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Assessment of Steroid 5 Alpha Reductase Enzyme Levels and Its Correlation with Sex Hormones in Infertile Iraqi Men

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ABSTRACT

This study aims to evaluate the 5-alpha reductase enzyme (SRD5A2) levels in serum and it's association 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 (30) healthful individuals as a control group aged (18 to 60 year) are collected from private clinics. Enzyme Linked Immunosorbent Assay (ELISA) has been used for estimation of serum SRD5A as enzymes and FSH, LH, prolactin and testosterone as hormones.According to types of sperm count patients have been divided to two group 49 person as azoospermia group (zero /ml) and 11 person as oligospermia group less than 20 million/ml. The levels of SRD5A2 and testosterone are significantly decreased to (P≤0.01) in the infertile men as compared with control group. While the level of FSH, LH and prolactin are significantly higher (P≤ 0.01) in the infertile men than control group. The results of SRD5A2 are non-significant, while, levels of FSH, LH and prolactin are higher significant (P≤ 0.01) except testosterone level which has significant differences (P≤ 0.05) in the age groups <20-30 year, 31–40 year and ≥ 40 year. There are significant differences (P≤ 0.01) in levels of SRD5A2, FSH and prolactin, but the levels of LH are non-significant in the infertility period ≤ 10 year, 11 – 20 year, ≥ 20 year. Smoker infertile men have low levels (P≤ 0.01) in the SRD5A2 and prolactin while have high levels in the LH hormones compared with control. Patients with family history have shown significant differences (P≤0.05) in the levels of SRD5A2, testosterone, LH and prolactin. In conclusion, this study revealed significantly decrease in the levels ofSRD5A2 in the Azoospermic and oligospermic infertile men and significant negative correlation (P<0.05) between SRD5A2 pg/ml and FSH (mIu/ml) R factor-0.328. Therefore, SRD5A2 has important role in the diagnosis of idiopathic male infertility and it's one of the important markers in the diagnosis of normal spermatogenesis.

Keywords- Male Infertility, Steroid 5 Alpha Reductase Enzyme (SRD5A2), Sex hormones.

I. INTRODUCTION

Human infertility is considered as a major health problem, it induces the incapability of marriages who are unfertilized from unprotected sexual correlation at least after 12 months of pregnancy. Impact of infertility on each male and female, making a reference to the word Infertility, in females is complete lack of ability for pregnancy(1). Male infertility is a serious disease involving environmental as well as genetic factors. Abnormal sperm production or activity may be related to various acquired or congenital factors that act on the pretesticular, post-testicular or directly testicular level(2). Male fertility can also be decreased due to acquired or congenital urogenital deformities, tumors, infections of urogenital tract, elevated scrotal temperature (e.g. in the case of varicocele), endocrine disorders, genetic mutations and immunological status(3). Infertility of male can be categorized by hormonal investigation and seminal fluid analysis by using of light microscopy. The total lack of sperms in semen was also termed azoospermia, but if it is less than 20 million / ml, it is termed oligospermia, where as if the total number is 20 million / ml, but really the motility is less than 50 percent, it is termed Asthenospermia(4).

5α-reductases are steroid metabolism enzymes and take part in 3 metabolic paths: bile acid biogenesis, synthesis of androgen and estrogen. The 5α-reductase substrates are steroids of 3-oxo (3-keto), 4,5 C 19 / C21. The "3-keto" group refers to the double bond of oxygen carbon at carbon 3. Delta 4, 5 refers to a double bond seen between 4 and 5 carbon atoms. The reaction occurs a stereo-specific, irreversible breaking of a double bond among both carbon 4 and 5 (delta 4, 5) with the assistance of the Nicotinamide adenine dinucleotide phosphate (NADPH) as cofactor and also the addition of the hydride anion (H−) into the carbon C-5 face of the α and the proton to β face of the C-4 position Substrate examples include testosterone, epi-testosterone, androstenedione, cortisol, progesterone, deoxycorticosterone and aldosterone. The physiological function of 5α-reduction of all these steroids (other than Testosterone) is unclear but possibly related to certain degradation & excretion and to other physiological functions(5). Three isoenzymes exist of 5α-reductase, SRD5A1, SRD5A2, and SRD5A3 that also vary in various tissues according to age. In many tissues of both men and women the enzyme is produced in prostate and multiple organs, seminal vesicles and epididymis(6) skin, tests, ovaries and reproductive tract(7). Steroid 5α-reductase is a major testosterone enzyme converting testosterone into dihydrotestosterone (DHT), a more active metabolite in males development of the prostate and external genitalia

