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Sex Hormone-Binding Globulin (SHBG) Level and It's Associated with Some Sex Hormones in Infertile Iraqi Men

Khaled S. Abd[1] and Adnan F. AL-Azzawie[2]
[1]Salah Al-Din Health Department, Ministry of Health, IRAQ.
[2]College of Science, University of Tikrit, IRAQ.

[1]Corresponding Author: dr_kh683@yahoo.com

ABSTRACT

This study aims to assessment of Sex hormone-binding globulin (SHBG) level and it's associated with some sex hormones such as Follicle stimulating hormone (FSH), Luteinizing hormone (LH), prolactin and testosterone hormone and the infertility type in some infertile Iraqi men.

Blood and seminal fluid samples from (60) idiopathic male infertile and (60) healthful individuals as a control group aged (18 to 60 year) were collected from private clinics. Serum hormones (SHBG, FSH, LH, prolactin and testosterone) were measurement using Enzyme Linked Immunosorbent Assay (ELISA).

The SHBG, FSH, LH and prolactin levels were significantly higher (P≤0.01) expect of the testosterone level was significantly decreased (P≤ 0.01) in the infertile men compared with control group. High significant differences (P≤0.01) were recorded when comparing the hormonal levels (SHBG, FSH, LH, prolactin and testosterone) according to the age groups. There are significant differences (P≤ 0.01) in levels of (SHBG, FSH, LH, prolactin and testosterone) in the infertility period. Smoker infertile men have high levels (P≤ 0.05) in the SHBG and LH while have low levels in the prolactin hormones compared with control. Patients with family history have shown significant differences (P≤0.05) in the levels of DHEA-S, FSH, LH and prolactin.

In conclusion, this study revealed significantly increase in the SHBG levels in the infertile men and negative correlation between SHBG and Testosterone. Therefore, SHBG has important role in the diagnosis and follow up of the male infertility.

Keywords- Male Infertility, SHBG, Sex hormones.

I. INTRODUCTION

Infertility is the inability to become pregnant after one year of normal, unprotected sexual intercourse with the same partner [1]. Or it is a condition in which males are unable to achieve pregnancy after one year of normal unprotected intercourse, often with a sperm count of less than 20 million/ml [2]. Infertility primarily affects the reproductive system of males and females at equal rates [3].

Human sex hormone-binding globulin (SHBG) is a homologous glycoprotein produced by the liver and mainly associated with steroidal sex hormones. Some clinical observations and published reports indicated an inverse relationship between the level of this hormone and markers of non-alcoholic fatty liver disease and insulin. The deficiency of this hormone increases the biological activity of androgens, which in turn cause ovarian diseases and affect the ovulation process and the phenotypic characteristics of PCOS [4]. It has a molecular weight of 90-100KDa, is bound to two peptide chains, and is encoded by a gene located on the short arm of chromosome 17 [5].

Natural steroid hormones are derived from cholesterol and can be categorized according to their different physiological roles through activation of their specific intracellular receptors into five classes: glucocorticoids, mineralocorticoids, androgens, estrogens, and progestogens [6].

Follicle-stimulating hormone (FSH) is a member of the glycoprotein family that has a central and essential role in reproduction. (FSH) is a hormone released by the anterior pituitary gland by stimulation of gonadotrophin secretion and possibly other factors. It is released in a pulsatile manner and is partially regulated by glycoproteins, including activin and inhibin. FSH reflects the status of spermatogenesis as a result of feedback between the testis, hypothalamus and pituitary gland [7].

LH is a glycoprotein that regulates testosterone synthesis by Leydig cells. The levels of these hormones are under the control of negative feedback from gonada [8]. In contrast, serum FSH has a longer shelf life, and fluctuations in serum levels are less pronounced. If an abnormal LH value is obtained in one sample, three samples of serum can be collected within a 20-minute interval between one sample and another [9].

