

ROLE OF SPERMATIC VEIN INHIBIN B AND LDH ACTIVITY AS PREDICTORS OF TESTICULAR DYSFUNCTION IN VARICOCELE PATIENTS

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ABSTRACT

Inhibin B generated by Sertoli cells provides negative feedback on FSH secretion. In men, inhibin B seems to be physiologically important form of inhibin. Lactic dehydrogenase (LDH), an intracellular enzyme that indicates cellular damage. Varicocele has been associated with infertility and disturbed spermatogenesis .

We aimed to investigate the relationship between varicocele, LDH and inhibin B.

This study was conducted on forty infertile men with varicocele and twenty age matched control men.

LDH and inhibin B were measured in the blood samples of these 40 patients with varicocele which were obtained synchronously from spermatic and peripheral veins during operation and in peripheral vein of control men.

Varicocele patients were classified into two groups: group I twenty patients with normal sperm concentration (> 20 million /ml), and group II twenty patients with low sperm concentration (< 20 million /ml).

FSH and testosterone were measured by chemiluminescence while inhibin B was measured by enzyme immunoassay method. LDH enzyme

activities were assayed by enzymatic U.V methods.

Sperm counts ranged from 3.9 to 60 million/ml, while motility ranged from 15 to 48% . LDH level & inhibin B in spermatic vein were significantly higher than the level in peripheral vein. There was no correlation between sperm counts and LDH level in spermatic vein. Inhibin B concentrations in spermatic vein correlated significantly with serum concentration of FSH ($r = -0.63$, $p < 0.001$) and free testosterone ($r = 0.34$, $p < 0.05$) and also correlated significantly with sperm counts ($r = 0.44$, $p < 0.01$) and total testicular volume ($r = 0.56$, $p < 0.01$). Inhibin B showed significant reduction in patients with varicocele than in control men, while LDH showed no significant difference. There were significant increase in inhibin B and LDH in both peripheral vein and spermatic vein of men with sperm count > 20 million /ml when compared with men who had count < 20 million/ml.

In conclusion : significant increase in spermatic vein LDH and inhibin B levels were observed in varicocele.

These findings suggest that inhibin B may offer an improved diagnosis of testicular dysfunction. Consequently, spermatic vein LDH activity and inhibin B level can be predictors of testicular dysfunction in varicocele.

INTRODUCTION

Varicocele has been associated with infertility and disturbed spermatogenesis (28). Inhibin are dimeric glycoproteins consisting of an alpha-subunit covalently joined by disulfide links to either Ba subunit (Inhibin A) or a Bb subunit (Inhibin B) (32). Inhibins are primarily produced by the gonads and the placenta, and have been initially characterized by their ability to exert a negative feedback on pituitary FSH synthesis and release (40). Although semen analysis and serum FSH levels have been well studied in relation to male infertility, the assay for inhibin B has become available (21). Inhibin B, produced by Sertoli cells of the seminiferous tubule, is the principal form of inhibin in men and regulates FSH secretion by a closed loop negative feedback mechanism (2,4,26). FSH in turn, is a stimulator of inhibin B production (2).

The serum inhibin B level has emerged as a good marker of spermatogenesis and Sertoli cell function (15,29). Studies have emphasized the fact that inhibins may act at the gonadal levels as paracrine and/or autocrine factors (6,22). Mormandi et al., (24) found direct correlation between inhibin B levels and LH, testosterone and testicular volume in normal adolescents.

Lactate dehydrogenase (LDH) activity is present in all cells of the body and is invariably found only in the cytoplasm of the cell. Enzyme levels in various tissues (liver, heart, kidney, etc) are very high compared with those in serum. Thus, leakage of the enzyme from even a small mass of damaged tissue can increase the observed serum level of LDH to a significant extent (28). LDH measurement in infertility has been done in seminal plasma especially LDH-X, an isoenzyme of LDH and specific for testis. It was found to be well correlated with sperm count (11,27).

In this study, we have investigated whether spermatic vein LDH activity and inhibin B levels can be useful

predictors of testicular dysfunction in varicocele.

