Invited Review Article

Effect of Varicocele and Its Treatment on Testosterone in Hypogonadal Men with Varicocele: Review of The Literature

Running title: Varicocele and Testosterone

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Abstract
Varicocele might cause deterioration in Leydig cell functions, and is a significant risk factor for hypogonadism. Some controversial issues have been to treat hypogonadal men with varicocele. Symptomatic hypogonadal men with varicocele might have two options to be treated either with testosterone replacement therapy or treatment of varicocele. However, both approaches have some advantages and disadvantages. This review summarizes effect of varicocele on plasma total testosterone level, and addresses whether varicocele repair is effective to improve testosterone levels in hypogonadal men with varicocele.
Experience from large clinical studies in the literature suggests that varicocele repair may increase serum testosterone level in men with varicocele and testosterone deficiency. Varicocele repair could be offered to men with clinically palpable varicocele and hypogonadism. As the treatment method, microsurgical varicocele repair could be preferred to provide the best improvement. Another advantage of varicocele repair for hypogonadism, instead of exogenous testosterone treatment, would be saving fertility status in men who will desire a child in the future. However, further studies are required to clarify varicocele related Leydig cell dysfunction, and also to advice hypogonadal patients for sufficient effectiveness of the varicocele repair.
Keywords: Adult, Urinary tract, Testicular, Testosterone, Varicocele

Varicocele might cause deterioration in Leydig cell functions, and is a significant risk factor for hypogonadism. There are some controversial issues in the treatment of hypogonadism and varicocele. Symptomatic hypogonadal men with varicocele might have two options to be treated either with testosterone replacement therapy or treatment of varicocele. However, both approaches have some advantages and disadvantages. Approximately 90% of men will remain azoospermic under exogenous testosterone treatment, leading to fertility issues. Even discontinuation of exogenous testosterone treatment, 35% of symptomatic men might have irreversible azoospermia (1). In hypogonadal men who desire child, stimulation of hypothalamic pituitary testis (HPT) axis with gonadotropins and clomiphene citrate could be difficult to monitor serum hormone levels. In case of men who prefer varicocele repair, it is unclear whether patients will have enough increase in testosterone after varicocele repair. Treatment success might depend on treatment method (surgery or radiologic interventions) and complications rates, including varicocele recurrence and testicular atrophy.
Varicocele can be treated in the presence of clinical findings such as inability to conceive, abnormality in semen parameters, and scrotal pain in case, analgesics and anti-inflammatory drugs fail (2). Infertile men with hypogonadism and varicocele can be managed with either treatment of varicocele via surgery (open, laparoscopic) or radiologic embolization or use of assisted reproductive technologies (ART). ART, consisting of intrauterine insemination (IUI), in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), is offered

based on total motile sperm count. If treatment of varicocele is preferred, improvement of testosterone level will take some time, and if ART is preferred to conceive, testosterone treatment might be given to these hypogonadal men for late onset hypogonadism (LOH) symptoms (3).

This review summarizes efficacy of varicocele itself on plasma total testosterone level, and addresses whether treatment of varicocele is effective in the improvement of serum testosterone levels in men with hypogonadism and varicocele.

Evidence for varicocele related hypogonadism and effect of treatment for varicocele on testosterone

Varicocele might cause decreased testosterone synthesis and impaired sperm production, predicting a link between varicocele and hormonal dysfunction. Evidence for varicocele related hypogonadism and effect of it's treatment on testosterone have been demonstrated with experimental and clinical studies.

Experimental studies

Experimental studies have shown impairment in Leydig cell functions in animal studies, decrease in intratesticular testosterone in human testicular tissues and measurement of human testicular temperature in men with varicocele at the beginning and after the treatment of varicocele.

Varicocele related hyperthermia might cause impairment in the cholesterol synthesis pathway by defecting 17α-hydroxylase and 17,20-lyase enzymes inhibition leading to increased ROS level (4). As experimental evidence to show varicocele related Leydig cell damage, Zheng et al divided 50 adolescent male rats into 4 groups as varicocele, sham, artery ligating and sparing varicocelectomy groups to measure Johnen's score, morphologic structure of seminiferous tubules and intratesticular testosterone level (5). They found that presence of varicocele impaired Leydig cell function, and artery sparing varicocelectomy repaired Leydig cell function, but artery ligating varicocelectomy led to additional deterioration.