Testosterone is responsible for normal growth, development of male reproductive organs, and maintenance of secondary sexual characteristics, as high levels within the testicles are a prerequisite for sperm production and development, improving their motility and improving epididymal function, and there is some controversy about the required relative levels [10].

The hormone prolactin, secreted by the anterior pituitary gland, has a detrimental effect on male fertility when it exceeds the physiological level [11]. It has an important role in the formation of sperm in males, prolactin may have a physiological role in regulating

testosterone [12], and hyperprolactinemia leads to infertility in about 11% of males [13]. Where Prolactin controls both LH and FSH production through the regulation of GnRH, as an elevated level of prolactin will decrease GnRH secretion by slowing down the frequency of GnRH pulsations and thus reducing FSH and LH pulsatility [14].

II. MATERIAL AND METHODS

The study included 90 men and included (60) infertile men, and (30) healthy men (control group) at Al-Sharqat General Hospital in Salah El-Din Governorate for the period from October 2020 to the end of December 2020. The samples were divided into age groups. The ages of infertile men ranged from 18 to 60 years and were divided into three groups (less than 20-30 years old, 31-40 years old and over 40 years old). Collected (5) ml was withdrawn from the carpal vein, then blood samples were placed in test tubes free of anticoagulant and left for about a quarter of an hour at room temperature Then it was placed in a centrifuge, G 151 for 10 minutes to obtain the serum, then kept the serum in the freezer in special test tubes at a temperature of -20ºC then the serum was frozen at -20ºC until the (SHBG, FSH, LH, Testosterone and Prolactin) measurement by (ELISA standard curve). The concentrations were quantitatively determined in sera of patients and healthy control subjects by means of ELISA (Enzyme Linked Immunosorbent Assay) using ready kits manufactured by Bioassay company (China).

This study aims to assessment of Sex hormone-binding globulin (SHBG) level and it's associated with some sex hormones such as Follicle stimulating hormone (FSH), Luteinizing hormone (LH), prolactin and testosterone hormone and the infertility type in some infertile Iraqi men.

Statistical analysis:

Statistical analyses are done using SPSS version 20 computer software. The mean, standard deviation (SD) and of p-value of hormones parameters are calculated using student's t-test and ANOVA test (which considered significant when $p<0.05$ and highly significant when $p<0.01$) for the patients and healthy group [15].

III. RESULTS

The effect of infertility on the concentration of hormones:

The results showed that the level of SHBG hormone was significantly increased at the probability level of $P \leq 0.01$ among infertile patients (9.950 ± 0.4111) compared with the level of the hormone in normal subjects (4.3186 ± 0.588). The results of the current study indicate a decrease in the level of Testosterone hormone 2.5658 ± 0.331 in sterile males when compared with the control group 3.960 ± 0.274. While it was found that there was a significant increase ($P \leq 0.01$) in the level of hormones FSH 14.620 ± 4.143 (mIu/ml), LH of 8.869 ± 2.646 (mIu/ml) and Prolactin 14.872 ± 2.834 (ng/ml) when compared with the control groups 4.565 ± 2.325, 4.632 ± 1.110, 9.303 ± 2.429, respectively, and as shown in Table (1).

Table 1: Shows comparison between hormonal levels of the infertile and fertile males

Groups / Hormones	Fertility (No. 60)	Infertility (No. 60)	P value
	mean±SD	mean±SD	
SHBG	4.3186 ± 0.588	9.950 ± 0.4111	≤0.01
Testosterone(ng/ml)	3.960±0.274	2.5658±0.331	≤0.01
FSH (mIu/ml)	4.565±2.325	14.620±4.143	≤0.01
LH (mIu/ml)	4.632±1.110	8.869±2.646	≤0.01
Prolactin (ng/ml)	9.303±2.429	14.872±2.834	≤0.01

Hormonal levels of infertile males by age:

The results of the current study showed a significant decrease ($P \leq 0.01$) in the level of SHBG hormone 8.7033±1.355 for the age group >30-20 years compared with the hormone level 10.402±2.073 for the age group 31-40 years, and the hormone level 10.355±1.743 for the age group ≥ 41 years. The significant differences ($P \leq 0.01$) in the level of testosterone ng/ml were 2.788 ± 0.356, 2.71 ± 0.461, 2.075 ± 0.202 for age groups <30-20 years, 31-40 years and age group ≥41 years, respectively. And statistically significant differences ($P \leq 0.01$) in FSH levels (mIu/ml) 15.490 ± 4.045, 11.758 ± 4.593, 18.061 ± 3.495. respectively, for the same age groups mentioned above. And significant differences ($P \leq 0.01$) in LH levels (mIu/ml) were 8.776±2.302, 7.648±2.600, and 10.887±1.375, respectively. As well as significant differences ($P \leq 0.01$) in the level of prolactin hormone (ng/ml) 17.876 ± 3.338, 15.427 ± 3.614, 10.806 ± 2, respectively. and as shown in Table (2).

Table 2: Shows hormonal and enzyme levels of the infertile males according to age

Age group / Hormones	20-30>years (19) sample	31-40 years (25) samples	≥41years (16) sample	P value
	mean±SD	mean±SD	mean±SD	
SHBG	8.7033±1.355	10.402±2.073	10.355±1.743	≤0.01
Testosterone(ng/ml)	2.788±0.356	2.71 ± 0.461	2.075±0.202	≤0.01
FSH (mIu/ml)	15.490±4.045	11.758±4.593	18.061±3.495	≤0.01
LH (mIu/ml)	8.776±2.302	7.648±2.600	10.887±1.375	≤0.01
Prolactin (ng/ml	17.876±3.338	15.427±3.614	10.806±2.49	≤0.01

Hormonal levels of infertile males according to the period of infertility:

The results of the study showed that the differences were not significant when comparing the level of SHBG between age groups, age group ≤10, age group 11-20 and age group ≥21, (9.353±2.581, 11.254±1.630, 9.845±2.054), respectively. Significant differences (P≤ 0.01) in hormone levels of Testosterone (ng/ml) 2.709±0.573, 2.536±0.607, 1.896±0.437. and FSH (mIu/ml) 14.216±2.177, 13.07,5±1.937, 20.455±2.577. and Prolactin (ng/ml) 16.794±1.797, 12.664±1.495, 10.351±0.981. respectively for age groups ≤10 years old, age group 11-20 years and age group ≥21 years. Also, non-significant differences were recorded in the level of LH hormone (mIu/ml) 8.632 ± 1.445, 9.375 ± 1.818, 8.86 ± 1.317, respectively for age groups ≤10 years old, age group 11-20 years and age group ≥21 years. and as shown in Table (3).

Table 3: Shows the hormonal levels of infertile males according to infertility period

Age group / Hormones	Age group ≤10 years (36) sample	Age group 11-20 years (17) sample	Age group ≥21 years (7) samples	P value
	mean±SD	**mean±SD**	**mean±SD**	
SHBG	9.353±2.581	11.254±1.630	9.845±2.054	0.02 *
Testosterone	2.709±0.573	2.536±0.607	1.896±0.437	≤ 0.01 **
FSH (mIu/ml)	14.216±2.177	13.075±1.937	20.455±2.577	0.039*
LH (mIu/ml)	8.632±1.445	9.375±1.818	8.86±1.317	0.04*
Prolactin (ng/ml)	16.794±1.797	12.664±1.495	10.351±0.981	≤0.01

Hormonal levels of infertile males according to smoking:

There were no significant differences (P≤ 0.01) when comparing the level of SHBG in smokers (10.090±0.939) and non-smokers (9.903±0.583). There were significant differences (P≤ 0.01) in the level of LH hormone (mIu/ml) when comparing the level of LH 11.368 ± 2,144 in smokers with the level of LH 8.036 ±2.137 in non-smokers. Also, the differences were significant (P≤ 0.01) in the level of the hormone ng/ml Prolactin when comparing the level of the hormone 13.308 ± 1.841 in the smokers with the level of the hormone 15.394 ± 2.215 in the non-smokers. The results of the current study did not record significant differences between the level of the hormone Testosterone (ng/ml) when comparing the level of the hormone 2.635 ± 0.559 in smokers with a level of 2.542 ± 0.532 in non-smokers. The same applies to FSH hormone (mIu/ml), as it was found that there were no significant differences in the level of the hormone when comparing between smokers 14,741 ± 2,477 and non-smokers 14.580 ± 2,399. and as shown in Table (4).

Table 4: Shows the hormonal levels of infertile males according to smoking

Groups / Hormone	Smokers (No.15)	Non-smokers (No.45)	P value
	mean±SD	**mean±SD**	
SHBG	10.090±0.939	9.903±0.583	0.066*
Testosterone (ng/ml)	2.635±0.559	2.542±0.532	0.649
FSH (mIu/ml)	14.741±2.477	14.580±2.399	0.960
LH (mIu/ml)	11.368±2.144	8.036±2.137	0.017*
Prolactin (ng/ml)	13.308±1.841	15.394±2.215	0.029*

Hormonal levels of infertile males by family history:

The results showed that there was a significant difference (P≤0.05) when comparing the level of SHBG 10.517±0.463 in people with a family history with SHBG level 9.856±0.935 in people without a family history. The results also showed a significant difference (P≤0.05) in the level of Testosterone (ng/ml) when comparing the level of the hormone 2.357 ± 0.376 in people with a family history of infertility with the level of the same hormone 2.607 ± 0.323 in people without a family history of infertility. For the same level of significance mentioned above, it was found that there was a significant difference in the level of the hormone Prolactin (ng/ml) when comparing its level of 12.18 ± 2.851 among people with a family history of infertility with the level of the same hormone 15.411 ± 3.767 in normal people with no family history of infection. The differences were significant (P≤0.01) in the level of FSH hormone (mIu/ml) when comparing its level 19.825 ± 2.543 among people with a genetic family history of infertility compared with the level of FSH 13.58 ± 2.073 in normal people without family problems of infertility, as well As for the LH hormone (mIu/ml), it was found that there was a significant difference (P≤0.01) in the level of this hormone when comparing its level 7.414 ± 1.993 among people with a family history of infertility with the level of the hormone 9.160 ± 1.714 in healthy people and not family history. and as shown in Table (5).

Table 5: Shows the hormonal levels of infertile males by family history

Group / Hormones	People with a family history (No. 15)	People who do not have a family history (No.45)	P value
	mean±SD	mean±SD	
SHBG	10.517±0.463	9.856±0.935	≤0.05
Testosterone(ng/ml)	2.357±0.376	2.607±0.323	0.09
FSH (mIu/ml)	19.825±2.543	13.58±2.073	≤ 0.01 **
LH (mIu/ml)	7.414±1.993	9.160±1.714	0.02 *
Prolactin (ng/ml)	12.18±2.851	15.411±3.767	*

Correlation between the concentration of SHBG with other hormones:

The results of the current study showed that the correlation value of R of SHBG with FSH was weakly positive (R = 0.014). While the value of SHBG's correlation with LH, Prolactin and testosterone was (-0.038, -0.312, -0.142) respectively, and this means that the relationship between them was weak negative. and as shown in Table (6).