DHT is necessary for differentiation at post-puberty.DHT is the major androgen taking responsibility for the maturation of sperm mostly in epididymis(8). Thus, the activity of 5α-reductase was Presumed needed for normal sperm maintenance and formation(9). Testicular activity of 5α-reductase in spermatogonia has also been observed(10). Most men pseudohermaphrodites with hereditary deficiency of SRD5A2 enzyme and thus reduced dihydratetestosteronproduction have already shown lower overall sperm numbers, although some maintain normal motility and concentration of sperm(11). Therefore, the aim of this study was to evaluate the SRD5A2 levels in serum and its relationship with some sex hormones such as FSH, LH, prolactin and testosterone hormones in some infertile Iraqi men.

II. MATERIALS AND METHODS

The study sample would include (90) men, (60) men who are infertile and (30) healthful individual as a control group from private clinics in Shirqat city in the province of Salahalddin for the period beginning October 2019 to the end of December 2019. Patients obtained the information and ranged from 18 to 60 years old and were divided into three categories. The period of infertility is recorded after marriage and the patients are classified into the effects of this factor in three categories (less than 10 years, 11-20 years and over 20 years). The impact of family history is investigated and the patients are classified into two categories on the basis of this factor. The impact of smoking is investigated and the patients are classified in to two groups (smoker and nonsmoker). Five milliliter of venous blood were collected from each patient and control in a plain tube, the serum was separated immediately after coagulation then stored frozen at -20°C in deep freeze. According to types of sperm count patients are divided to two group 49 person as azoospermia group and 11 person as oligospermia. SRD5A2 enzyme and gonadal hormone such as FSH, LH, testosterone and prolactin are measurement by using ELISA method according to the manufacturer's instructions (Sunlong Biotech company).

III. 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.

IV. RESULTS AND DISCUSSION

Results of impact of infertility on the concentration of hormones and enzymes were shown in table 1 that indicated a significant decrease ($P\leq0.01$) in the levels of SRD5A2 (778.304±41.211 pg/ml) and testosterone (2.5658±0.331) (ng/ml) compare with control group (874.777±21.737) and (3.960±0.274) respectively and significantly increase ($P\leq 0.01$) in the level of FSH (14.620±4.143 mIu/ml), (LH 8.869±2.646 mIu/ml), prolactin (14.872±2.834 ng/ml) compared with control group (4.565±2.325, 4.632±1.110, 9.303±2.429) respectively.

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

Hormones and Enzyme	Patients (No. 60)	Control (No. 30)	*P* value
	Mean ± SD	Mean ± SD	
SRD5A2pg/ml	778.304±41.211	874.777±21.737	≤ 0.01 **
Testosterone (ng/ml)	2.5658±0.331	3.960±0.274	≤ 0.01 **
FSH (mμ/ml)	14.620±4.143	4.565±2.325	≤ 0.01 **
LH (mμ/ml)	8.869±2.646	4.632±1.110	≤ 0.01 **
Prolactin (ng/ml)	14.872±2.834	9.303±2.429	≤ 0.01 **

(*Significant, $p<0.05$, ** Significant, $p<0.01$). Color indicates the lowest level.

Results of hormonal levels of the infertile males according to infertility type were shown in table 2. There are a significantly decrease ($P\leq0.01$) in the levels of SRD5A2 pg/ml/ml (771.820±29.302, 807.183±32.674, 157.156±20.169) and testosterone (2.610±0.350, 2.368±0.244) respectively in the azoospermic and oligospermic group compared with control group (874.777±21.737, 203.598±14.343)and(3.960±0.274) respectively. While significantly increase ($P\leq 0.01$) in the level of FSH(14.929±1.055, 13.248±2.472), LH (mIU/ml) (9.424±2.313, 6.394±2.237), prolactin (ng/ml) (15.924±2.463, 10.722±1.953), compared with control group 4.565±2.325, 4.632±1.110, 9.303±2.429 respectively.