SUBJECTS AND METHODS

Subjects

This study comprised 40 infertile patients with left varicocele. All of the patients had stress pattern in their seminogram. The count ranged from 3.9 to 60 million/ml and motility from 15% to 48%. The patients, age was 23-34 (mean 25.2 ± 4.9 years).

Blood samples from the left internal spermatic vein were obtained through a polyethylene catheter inserted 3 - 4 cm proximal to the ligation site of the vessel during varicocele operation. Blood samples from brachial vein were obtained simultaneously. Sera were separated and kept frozen at -70 C until analysis of inhibin, LH, FSH and testosterone.

In all patients, body mass index (BMI) was calculated by dividing body weight (in kilograms) by height (in square meters). Each testis was measured with a caliber and the testicular volume was calculated using the formula $\text{volume (V)} = 1/6 \text{ length}$

width² (7). The patients were further subclassified according to sperm count.

METHODS

Collection of semen samples :

The samples were collected by masturbation into sterile plastic screw capped 50 ml containers after sexual abstinence for 3-5 days. A single sample provided by each subject was examined by conventional method (38). The samples were incubated at 37° C for an average of 20-30 minutes to allow liquefaction. Semen samples were examined for the physical characters including appearance, viscosity, volume, odour, and time of liquefaction. Each specimen was thoroughly mixed and subjected for laboratory analysis.

Semen analysis was done by the "conventional analysis" according to the method described by Mortimer (25) and WHO (38), the total sperm concentration (millions/ml), the percentage of motile sperms, and the percentage of abnormal forms were assessed. Assessment of sperm concentration was done through making "volumetric dilution and haemocytom-

etry" using improved Neubauer haemocytometer chamber.

All subjects were blood sampled after an overnight fast for serum levels of FSH, LH, testosterone (free and total) in addition to inhibin B. All subjects did not take any medication especially gonadotropins during the 2 weeks proceeding sampling.

For gonadotrophins (FSH & LH): Additional two blood samples 20 minutes apart were pooled with part (2 ml) of the first morning sample and the three samples were mixed, centrifuged and stored, to avoid cyclic and episodic changes.

The blood samples were collected in pyrogen free collection tubes and the serum was separated, divided into aliquots and stored at -70 °C until use for estimation of hormones.

Serum FSH, LH were determined using solid phase, two site chemiluminescent enzyme immuno-metric assay for use with the immulite automated analyzer (Immulite, Diagnostic products corporation, Los Angeles, CA). The immulite system

automatically handles samples and reagents additions, the incubations, separation, and measurement of the photon output via temperature controlled luminometer. Immulite system automatically calculates the sample concentration from master curve checked by 2 level high and low adjusters.

Serum total testosterone was measured using electrochemiluminescence immunoassay (ECLIA) method (Elecys 1010), Boehringer Mannheim, Germany). It is a competition principle where sample is incubated with a testosterone specific biotinylated antibody and a testosterone derivative labeled with a ruthenium complex. After the addition of streptavidin coated microparticles the entire complexes become bound to the solid phase via interaction of biotin and streptavidin. The microparticles are magnetically captured onto the surface of the electrode. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.

Free testosterone in serum was

measured using a ^{125}I solid phase radioimmunoassay. The materials were supplied by DPC, Los Angeles CA, USA).

Serum inhibin B was measured by enzyme immunoassay according to the method previously described by Lambert-Msserlian et al., (20) and Groome et al., (13). Total LDH enzyme activities were measured in serum by the enzymatic UV method (bio-Merieux, France).

STATISTICAL ANALYSIS

Statistical analysis was carried out with SPSS 7.5 for windows statistical software package. The studied parameters were tested by paired t test. The criterion of significance was value of $p < 0.05$. Correlation was calculated with Pearson's method.

RESULTS

Significant increase was observed in FSH, in patients with varicocele in comparison to controls. On the other hand, testicular volume, sperm density, sperm motility, percentage of spermatozoa with normal morphology, and inhibin B showed significant decrease in patients with varicocele

than in control men. While age, BMI, LH, LDH, total testosterone and free testosterone showed no significant differences (Table 1).