Table 6: Shows the correlation between the concentration of SHBG with other hormones

	Hormones	Value R
SHBG (ng/ml)	FSH (mμ/ml)	0.014
	LH (mμ/ml)	-0.038
	Prolactin (ng/ml)	-0.312
	Testosterone (ng/ml)	-0.142

IV. DISCUSSION

The effect of infertility on the concentration of hormones:

The results of the current study are in agreement with the study conducted by [16], and the result of the current study is in agreement with the study conducted by [17]. in Iran. The study showed that there was a significant increase in the level of FSH hormone in infertile men, while the level of testosterone and LH hormone was lower when compared with the control groups. Which showed an increase in FSH hormone with a decrease in Testosterone, while there was no effect on LH. In general, increased FSH levels are a good indicator of germinal epithelial cell destruction and are usually associated with azoospermia or oligospermia. Low testosterone levels are signs of hypogonadism, hypothalamus or pituitary gland [16]. Hyperprolactinemia reduces male fertility by suppressing the action of testosterone, as hyperprolactinemia is well known to lower libido and lead to reduced sperm production, on the other hand, hyperprolactinemia may be caused by a number of pathological factors, such as, disorders of Hypothalamus, pituitary gland tumor, hypothyroidism, and hypogonadism and this may mean some disturbances in the stages of spermatogenesis in infertile patients [18]. The high level of SHBG hormone in infertile patients indicates a low level of testosterone, which in turn explains the increase in the hormone as a result of its lack of association with testosterone and thus will lead to its increase in the serum of infertile people [19]. The

results of the current study in the level testosterone hormone and according to the type of infertility agreed with the study [20]. and the study that he conducted [21]. Since testosterone is important in regulating germ cell growth, it becomes necessary to measure the level of testosterone to monitor male infertility [22]. Sperm formation requires the presence of gonadotropins and testosterone [23]. Spermatogenesis is associated with higher levels of intracellular testosterone, and our results were in agreement with that of [24], thus not only explaining impaired spermatogenesis but also reduced function of Leydig cells and causes of pretesticular azoospermia were also suspected [24].

Hormonal levels of infertile males by age:

The influence of age on infertility varies and interacts with many genetic, social, psychological and health factors related to the patient's history [25]. And it did not find an association or effect on the age factor with infertility, as this was not statistically significant, while the results of [26]. It found that males had a higher rate of infertility between 20-29 years (46%), followed by 30-39 years (40%). While [27]. specifically indicated in his study that the incidence of infertility at the age of less than 30 years is higher in men, followed by 30-34 years and decreases with age. The results of a study also found that the vast majority of sterile patients ranged in age from 20-29 years [28]. Their results were attributed to early marriage, semen quality, and ejaculation process, which gradually decrease with age. It begins to decline after the age of 35 [29]. As well as the presence of many other genetic disorders that have an effect on the reproductive process, as is the case in the X chromosome [30]. Current guidelines support the combination of clinical symptoms/signs and low tT values for the diagnosis of male hypogonadism, but they all highlight that tT can provide misleading information in all those conditions known to alter SHBG levels [31]. A significantly wide distribution of SHBG concentrations was demonstrated in a study with 1,000 men presenting with sexual symptoms [32]. The authors found a nearly 20-fold difference in values across the SHBG outcome scale, in which younger men had lower SHBG concentrations than older men. Similarly, [33] They analyzed the effect of age and BMI on SHBG in 3,671 men who had undergone laboratory tests for testosterone deficiency. As expected, their results showed that SHBG was negatively correlated with BMI but positively correlated with age. In particular, the association between obesity and decreased SHBG was greater than that of aging with increased SHBG [33]. Data from the European Male Aging Study (EMAS) showed a consistent rise in SHBG with increasing age among men aged 40-70 years [34]. However, the reason for this increase is unknown. Some studies confirm a linear relationship between age and SHBG along with a negative association between age and BMI even in younger men, who are generally less likely to have co-morbidities than those of an older age, if they are not, they are infertile and, therefore, with an epidemiologically recognized risk of lower health than that of childbearing [35].

Hormonal levels of infertile males according to the period of infertility:

The effect of post-marital infertility differed on hormonal behavior. Although no studies have been conducted on the effect of this factor on concentrations of specific hormones, the effect of age can depend mainly on the fact that testosterone tends to decrease with increasing infertility as well as an increase in the level of FSH. These findings can also be associated with poor mental status and emotional distress in patients.