In another rat study, Luo et al measured serum and intratesticular testosterone, apoptosis and expression of steroidogenetic acute regulatory (StAR) protein, which is transporter of cholesterol and androgen products into the mitochondria (6). They found that varicocele itself impaired Leydig cell function by increasing apoptosis and suppressing the expression of the StAR protein.

In an experimental rat study, Rajfer et al compared measurement of intratesticular testosterone and Δ4 pathways of testosterone synthesis, including 17-alpha-hydroxylase, 17,20- desmolase and 17-βeta-hydroxysteroid dehydrogenase between the time dependent varicocele groups and control (sham) group (7). They concluded that varicocele provides detrimental effects in the biosynthesis of testosterone in both testes, and this effect seems to be primarily at the 17,20- desmolase step.

Wright et al measured testicular temperature before and after microsurgical varicocele repair in 119 men with varicocele and 45 controls with no varicocele (8). They found that presence of varicocele increased testicular temperatures on both sides even in men with unilateral and bilateral varicoceles. Microsurgical varicocele repair provided a decrease in testicular temperatures on both sides.

Clinical studies

Several clinical studies have reported effect of varicocele on serum testosterone. Ando et al compared measurement of serum gonadotropins, testosterone, 17-OH-progesterone, dihydrotestosterone (DHT) and estradiol (E2), and hormonal response to human chorionic gonadotropin (hCG) stimulation between 108 patients with varicocele and 46 controls (4). They found that 17-hydroxy-progesterone significantly increased and testosterone significantly decreased in the patients with varicocele, compared to the controls. They concluded that presence of varicocele affects testicular hormone production due to enzymatic impairment.

In the literature, very limited clinical studies have focused on the effect of varicocele repair on serum testosterone and effect of varicocele repair on sexual functions in hypogonadal men with varicocele. The first study in 1975 reported that 10 out of 33 (30%) men with varicocele had decreased testosterone level and erectile dysfunction, and after varicocelectomy both symptoms improved in those men (9). Rodriguez-Rigau and colleagues in 1978 reported that men with varicocele and normal range of testosterone level demonstrated decrease in Leydig cell counts on testicular biopsy in men who underwent varicocelectomy (10). In addition to plasma total testosterone level, we demonstrated that men with varicocele had also decrease in free testosterone level and increase in plasma follicle stimulating hormone (FSH) level, and after microsurgical varicocele repair, plasma total and free testosterone level significantly increased, and FSH level significantly decreased (11). In 2011, Tanrıkut et al demonstrated that men with varicocele had lower serum total testosterone level compared to controls (12). Of the men with low serum total testosterone level, 79% had normal serum total testosterone level after varicocelectomy, and 16% of controls had normal testosterone level over the same period.

Hayden &Tanrıkut reviewed 18 studies to investigate effect of varicocele repair on serum total testosterone level (13). Although symptomatic hypogonadal men showed greater improvement in postoperative serum testosterone levels, the presence of low testosterone level in men with varicocele remains a controversial indication for repairing varicoceles.

Li et al reported a meta-analysis consisting of 9 studies with 814 patients to investigate effect of varicocele treatment on testosterone level in infertile men with varicocele (14). They found that mean plasma total

testosterone level increased 97.48 ng/dL after varicocele repair, suggesting improvement in Leydig cell functions.

Guercio et al investigated all indications for varicocele repair in a contemporary cohort of 18-45 years old men with varicocele, using a commercial database in the USA (15). They found semen analysis (OR: 2.78) and serum testosterone evaluation (OR: 1.67) as the strongest predictors of varicocele repair. Therefore, they concluded that although presence of fertility problems still remains # 1 indication for varicocele repair, presence of decreased testosterone level is an independent predictor in the clinical practice to manage varicoceles in the USA.

Hsiao et al included 78 patients with varicocele who underwent microsurgical varicocele repair, and compared serum testosterone level from pre-treatment to post-treatment, according to varicocele grades (16). They found that 83% of the patients had increase in postoperative testosterone, and varicocele repair provided increased level of serum testosterone, regardless of the varicocele grading. Repair of even small varicoceles provided increased serum testosterone levels. In another study, the same group compared serum testosterone level according to patients' age groups in 272 patients with varicocele and testosterone level of <400 ng/dl who underwent microsurgical varicocele repair (17). They found that surgical treatment of varicocele yielded significant improvement in sperm parameters and testosterone even men in the older ages, and therefore, varicocele repair could be offered to older infertile men with hypogonadism (17).

