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IS INHIBIN B A BETTER MARKER OF SPERMATOGENESIS THAN OTHER HORMONES IN INFERTILE MEN IN MOSUL CITY ?

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ABSTRACT : Endocrine evaluation is an important investigation for the evaluation of male infertility. Estimation of the markers of FSH and LH is important to determine whether the subfertility is caused by testicular impairment or an obstructive disorder. Inhibin B has been showed to be a marker of spermatogenesis and subfertile men have decreased or even undetectable serum levels of inhibin B. To assess the role of inhibin B in the evaluation of male factor infertility. All investigations are performed in Infertility clinic at Al-Batool Teaching Hospital in Mosul and private clinic of the researchers. One hundred patients with infertility problems (mean age 34.27±0.76 years) and 50 controls (mean age 34.92±1.03 years) with proven fertility shared in the study for the period from May 2013-March 2014. Serum levels of inhibin B (ng/ml), LH(mIU/ml), FSH(mIU/ml), prolactin (ng/ml) testosterone (ng/ml) and seminal inhibin B were assessed. The mean ±SEM serum and seminal inhibin B and testosterone levels were significantly lower in the patients than in the controls (serum inhibin B 1.38±0.13 vs 192.7±5.8, p=0.000; seminal inhibin B 45.9±4.1 vs 180.6±5.9, p = 0.000; testosterone 4.07±0.28 vs 7.04±0.26, p = 0.000). Whereas, the mean±SEM serum LH, FSH and prolactin were significantly higher in the patients than in the controls (Serum LH 6.39±0.53 vs 3.86±0.27, p = 0.000; FSH 13.2±1.3 vs 5.92±0.3, p = 0.000; prolactin 14.06±0.87 vs 7.78±0.41, p = 0.000). Serum and seminal inhibin B were significantly higher in patients with obstructive azoospermia than in patients with non-obstructive azoospermia (serum inhibin B 35.5±6.4 vs 24±2.7, p = 0.000; seminal inhibin B 36.6±5.7 vs 13.5±1.8, p = 0.000), while serum FSH was significantly higher in patients with non-obstructive azoospermia as compared to obstructive azoospermia patients (FSH 32.39±3.9 vs 10.7±1.7, p=0.000). Serum and seminal inhibin B in patients was negatively correlated with FSH (r = -0.46, r = -0.4 respectively, p = 0.000) and with LH (r = -0.45, r =-0.35, p = 0.000) and was positively correlated with testosterone (r = 0.32, p = 0.001, r = 0.04, p = 0.68). Inhibin B measurement can serve as a direct marker in male infertility and may provide a useful information on obstructive and non-obstructive azoospermia.

Key words : Inhibin B, FSH, LH, male infertility.

INTRODUCTION

Infertility affects 15% of all couples in the world (Sharlip *et al*, 2002). Endocrine evaluation is an important investigation for the evaluation of male infertility, estimation of the levels of endocrine markers such as FSH and LH is important to determine whether the infertility is caused by testicular impairment or an obstructive disorder (Behre *et al*, 1997).

Inhibin B is a protein secreted by granulose cell in the female and Sertoli cell in the male in response to FSH. It is found in great quantities in seminal plasma and follicular fluid (Ying, 1988). Within the human reproductive disease field, the measurement of inhibin has become a catchy, new way to monitor reproductive function (Hall *et al*, 1999).

Inhibin down regulates FSH synthesis and inhibits FSH secretion (Van Zonneveld *et al*, 2003) in accordance with a negative feedback relationship between inhibin and FSH, inhibin secretion is increased by FSH (Hall *et al*, 1999). Androgens stimulate inhibin production; this protein also helps to locally regulate spermatogenesis (Skinner *et al*, 1989).

Serum FSH measurement can be a useful marker for spermatogenesis. However, the diagnostic accuracy of FSH was questioned due to a wide overlap of FSH levels in normal and reduced spermatogenesis (Bergmann *et al*, 1994).

As serum inhibin B in combination with serum follicle stimulating hormone is a more sensitive marker than serum FSH alone for impaired spermatogenesis in men

(Kumanov *et al*, 2006). Therefore, we investigated the infertile men by measuring these markers.