Table (2) shows that inhibin B, LDH and total testosterone levels were significantly higher in spermatic vein compared to peripheral vein values in patients with varicocele.

Table (3) shows comparison of hormonal levels and LDH between the men who had sperm density above 20 million versus those below 20 millions. There were significant increase in inhibin B, FSH, LDH and testosterone in peripheral vein of men with sperm count > 20 million/ml when compared with men who had count < 20 million/ml. Also, the same findings for inhibin B, LDH and testos-

terone in spermatic vein.

Table (4) shows that spermatic vein inhibin B has significant negative correlation with measured peripheral vein FSH, and LH. On the other hand, spermatic vein inhibin B has significant positive correlation with measured peripheral vein free testosterone, inhibin B, and LDH, measured spermatic vein LDH and total testosterone and with measured testicular volume, sperm density, sperm motility and sperm morphology.

Table (5) shows that peripheral vein inhibin B has significant negative correlation with measured peripheral vein FSH, and LH. It shows non significant correlation with other measured peripheral vein and seminal parameters and testicular volume in control men.

Results:

Table (1) Clinical and serum laboratory data of the whole studied group.

Parameters		Patient group (n=40)	Control men (n=20)	P value
Age (years)		25.2±4.9	26.1 ± 4.3	>0.05 NS
BMI (Kg/m ²)		23.8±4.2	24.1 ± 4.1	>0.05 NS
Testicular volume	Right (ml)	12.9±5.8	20.3 ± 1.1	<0.001
	Left (ml)	9.4 ± 5.3	19.8 ± 1.1	<0.001
FSH (Iu/ml)		9.5± 4.1	4.4 ± 2.6	<0.001
LH (Iu/ml)		5.0 ± 2.54	4.3 ± 2.8	>0.05 NS
LDH (U/L)		159.8 ± 47.3	152.2 ± 45.4	>0.05 NS
Testosterone (ng/ml)		4.5 ± 1.3	4.7 ± 1.2	>0.05 NS
Inhibin B (pg/ml)		135.5 ± 21.5	159.1 ± 43.1	<0.001
Sperm motility (%)		30.5 ± 4.5	72.5 ± 11.2	<0.01
Sperm concentration (million/ml)		15.3 ± 7.9	51.5 ± 10.4	<0.01
Free testosterone (pg/ml)		20.4 ± 4.6	21.4 ± 5.1	>0.05 NS
Sperm morphology (%normal)		39.5 ± 5.3	53.5 ± 8.2	<0.001

Table (2) Comparison between spermatic vein and peripheral vein laboratory data in the whole varicocele patients.

Parameters	Peripheral vein	Spermatic vein	P value
Inhibin B (pg/ml)	135.5±21.5	216.3 ± 26.8	<0.001
LDH (U/L)	159.8±47.3	196.8 ± 51.4	<0.01
Total testosterone (ng/ml)	4.5±1.3	42.3 ± 6.4	<0.001

Table (3) Comparison between two subgroups of varicocele patients. Categorized according to sperm density.

Parameters	Group I (n=20) (Sperm count > 20 million/ml)	Group II (n=20) (Sperm count < 20 million/ml)	P value
<i>I- Peripheral vein data</i>			
Inhibin B (pg/ml)	168.8 ± 31.8	102.2 ± 18.9	<0.001
LDH (U/L)	175.1 ± 49.5	144.5 ± 45.1	<0.001
FSH (IU/ml)	6.8 ± 3.5	12.2 ± 4.6	<0.001
Total testosterone (ng/ml)	4.98 ± 1.22	4.02 ± 1.21	<0.05
<i>II- Spermatic vein data</i>			
Inhibin B (pg/ml)	271.5 ± 32.5	161.1 ± 21.9	<0.001
LDH (U/L)	226.4 ± 54.6	167.2 ± 47.7	<0.001
Total testosterone (ng/ml)	46.2 ± 7.3	37.4 ± 5.5	<0.001

Table (4) Correlation coefficients of spermatic vein inhibin B with other parameters in varicocele patients.