Table 2: Showshormonal and enzyme levels of the infertile males according to infertility type

Hormones and Enzyme	Azoospermia (No. 49)	Oligospermia (No. 11)	Control (No. 30)	*P* value
	Mean ± SD	Mean ± SD	Mean ± SD	
SRD5A2 pg/ml/ml	771.820±29.302	807.183±32.674	874.777±21.737	≤ 0.01 **
Testosterone (ng/ml)	2.610±0.350	2.368±0.244	3.960±0.274	≤ 0.01 **
FSH (mμ/ml)	14.929±1.055	13.248±2.472	4.565±2.325	≤ 0.01 **
LH (mμ/ml)	9.424±2.313	6.394±2.237	4.632±1.110	≤ 0.01 **
Prolactin (ng/ml)	15.924±2.463	10.722±1.953	9.303±2.429	≤ 0.01 **

(*Significant, p<0.05, ** Significant, p<0.01). Color indicates the lowest level.

In this study it is observed that the LH as well as FSH and prolactin in infertile men are significantly (P≤ 0.01) increased compared with controls. Conversely, the total testosterone had also been significantly lower in infertile men compared to control, these results are significantly with the signaling of negative feedback system. In the Egyptian community of(12) (Zalata et al., 2008) did agree with our study that the serum FSH level in infertile men has increased significantly compared with the fertile group and level of serum testosterone decreased significantly while no statistically significant relationship with serum LH was recognized. In general, increased FSH levels are a good predictor of germinal epithelial destruction and are commonly associated with azoospermia or oligospermia, and lower Total testosterone levels are markers of hypothalamic or pituitary origin hypogonadism(12). I agree with (Safarinejad, Shafiei and Safarinejad, 2011). In the Iranian population, discovered that the FSH serum level in infertile men are greater than in control and the Luteinizing hormone and testosterone serum levels in sperm count are lower than the control group, but the difference did not reach statistical significance among two groups (P=0.08 and P=0.06)(13).(Grigorova et al., 2013) found that in the oligozoospermia subgroup the connection with significantly elevated FSH (P=0.01)(14). Type 2 enzyme5a-reductase is involved the differentiation of male sex organs by conversion of testosterone to 5a-dihydrotestosterone (DHT) which could then stimulate external genital development(15).This may associate the activity of SRD5A2 with seminal volume, sperm motility, and even total count of sperm, therefore the SRD5A2 level was decreasedin serum of infertile men compared with the results of control group as in table(1-1) and significantly reduced in levels of 5alpha reductase enzyme in the azoospermic group compared with oligospermic group and control group as in the table 2.

The results of table 3 have shownthe hormonal and enzyme levels of the infertile males according to age. There was a non-significantly difference in levels of SRD5A2 pg/ml (774.354±13.256, 771.315±14.976, 793.913±15.173), according to the age groups <20-30 Year, 31 – 40 year, ≥ 40 year.Also show significant differences (*P≤0*.05) in the level of testosterone ng/ml (2.788±0.356, 2.71±0.461, 2.075±0.202) respectively according to age group .and significant differences (P≤ 0.01) in the levels of FSH (mIu/ml) 15.490±4.045, 11.758±4.593, 18.061±3.495. LH (mIu/ml) (8.776±2.302, 7.648±2.600, 10.887±1.375).Prolactin (ng/ml) (17.876±3.338, 15.427±3.614, 10.806±2.490) respectivly according to age groups<20-30 year, 31 – 40 year, ≥ 40 year.

Table 3: Showshormonal and enzyme levels of the infertile males according to age

Hormones and Enzyme	<20-30 Year (No. 19)	31 – 40 Year (No. 25)	≥ 40 Year (No. 16)	*P* value
	Mean ± SD	Mean ± SD	Mean ± SD	
SRD5A2pg/ml	774.354±13.256	771.315±14.976	793.913±15.173	0.835
Testosterone (ng/ml)	2.788±0.356	2.71±0.461	2.075±0.202	0.018 *
FSH (mμ/ml)	15.490±4.045	11.758±4.593	18.061±3.495	≤ 0.01 **
LH (mμ/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±2.490	≤ 0.01 **

(*Significant at p≤0.05, ** Significant at p≤0.01). Color indicates the lowest level.