Hormonal levels of infertile males according to smoking:

The results of the current study agreed with the results of the study conducted by [36], and differed with the results of the study conducted by [37]. Many other studies have shown that the relationship of smoking and male infertility is uncertain, ie. The issue of smoking and its effect on infertility did not have a clear effect and the results of studies varied from one study to another [38], and studies showed that there are no reliable effects among male smokers on semen parameters. Nicotine may modulate the pituitary axis by enhancing the production of cortisol, growth hormone, oxytocin and vasopressin, which in turn inhibit prolactin and luteinizing hormone [39]. In a study looking at the effectiveness of tobacco smoking on hormone levels [40], average levels of estradiol were observed to be higher, and the average levels of prolactin, follicle-stimulating hormone (FSH) and LH levels were lower in smokers compared to non-smokers, while the average levels of FSH were not. Testosterone and dehydroepiandrosterone are different. Many components of tobacco smoke have effects on testosterone. Nicotine has been reported to impair the male reproductive hormone system by causing Leydig apoptosis and inhibiting androgen synthesis [41]. Toxins, including lead in tobacco, appear to directly impair spermatogenesis itself as well as sperm function through reproductive axis impairment or testicular degeneration. Also, semen parameters (total number, motility, and morphology) are decreased in infertile smokers compared to infertile non-smokers. Smoking caused a significant decrease in sperm count and morphology. However, it had no significant effect on movement in the study subjects [42]. Some studies have noted much lower levels of GPX and SHBG in smokers. Among the markers of stress, average cortisol levels were significantly higher 78among smokers than among non-smokers. Increased cortisol levels have an inhibitory effect on male reproductive function which could be due to a significant increase in intracellular ROS levels and induction of Leydig cell apoptosis [43].

Hormonal levels of infertile males by family history:

In a study that analyzed data from 2,622 men with ED in a single center and found that elevated

SHBG, regardless of diffuse tT, was associated with subjective or subjective androgen deficiency traits [44]. Therefore, they emphasized the clinical importance of SHBG testing in conjunction with Testosterone in order to evaluate men with sexual dysfunction suspected of suffering from a hypogonadal state. Similarly, [45]. Determine the utility of adding SHBG to the standard Testosterone test for diagnosing hypogonadism in 168 infertile men. The authors found that using Testosterone levels alone was likely to misclassify 20-53% of men as eugonadal when in fact they were hypogonadal. Conversely, 20% of patients were diagnosed with hypogonadism but were actually eugonadal when SHBG was used to assess cFT [45]. Therefore, in addition to standard Testosterone serum levels, SHBG should be considered as an important tool during the diagnostic work-up of infertile men for a more accurate definition of the androgen environment. Furthermore, since the main peripheral organ that produces SHBG is the liver, which is the central metabolic organ, assessment of SHBG levels is useful in a more comprehensive understanding of the significance of certain metabolic diseases that ultimately alter SHBG serum levels [46]. It included several subgroups of infertile subjects which in all cases indicated no family history of infertility. In their survey, this included the chromosomal assessment of the members of the infertility group studied [47]. While some studies have indicated that families with a medical history of infertility and a family history of infertility called PRM1 homozygous PRM1 genetic mutations have a 40% higher risk of infertility than those with no family history of infertility [48].

Correlation between the concentration of SHBG with other hormones:

The results of the current study in the relationship of SHBG hormone with testosterone are in agreement with the study conducted by [49], and the study conducted by [50]. The strength of the relationship indicates that SHBG is the main carrier of testosterone in the blood, and therefore this hormone has a major role in the fertilization process [51, 52].

In conclusion, this study revealed significantly increase in the SHBG levels in the infertile men and negative correlation between SHBG and Testosterone. Therefore, SHBG has important role in the diagnosis and follow up of the male infertility.

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