MATERIALS AND METHODS

In this prospective study, 100 hundred men their mean age 34.27±0.76 years were studied for the period from May 2013-March 2014, they were presented with different infertility problems to infertility clinic at Al-Batool Teaching Hospital and private clinic of the researchers after one year of unprotected coitus and after obvious problems in the female partner has been excluded.

Fifty healthy fertile men with proven fertility their mean age 34.92±1.03 years served as controls.

After a written consent was taken from all subjects, they were evaluated by a complete clinical examination by the urologist.

Previous surgical history for varicocelectomy and undescended testis was noted.

The patients were classified into two groups, according to semen analysis as oligospermics (n = 46) and azoospermics (n = 54). The normal values of semen parameters were as follows: sperm count ≥20×10^6/ml, progressive motility ≥50% and normal morphology ≥60% (World Health Organization, 1999).

Azoospermic group were further sub classified into group of men with obstructive azoospermia (n = 38) and men with non-obstructive azoospermia (n = 16).

Blood hormone analysis (FSH, LH, prolactin, testosterone and inhibin B levels) was performed for all patients and controls.

Blood samples were taken at the morning, they were drown from an antecubital vein and centrifuged after clotting,and serum was stored at -20^{0}C until analysis.

Serum FSH, LH, prolactin and testosterone were with commercially available kits using Minividas.

Serum and seminal inhibin B was measured using ELISA/CLIA kit (www.anshlabs.com/Inhibin-B).

Statistical analysis : Hormone levels in the different groups and subgroups are presented as mean±S.E. the unpaired t-test was used to test for the difference in the hormone levels between the different groups. Correlations between serum hormone levels were tested using Pearson correlation. P<0.05 was considered statistically significant value. Statistical analysiswas performed using Minitab Ver. 13.

RESULTS

Serum and seminal inhibin B and testosterone concentrations were significantly lower in patients than in controls (p = 0.000).

Moreover, serum FSH, LH, prolactin concentrations significantly higher in patients than in controls (p = 0.000). (Table 1).

Comparing serum hormonal levels in azoospermics and oligospermics, serum FSH, LH and prolactin concentrations were significantly higher in azoospermics while serum and seminal inhibin B and serum testosterone levels were significantly lower (Table 2).

We further analyzed the inhibin B levels in obstructive (n = 38) vs non obstructive azoospermia (n = 16). Inhibin B levels in men with obstructive azoospermia were significantly higher than its levels in men with non-obstructive azoospermia (p = 0.000).

However, serum FSH level in patients with obstructive azoospermia were significantly lower than its levels in patients with non-obstructive azoospermia (p = 0.000). (Table 3).

Serum inhibin B demonstrated a significant negative correlation with serum FSH level (r = -0.467, p=0.000)

Table 1 : Characteristics of the study population (mean±SEM).

Variable	Patients (n=100)	Control (n=50)	p-value
LH mIU/L	6.39±0.53	3.86±0.27	0.000
FSH mIU/L	13.2±1.3	5.92±0.3	0.000
Prolactin ng/ml	14.06±0.87	7.78±0.41	0.000
Testosterone ng/ml	4.07±0.28	7.04±0.26	0.000
Serum inhibinB ng/ml	1.38±0.13	192.7±5.8	0.000
Seminal inhibinB ng/ml	45.9±4.1	180.6±5.9	0.000

*unpaired t test was used.

Table 2 : Characteristics of the cases classified as oligospermics and azoospermics (mean±SEM).

Variable	Oligospermics (n=46)	Azoospermics (n=54)	p-value
LH mIU/L	4.46±0.44	8.04±0.85	0.000
FSH mIU/L	8.62±1.2	17.2±2.1	0.001
Prolactin ng/ml	13.39±1.1	14.61±1.3	NS
Testosterone ng/ml	4.96±0.44	3.31±0.32	0.003
Serum inhibinB ng/ml	1.86±0.2	0.97±0.15	0.000
Seminal inhibinB ng/ml	64.9±6.7	29.8±4.0	0.000

*unpaired t test was used.

Table 3 : Characteristics of the azoospermics classified into obstructive and non obstructive azoospermia (mean±SEM).