Parameters	Correlation coefficient	P value
<i>A- Peripheral vein data</i>		
FSH	-0.63	<0.001
LH	-0.37	<0.05
Testosterone total	0.28	>0.05
Free testosterone	0.34	<0.05
Inhibin B	0.89	<0.001
LDH	0.36	<0.05
<i>B- Spermatic vein data</i>		
LDH	0.34	<0.05
Testosterone	0.26	>0.05
<i>C- Other data</i>		
Testicular volume	0.56	<0.01
Sperm density	0.44	<0.01
Sperm motility	0.38	<0.05
Sperm morphology	0.39	<0.05

Table (5) Correlation coefficients of peripheral vein inhibin B with other measured peripheral vein, seminal and testicular volume parameters in control men.

Parameters	Correlation coefficient	P value
FSH	-0.51	<0.01
LH	-0.62	<0.01
Testosterone total	0.11	>0.05
Free testosterone	0.16	>0.05
LDH	0.22	>0.05
Testicular volume	0.19	>0.05
Sperm density	0.17	>0.05
Sperm motility	0.13	>0.05
Sperm morphology	0.18	>0.05

DISCUSSION

In this study, a significant correlation was demonstrated between sperm concentration, sperm motility and testicular volume. On the one hand, and serum inhibin B levels on the other in varicocele patients. This interrelationship is not typically found among groups of normal men. These results provide strong evidence that inhibin B is an important marker of the competence of Sertoli cells and spermatogenesis in humans, which is in accordance with the reports on inhibin B and quality of spermatogenesis (1,16,18,19,21,23,29). In the first two studies, a lower inhibin B concentration, was noted in small groups of men with azoospermia, testicular disorders, and infertility, as compared with fertile controls. The results of two larger study populations become available, showing a significant positive correlation of inhibin B with sperm concentration in 349 normal men (18), and with sperm concentration and testicular volume in 65 men with normal and impaired spermatogenesis (19). However, Lee et al. (21) concluded that the significant correlation of inhibin B with FSH, LH, testosterone, sperm density, and sperm

motility among the formerly cryptorchid men reveals interrelationship not apparent in the noncryptorchid control group and not typically found among groups of normal men. Also, Lee et al., (21) showed that no relationship is between Leydig cells and inhibin B secretion. The testes are the source of inhibin B in the monkey is evident from the finding that circulating concentrations of this dimeric inhibin are undetectable in castrated males, in orchidectomized men (1). The finding that serum inhibin B levels are low in men with impaired Sertoli cell function (1) suggests that this cell is probably the major site of testicular inhibin B production. In this respect, inhibin B has been isolated from conditioned media of cultured rat Sertoli cells (14). Moreover, an immunocytochemical investigation utilizing antisera to inhibin alpha and beta subunits provided results consistent with the notion that the primate Sertoli cells produces inhibin B (37). In addition, stimulation of Sertoli cell activity by administration of rh-FSH to normal men results in a significant increase in circulating inhibin B levels (1). For the analyses performed in this study, only a single sample result for the

blood and semen parameters has been used. Although repeated sampling may increase the reliability of the use of these indices as evidence of compromised fertility, we have chosen to analyze using a single data point, because this is far more reasonable approach and clinical assessment (21). Further, there is indirect evidence that a single semen sample is related to fertility (33, 41).

In this study, there is a significant negative correlation between inhibin B and FSH in varicocele patients. This inverse correlation is expected between inhibin B and FSH among men due to feedback relationship between these two hormones. Inhibin B, sperm motility and sperm count were significantly lower in varicocele patients than in control men. These results could be explained on the basis that varicocele affects spermatogenesis. On the other hand, FSH was significantly higher in patient group than in control men.