Zohdy et al reported 141 infertile men with varicocele, and compared serum total testosterone and international index of erectile function (IIEF-5) score from the beginning to the end of the study between 103 men who underwent subinguinal microsurgical varicocelectomy, and 38 men who preferred assisted reproduction procedures (ART) (18). They found that the IIEF-5 scores significantly increased from 17.1±2.6 to 19.7±1.8, and serum testosterone significantly increased from 379.1±205.8 ng/dl to 450.1±170.2 ng/dl, and 75.5% of the patients had normalization of testosterone following varicocele repair. However, no significant change was found in the patients with varicocele who preferred ART.

Tanrikut et al included 325 men with varicocele and 510 controls (vasectomy reversal) to compare serum total testosterone, by age before and after varicocele repair (12). They found that plasma testosterone level significantly increased from 358±126 ng/dl to 454±168 ng/dl after surgery, and 70% had increased level of testosterone (increase of 0-50% in 41%, 51-100% in 19% and >100% in 10%). Therefore, they concluded that varicocele might cause androgen deficiency, and treatment of varicocele might increase testosterone levels in hypogonadal men with varicocele.

Abdel-Meguid et al conducted a prospective controlled study with four groups to compare serum total testosterone at 6 and 12 months: infertile men with and without varicocele (hypogonadal/ eugonadal) and fertile men with and without varicocele (hypogonadal/eugonadal) (19). They found significantly lower testosterone level in men with varicocele compared to normal men. Varicocelectomy provided significant increases in total testosterone among hypogonadal men, but no improvement in eugonadal men. Increase in testosterone level showed strong correlation with preoperative testosterone and sperm concentrations.

Serum total testosterone can even increase after treating recurrent varicoceles. Çayan and Akbay divided 217 infertile men with recurrent varicocele into two groups: 120 underwent redo microsurgical subinguinal varicocele repair, and 97 were observed only, as the control group (20). In their study, postoperative semen parameters, serum total testosterone level and spontaneous pregnancy rates significantly improved with microsurgical varicocele repair for recurrence of varicocele, compared to the controls. Pregnancy was achieved in 52.5% of the couples in the surgical treatment group, and in 39.2% of the control group. The surgical group had a mean of 1.36 ng/ml increase in total testosterone while the control group had a mean of 0.23 ng/ml decrease at the end. Treatment of recurrent varicoceles also decreased need for use and level of ART (20).

In one meta-analysis, Chen et al included 7 studies, consisting of 712 patients, to compare pre-and post-surgical serum testosterone levels (21). The mean post-operative serum testosterone improved by 34.3 ng/dl, compared with pre-treatment levels. The mean testosterone level increased by 105.65 ng/dl in the hypogonadal men, favouring varicocele repair (21). However, results must be treated with caution and adequate cost benefit analysis must be undertaken to determine weighing up the risks and benefits of surgical intervention over exogenous testosterone treatment in this setting.

Table 1 shows all studies in the literature, reporting effect of microsurgical varicocele repair on serum testosterone level in hypogonadal men with clinical varicocele. All of the 6 studies included in the table provided significant improvement in the mean serum total testosterone level after microsurgical varicocele repair in the hypogonadal men with varicocele.

Novel treatment options for varicocele in hypogonadal men

Hypogonadal men with varicocele can be treated with open surgery, radiologic interventions and laparoscopic approaches (23,24). When infertile men with varicocele are treated, the best seminal improvement is aimed with the lowest complication rates such as varicocele recurrence, hydrocele and testicular atrophy. Studies suggest that only 35-50% of men who have treatment for varicocele would have a positive seminal response to varicocele treatment, and the others would have a negative response to varicocele treatment due to varicocele

recurrence, genetic disorders and technical failure (23,24). Table 2 shows complications and fertility outcomes of the studies in the literature for the treatment for varicocele.