Variable	Non obstructive (n=16)	Obstructive (n=38)	p-value
FSH mIU/L	32±0.39	10.7±1.7	0.000
Serum inhibinB ng/ml	24±2.7	35.5±6.4	0.000
Seminal inhibinB ng/ml	13.5±1.8	36.6±5.7	0.000

*unpaired t test was used.

Table 4 : Correlation among inhibin B and FSH, LH, prolactin and testosterone.

Variable	Patient(n=100)				Oligospermics(n=46)				Azoospermics(n=54)			
	FSH	LH	Prolactin	Testosterone	FSH	LH	Prolactin	Testosterone	FSH	LH	Prolactin	Testosterone
Serum inhibin B ng/ml	-0.46*	-0.45*	-0.08***	0.32**	-0.42**	-0.41**	0.03***	0.09***	-0.44**	-0.42**	-0.14***	0.44**
Seminal inhibinB ng/ml	-0.4*	-0.35*	-0.004***	0.04***	-0.31**	-0.22***	0.13***	-0.22***	-0.39**	-0.33**	-0.08***	0.11***

*Pearson correlation was used. *p=0.000, **p=0.001, ***p=NS

and LH levels (r = -0.458, p=0.000). A significant positive correlation was observed between inhibin B and testosterone levels (r = 0.326, p=0.001) in whole patient group (n = 100), which was similar to a trend observed in oligospermic and azoospermic groups (Table 4).

DISCUSSION

The role of inhibin B in male factor infertility was uncertain until the development of a highly sensitive specific dimeric assay in the mid 1990s.

Several authors reported that serum inhibin B levels reflect testicular function and, more precisely, Sertoli cell function (Anawalt *et al*, 1996; Klingmuller *et al*, 1997).

Our results revealed that inhibin B levels are significantly reduced in men with infertility problems compared with fertile men.

Inhibin B may be used as a marker of spermatogenesis function and male infertility and subfertile men generally have decreased or even undetectable serum levels of inhibin B (Philip *et al*, 2006; Myers *et al*, 2008).

However, a significant increase was observed in the level of other hormones (FSH, LH, prolactin) between the fertile and infertile men and this result disagrees with what was found by other researchers (Philip *et al*, 2006).

Testosterone level is significantly reduced in infertile men compared with fertile men. Testosterone has positive correlation with testicular function (Byrd *et al*, 1998; Raivio *et al*, 1998).

Our results in this study revealed a significant reduction in inhibin B levels in azoospermics as compared to oligospermics confirming the fact that serum inhibin B levelsreflect testicular function (Anawalt *et al*, 1996; Klingmuller *et al*, 1997).

Infertility has been one of the common complications in patients with azoospermia studies reported that infertile men with a previous history of cryptorchidisim have low inhibin B levels compared with the controls (Lee *et al*, 2001).

Inhibin B levels are low in infertile men with cryptorchidisim compared with men with idiopathic subfertility and normal controls (Brazoa *et al*, 2003). Similarly in our study, inhibin B levels significantly lower in patients with non obstructive azoospermia compared to men with obstructive azoospermia. This decrease in inhibin B levels mostly due to irreversible damage that had occurred in these patients. This low inhibin B level is associated with a significant increase in FSH levels.

In our study, an inverse significant relationship between inhibin B and FSH in infertile men was noticed. Similar results were observed in the study of IIIingworth

et al (1996).

Inhibin B and testosterone originate from different types of cells in the testis. Even so; studies reported that both have a positive correlation with testicular function (Byrd *et al*, 1998; Raivio *et al*, 1998).

Inhibin B showed significant positive correlation with testosterone in infertile men. Several authors proposed that some unidentified factors produced by Leydig cells may modulate the inhibin B production in the tubular compartment of the human testis (Byrd *et al*, 1998).

However, a study indicated no significant correlation between inhibin B and testosterone levels (Kolb *et al*, 2000).

For years, FSH has been the most useful marker for assessing a man's fertility status and differentiating between central and peripheral disorders. However, inhibin B may be a more useful direct marker of testicular function and may be a better marker for evaluating male factor fertility than FSH and LH. Measuring inhibin B levels may provide useful information on spermatogenesis than FSH in infertile men.

CONCLUSION

Inhibin B measurement can serve as a direct marker in male infertility and may provide a useful information on obstructive and non-obstructive azoospermia.

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