The hormonal and seminal fluid analysis indicate compromised seminiferous tubule action among the varicocele patient group. Peripheral vein

inhibin B showed significant negative correlation with FSH and LH. On the other hand, inhibin B showed significant positive correlation with free testosterone and LDH activity. The interrelationships demonstrable among these men are similar to those found among a group of men with different medical histories who presented for evaluation of infertility (18,21). Both these two previous reports and the current study suggest that low inhibin B levels correlate with diminished spermatogenesis and may provide an indication for risk of infertility. Although Lee et al., (21) demonstrated that some men with low inhibin B levels were able to father children. It is well known that men with low sperm counts may be successful at paternity (34,38,41) and it should not be surprising that men with low inhibin B levels may also be successful.

The lack of difference between the two groups for LH, testosterone and free testosterone suggests that although a correlation exists between the different indices of testicular function, Leydig cell function is not compromised below the normal range among the varicocele patients. These

findings agree with Lee et al., (21) who studied these parameters in the cryptorchid men.

Published reports of inhibin B levels among groups that include infertile or subfertile men show a negative correlation between FSH and inhibin B (4); with a positive correlation between inhibin B levels and sperm parameters (26,30). A study of two groups of normal men with different mean sperm counts showed the expected correlation between sperm counts and inhibin B and FSH levels (18). A study of 218 consecutive men referred for fertility problems by Pierik et al., (30), which included 17 cryptorchid men (8%), also found correlation of inhibin B to LH and testosterone. However, Lee et al., (21) showed that correlation between inhibin and LH failed to show a correlation when controlled for FSH.

LDH is a marker of tissue damage because LDH tissue level is much higher than LDH serum level. It is an important marker of some disorders including some malignancies, myocardial infarction, liver disease etc.

In this study, no significant difference in serum peripheral LDH level was observed between patients with varicocele and control men. This agrees with Aydin et al., (3) who found no significant difference in serum LDH level after testicular torsion. However, LDH-I isoenzyme increases in some testicular tumors such as teratoma and seminoma as well (28). Some damage to testis has been proven by existing pathology in patients with varicocele. Hypospermatogenesis and maturation arrest patterns, as well as, premature sloughing of spermatids into the tubular lumen are commonly found in testicular biopsy specimens from patient with varicocele and may account for the seminal abnormalities noted (9). Increased intratesticular temperature (39), reflux of renal and adrenal metabolites from the renal vein (8), decreased blood flow (33), and hypoxia (5) have been postulated to account for the varicocele effect. However, infertility in varicocele patients may be multifactorial (28).

Our findings showed that spermatocytic vein LDH level was higher than peripheral vein LDH level in patients

with varicocele. This finding agrees with Odabas et al., (28). So this suggestion should be confirmed by further controlled study of LDH sampling from bilateral spermatic veins in varicocele patients would clarify this relationship of LDH.

In the present study, inhibin B concentrations in testicular venous blood was significantly higher than those observed in the peripheral circulation. Similar results for these findings have been reported for testicular/peripheral vein ratio of immunoactive inhibin (A & B) concentration of 2:1, 5:1, and 10:1 for rats, monkey and human respectively (12, 17, 31,35). This finding in this study suggests that inhibin B is produced by testis. Certainly, the very high testicular/peripheral vein ratio for testosterone (9.4/1) observed in the present study would suggest that the lymphatic route is important for inhibin access to the peripheral circulation, a notion that Plant et al., (31) and Winters et al., (36) have proposed previously. Plant et al., (31) found very high testicular/peripheral vein ratio for testosterone (7.1-37.1) in the male Rhesus monkey.

When hormone levels were compared between the men who had sperm density above or below 20 million/ml, there were significant increase in inhibin B, FSH, and testosterone in peripheral vein of men with sperm count > 20 million/ml when compared with men with sperm count < 20 million/ml. Also, the same findings for inhibin B and testosterone in spermatic vein were reported in this study. There was a significant difference not only for hormones but also for LDH in both peripheral and spermatic veins when men who had sperm density above or below 20 million/ml were compared. These data and differences are further evidence that testicular dysfunction in varicocele patients involves the entire testis, not just the seminiferous tubule. These results agree with Lee et al., (21) who found such differences in patients suffering from cryptorchidism.