Advantages of the radiologic interventions for the treatment of varicocele seem to be faster recovery period with relative low cost, however such interventions include interventional unsuccess to enter access sheath, contrast agent allergy, trombosis and higher recurrence rate due to anatomical vein structures. Laparoscopic approach could provide faster postoperative recovery period. However, disadvantages of laparoscopic and the Palomo technics include no possibility to ligate external spermatic veins that could cause persistent or recurrence of varicocele. In addition to ligation of the internal spermatic vein branches, open surgical inguinal and sub-inguinal approaches provide also ligating external spermatic vein. Sub-inguinal approach provides less postoperative pain compared to inguinal approach, because the aponeurosis of the external oblique muscle is not opened with the sub-inguinal approach. However, the inguinal approach provides ligating less number of internal spermatic vein channels, and the arteries could be preserved easily at the proximal level, because of less number of artery branches, compared to the distal level with the sub-inguinal approach.

All treatment methods for primary varicocele were compared in a meta-analysis (23). This meta-analysis demonstrated that the highest spontaneous pregnancy rate was achieved with the microsurgical varicocelectomy series (42%). This rate, in order, with other methods was 37.7% for the Palomo technique series, 36% for the macroscopic inguinal varicocelectomy series, 33.2% for the radiologic interventions and 30% for the laparoscopic varicocelectomy techniques. This meta-analysis also demonstrated the lowest complication rates with the microsurgical varicocelectomy techniques (1.05% for recurrence of varicocele and 0.44% for hydrocele formation), compared to other varicocelectomy methods.

CONCLUSIONS

Varicocele might cause deterioration in Leydig cell functions, and is a significant risk factor for hypogonadism. Experience from large clinical studies in the literature suggests that varicocele repair may increase serum testosterone level in men with varicocele and testosterone deficiency. Approximately 60-80% will have normalization of testosterone level after varicocele repair in men with low level of serum testosterone. Varicocele repair could be offered to men with clinically palpable varicocele and hypogonadism. As the treatment method, microsurgical varicocele repair might provide the most improvement in serum total testosterone level, compared to other varicocelectomy methods.

Another advantage of varicocele repair for hypogonadism, instead of exogenous testosterone treatment, would be saving fertility status in men who will desire a child in the future. However, further prospective randomized controlled studies are required to clarify varicocele related Leydig cell dysfunction, and also to advice hypogonadal patients for sufficient effectiveness of the varicocele repair.

REFERENCES

1. Samplaski MK, Loai Y, Wong K, Lo KC, Grober ED, Jarvi KA. Testosterone use in the male infertility population: prescribing patterns and effects on semen and hormonal parameters. Fertil Steril 2014;101(1):64-9.
2. Schlegel PN, Goldstein M. Alternate indications for varicocele repair: non-obstructive azoospermia, pain, androgen deficiency and progressive testicular dysfunction. Fertil Steril 2011; 96: 1288-93.
3. Practice Committee of the American Society for Reproductive Medicine. Management of nonobstructive azoospermia: a committee opinion. Fertil Steril 201;110(7):1239-45.
4. Ando S, Giacchetto C, Colpi G, Beraldi E, Panno ML, Lombardi A, Sposato G. Physiopathologic aspects of Leydig cell function in varicocele patients. J Androl 1984;5:163-170.
5. Zheng YQ, Zhang XB, Zhou JQ, Cheng F, Rao T, Yao Y. The effects of artery-ligating and artery-preserving varicocelectomy on the ipsilateral testes in rats. Urology 2008;72:1179-84.
6. Luo DY, Yang G, Liu JJ, Yang YR, Dong Q. Effects of varicocele on testosterone, apoptosis and expression of StAR mRNA in rat Leydig cells. Asian J Androl 2011;13:287-91.
7. Rajfer J, Turner TT, Rivera F, Howards SS, Sikka S. Inhibition of testicular testosterone biosynthesis following experimental varicocele in rats. Biol Reprod 1987;36:933-7.