The age factor impact on male infertility is different and interacts with many, genetic, social and psychological factors and health related to patient history studied by(16). Who hasn't found a correlation or influence the age factor to the infertility, Since that was statistically non-significant, while the findings by(17) (Khadhim, Al-quizwini and Hussian, 2015) found that males had a higher rate of infertility between 20-29 years of age (46%), followed by 30-39 years of age (40%), While(18) (Al-Haija, 2011) specifically referred in his study that infertility was infected at an age less than 30 years by the higher percentage for men. This is followed by 30-34 years of age and low with age progression. Results of astudy found that the vast majority of patients were between 20-29 years of age(19) (Moghadam et al., 2011) their results are attributed to early marriage. The quality of liquid semen of frequency, as shown by evaluation; ejaculation that jobs the sperms are gradually decreasing with age advancement. It begins to decline after the age of 35(20)(Omran, Bakhiet and Dashti, 2013). Several other genetic disorders have an effect, such as in a chromosome X(21)(Raman and Schlegel, 2002).

The result of hormonal and enzyme levels of the infertile males according to infertility period as shown in table 4 revealeda significant differences (P≤ 0.01) in levels of SRD5A2 pg/ml (762.420±74.391, 832.838±72.073, 727.55±37.305). Testosterone ng/ml(2.709±0.573, 2.536±0.607, 1.896±0.437). FSH mIu/ml(14.216±2.177, 13.07,5±1.937, 20.455±2.577). Prolactin ng/ml(16.794±1.797, 12.664±1.495, 10.351±0.981) respectively according to infertility period ≤ 10 year, 11 – 20 year, ≥ 20 year. Non-significant differences in levels LH mIu/ml(8.632±1.445, 9.375±1.818, 8.86±1.317)respectively according to infertility period ≤ 10 year, 11 – 20 year, ≥ 20 year.

Table4: Showshormonal and enzyme levels of the infertile malesaccording to infertility period

Hormones and Enzyme	≤ 10 Year (No. 36)	11 – 20 Year (No. 17)	≥ 20 Year (No. 7)	*P* value
	Mean ± SD	Mean ± SD	Mean ± SD	
SRD5A2pg/ml	762.420±74.391	832.838±72.073	727.55±37.305	≤ 0.01 **
Testosterone (ng/ml)	2.709±0.573	2.536±0.607	1.896±0.437	≤ 0.01 **
FSH (mμ/ml)	14.216±2.177	13.075±1.937	20.455±2.577	≤ 0.01 **
LH (mμ/ml)	8.632±1.445	9.375±1.818	8.86±1.317	0.796
Prolactin (ng/ml)	16.794±1.797	12.664±1.495	10.351±0.981	≤ 0.01 **

(*Significant at p≤0.05, ** Significant at p≤0.01). Color indicates the lowest level.

The impact of the infertility period after getting married has been different on the hormonal behavior although no studies have been carried out on this factor's effects of the concentrations of certain hormones, the effect of age can be mainly based on the fact that testosterone, and SRD5A2 tend to decrease with increased infertility as well as increased in level of FSH. These results also can be related to the weakening mental state and emotional disorder of the patients.

The results of table 5 have shown the hormonal and enzyme levels of the infertile males according to smoking. There was a significantly differences (P≤ 0.01) in the levels of SRD5A2 pg/ml (721.515±56.545, 783.661±62.358). LH mIu/ml (11.368±2.144, 8.036±2.137). Prolactin ng/ml(13.308±1.841, 15.394±2.215) respectively according to smoking status.and non-significantly differences in the levels of DHT pg/ml (151.415±27.426, 148.306±26.675). Testosterone ng/ml(2.635±0.559, 2.542±0.532). FSH (mIu/ml) (14.741±2.477, 14.580±2. 399) respectively according to smoking status.

Table5: Showshormonal and enzyme levels of the infertile malesaccording to smoking

Hormones and Enzyme	Smokers(No. 15)	Non-Smokers (No. 45)	*P* value
	Mean ± SD	Mean ± SD	
SRD5A2pg/ml/ml	721.515±56.545	783.661±62.358	≤ 0.01 **
Testosterone (ng/ml)	2.635±0.559	2.542±0.532	0.565
FSH (mμ/ml)	14.741±2.477	14.580±2.399	0.886
LH (mμ/ml)	11.368±2.144	8.036±2.137	≤ 0.01 **
Prolactin (ng/ml)	13.308±1.841	15.394±2.215	≤ 0.01 **

(*Significant at p≤0.05, ** Significant at p≤0.01). Color indicates the lowest level.