Sperm parameters, FSH and inhibin B levels can be used to assess the potential for fertility. Abnormalities among two or three of the parameters suggest a greater likelihood of infertility (21). Also, a change in serum

inhibin B concentration after varicocelelectomy might be helpful to evaluate the improvement of testicular function after varicocelelectomy (10).

In summary, although azoospermia is the only certain predictor of infertility, decreased sperm counts, low inhibin B, low LDH in spermatic vein and elevated serum peripheral vein FSH levels are associated with increased risk of infertility. Inhibin B is the most sensitive index of the integrity of the seminiferous tubule unit, but FSH and sperm density data are also valuable predictors.

Based on the significant correlations among the varicocele patients between peripheral vein inhibin B and spermatic vein LDH and inhibin B levels. These data indicate that spermatic vein LDH activity and inhibin B level can be predictors of testicular dysfunction in these patients. Also, the findings in this current study, of peripheral vein FSH, both spermatic and peripheral vein inhibin B & LDH as well as sperm density are markers for compromised fertility among varicocele men, but also that a greater portion of these men have compromised testicular function.

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تقييم دور الإنهبيين ب ونشاط إنزيم إل.دى. إتش فى الوريد المنوى فى الرجال المصابون بمرض دوالى الحبل المنوى.

بواسطة

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استهدف هذا البحث تقييم دور الإنهبيين ب ونشاط إنزيم إل.دى. إتش فى الوريد المنوى فى الرجال المصابون بمرض دوالى الحبل المنوى. شمل هذا البحث أربعين مريضاً يعانون من العلامات الإكلينيكية والمعملية لمرض دوالى الحبل المنوى بالإضافة إلى عشرين رجلاً كمجموعة ضابطة. تم تقسيم المرضى المصابين بمرض دوالى الحبل المنوى إلى مجموعتين: المجموعة الأولى (٢٠ رجلاً) ذوى عدد حيوانات منوية أكثر من ٢٠ مليون/مل والمجموعة الثانية (٢٠ رجلاً) ذوى عدد حيوانات منوية أقل من ٢٠ مليون/مل وقد تم قياس هرمونات تستوسترون والهرمون المنبه للجريب وهرمون ملوتن والإنهبيين ب ونشاط إنزيم إل.دى. إتش فى مصل الدم من الوريد العضدى (الذراعى) و أيضاً تم قياس هرمونات تستوسترون الكلبي والإنهبيين ب ونشاط إنزيم إل.دى. إتش فى الوريد المنوى فى الرجال المصابون بمرض دوالى الحبل المنوى .

وقد أظهرت نتائج البحث أن مستويات الإنهبيين ب ونشاط إنزيم إل.دى. إتش كانت مرتفعة بدلالة إحصائية فى الوريد المنوي مقارنة بالوريد العضدي (الذراعى) فى مرضى دوالى الحبل المنوى. كما وجد أن مستوى الإنهبيين ب كان منخفضاً ذو دلالة إحصائية فى الوريد العضدى (الذراعى) فى مرضى دوالى الحبل المنوى مقارنة بالمجموعة الضابطة بينما لا يوجد اختلاف ذو دلالة إحصائية فى مستوى نشاط إنزيم إل.دى. إتش. وقد وجدت علاقة طردية ذات دلالة إحصائية بين مستوى الإنهبيين ب ونشاط إنزيم إل.دى. إتش فى المرضى ذو عدد الحيوانات المنوية أكثر من ٢٠ مليون/مل عن المرضى ذو عدد حيوانات منوية أقل من ٢٠ مليون/مل.

ونستطيع الاستنتاج من هذه الدراسة أن مستوى الإنهبيين ب ونشاط إنزيم إل.دى. إتش فى الوريد المنوى من الممكن أن يستخدم كداليتين لتشخيص تأثر عملية تكوين الحيوان المنوى وأذى الخصية فى مرض دوالى الحبل المنوى.