8. Wright EJ, Young GPH, Goldstein M. Reduction in testicular temperature after varicocelectomy in infertile men. Urology 1997;50:257-9.
9. Comhaire F, Vermeulen A. Plasma testosterone in patients with varicocele and sexual inadequacy. J Clin Endocrinol Metab 1975;40:469-74.
10. Rodriguez-Rigau LJ, Weiss DB, Zukerman Z, Grotjan HE, Smith KD, Steinberger E. A possible mechanism for the detrimental effect of varicocele on testicular function in man. Fertil Steril 1978;30:577-85.
11. Çayan S, Kadioglu A, Orhan I, Kandirali E, Tefekli A, Tellaloglu S. The effect of microsurgical varicocelectomy on serum follicle stimulating hormone, testosterone and free testosterone levels in infertile men with varicocele. BJU Int 1999;84(9):1046-9.
12. Tanrikut C, Goldstein M, Rosoff JS, Lee RK, Nelson CJ, Mulhall JP. Varicocele as a risk factor for androgen deficiency and effect of repair. BJU Int 2011;108:1480-4.
13. Hayden RP, Tanrikut C. Testosterone and varicocele. Urol Clin N Am 2016;43:223-32.
14. Li F, Yue H, Yamaguchi K, Okada K, Matsushita K, Ando M, Chiba K, Fujisawa M. Effect of surgical repair on testosterone production in infertile men with varicocele: a meta-analysis. Int J Urol 2012;19:149-54.
15. Guercio C, Patil D, Mehta A. Hypogonadism is independently associated with varicocele repair in a contemporary cohort of men in the USA. Asian J Androl 2019;21:45-9.
16. Hsiao W, Rosoff JS, Pale JR, Powell JL, Goldstein M. Varicocelectomy is associated with increases in serum testosterone independent of clinical grade. Urology 2013;81:1213-1218.
17. Hsiao W, Rosoff JS, Pale JR, Greenwood EA, Goldstein M. Older age is associated with similar improvements in semen parameters and testosterone after subinguinal microsurgical varicocelectomy. J Urol 2011;185:620-5.
18. Zohdy W, Ghazi S, Arafa M. Impact of varicocelectomy on gonadal and erectile functions in men with hypogonadism and infertility. J Sex Med 2011;8:885-93.
19. Abdel-Meguid TA, Farsi HM, Al-Sayyad A, Tayib A, Mosli HA, Halawani AH. Effects of varicocele on serum testosterone and changes of testosterone after varicocelectomy: a prospective controlled study. Urology 2014;84:1081-7.
20. Çayan S, Akbay E. Fate of recurrent or persistent varicocele in the era of assisted reproduction technology: Microsurgical subinguinal redo varicocelectomy versus observation. Urology 2018;117:64-9.
21. Chen X, Yang D, Lin G, Bao J, Wang J, Tan W. Efficacy of varicocelectomy in the treatment of hypogonadism in subfertile males with clinical varicocele: A meta-analysis. Andrologia 2017;49(10):1-8.
22. Sathya Srini V, Belur Veerachari S. Does varicocelectomy improve gonadal function in men with hypogonadism and infertility? Analysis of a prospective study. Int J Endocrinol 2011;2011:916380.
23. Çayan S, Shavakhabov S, Kadioglu A. Treatment of palpable varicocele in infertile men: a meta-analysis to define best technique. J Androl 2009;30:33-40.
24. Rotker K, Sigman M. Recurrent varicocele. Asian J Androl 2016;18:229-33.

TABLE 1. Studies in the literature, reporting effect of varicocele repair on serum testosterone level in hypogonadal men with clinical varicocele.

Studies	Year	# cases	Treatment method	Preoperative testosterone (ng/dL)	Postoperative testosterone (ng/dL)
Zohdy et al (18)	2011	49	Microsurgical	219.3±65.8	358.1±94
Sathya Srini&Belur Veerachari (22)	2011	100	Microsurgical	177±18	301±43
Hsiao et al (17)	2011	72	Microsurgical	309±7.4	431±16.2
Tanrikut et al (12)	2011	200	Microsurgical	358±126	454±168
Hsiao et al (16)	2013	78	Microsurgical	308.4±7.1	417.5±14.8
Abdel-Meguid et al (19)	2014	28	Microsurgical	233.8±50.7	336.1±53.8

TABLE 2. Complications and fertility outcomes of the studies in the literature for the treatment for varicocele					
Treatment methods	**Preservation of artery**	**Hydrocele**	**Recurrence**	**Morbidity**	**Spontaneous pregnancy***
Retroperitoneal	No	1-24%	0-17%	No	37.69%
Macroscopic inguinal	No	3-32%	12-45%	No	36%
Laparoscopic	Yes	2-12%	1-15%	Yes	30.07%
Radiologic	Yes	0	15-25%	Yes	33.2%
Microscopic	Yes	0-3%	0-3%	No	41.97
*Based on the meta-analysis by Çayan et al (23).					