels and biochemical hypogonadism (\geq or $<$ 400 ng/dL, respectively). As was the case with Su's initial finding in 1996, men with lower initial serum testosterone experienced far greater increases in their androgen levels as opposed to the eugonadal individuals.¹⁷ Many of the studies that did not find significant improvements of serum testosterone following varicocele repair had cohorts characterized by normal preoperative testosterone levels (ie, greater than 400 ng/dL).^{20-22,25} For instance, the study subjects of Rodriguez-Peña and colleagues²² had a mean preoperative testosterone level of 648 ng/dL. The cohort of Pierik and colleagues²⁰ was also eugonadal in 90% of the cases.

Several studies have corroborated Hsiao's finding.²⁴ Tanrikut and colleagues²⁶ examined a large series of 325 men who had undergone varicocelectomy for infertility and contrasted them against 510 men who presented for vasectomy. The varicocele group had significantly lower serum testosterone levels than control subjects. Of the 200 men in whom both preoperative and postoperative hormonal profiles were available, a mean testosterone increase of 96 ng/dL was demonstrated. They found that 79% of the men with initial testosterone levels less than 300 ng/dL had normal testosterone concentrations following varicocelectomy. A similar study

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