Many other studies have also shown that smoking and male relate Infertility is uncertain, the (22) (Wallach, Hughes and Brennan, 1996) studies showed that there are no reliable impacts among male smokers on the semen parameters. Nicotine may modify the hypothalamic_pituitary axis through enhancing production of cortisol, growth hormone,oxytocin and vasopressin, which in turn inhibits prolactin and luteinizing hormone (23)(Weisberg, 1985). In a study investigating the efficacy of smoking tobacco on the levels of hormones(24) (Ochedalski et al., 1994) observed higher mean levels of estradiol, and the mean of prolactin, follicle-stimulating hormone (FSH) and LH levels are lower in smokers than in non-smokers, whilst the mean of the testosterone and dehydroepiandrosterone levels are not different. Similar findings other researchers investigated seminal fluid or plasma hormone levels are reported (25) (Jurasović et al., 2004). (26) (Ramlau-Hansen et al., 2007) noted a significant dose-response correlation among smoking and LH, testosterone, and the free testosterone, and ratio of LH to free testosterone. In addition, levels of FSH also reported to be higher in smokers. with reference to the physiology of its axis of the hypothalamic_pituitary_gonadal (HPG), whenever the levels of LH and FSH rise, the outcome is Testosterone elevation, which in turn lower LH and FSH levels through negative responses of feedback. The findings of this study lead to the suggestion that tobacco smoke elements could disrupt the regularity of HPG system functioning, going to lead to a Leydig cell malfunction in smokers (26).

Hormonal and enzyme levels of the infertile males according to family history were shown in table 6.The results of reveled a significant difference (P≤0.05) in the levels of SRD5A2 pg/m (l751.515±29.485, 783.661±36.489). Testosterone ng/ml (2.357±0.376, 2.607±0.323). Prolactin ng/ml (12.18±2.851, 15.411±3.767) respectively according to family history of infertility .and significant differences (P≤ 0.01) in the level of FSH mIu/ml(19.825±2.543, 13.58±2.073). LH mIu/ml(7.414±1.993, 9.160±1.714) respectively according to family history of infertility.

Table6: Shows hormonal and enzyme levels of the infertile males according to family history

Hormones and Enzyme	Havefamily history (No. 10)	Don't have family history (No. 50)	*P* value
	Mean ± SD	Mean ± SD	
SRD5A2pg/ml	751.515±29.485	783.661±36.489	0.011 *
Testosterone (ng/ml)	2.357±0.376	2.607±0.323	0.034 *
FSH (mμ/ml)	19.825±2.543	13.58±2.073	≤ 0.01 **
LH (mμ/ml)	7.414±1.993	9.160±1.714	≤ 0.01 **
Prolactin (ng/ml)	12.18±2.851	15.411±3.767	0.021 *

(*Significant at p≤0.05, ** Significant at p≤0.01). Color indicates the lowest level.

In the case of genetic and chromosomal disorders, parental history is very important. Anomalies, in the event of injury deletion in the chromosome Y in family medical history, result in similar genetic deficiencies in offspring, before even submitting with any technologies the genetic test suitable for those persons must be submitted for influence on reproduction(27). Klinefelter syndrome, which is regarded as a widely recognized gland syndrome Places which are an inherited disorder that occur in the chromosome X in men(28). Elevated levels of genital glands in some ways, particularly FSH, are one of its most prominent symptoms. Results SHBG high in a concentration there are so few either Sertoli syndrome with studies have examined the impact of family history, although most research teams avoid them due to the differences and overlaps and need for large genetic analyses. In the study of(29) that includes many sub - groups of infertile peoples indicating in all cases no date of family infertility. In their survey, that included chromosomal assessment of members of the infertility group those who studied(30) discovered that no familial history of infertility. Patients with a family medical history of homozygous PRM1 genetic mutations also had increased risk (40percent) than those without a family medical history; a substantial difference of even more than one and a half times (OR = 1.625) was observe(31).

The correlation between SRD5A2 enzyme and hormonal levels of the infertile males was shown in the table 7.The results indicates significant positive correlation (P<0.05) between SRD5A2 pg/ml and testosterone pg/ml R factor0.288 and significant negative correlation (P<0.05) between SRD5A2 pg/ml and FSH (mIu/ml) R factor-0.328.and non-significant negative correlation (P>0.05) between SRD5A2 pg/ml and LH (mIu/ml) R factor -0.088. Non-significant positive correlation(P>0.05) between SRD5A2 pg/ml enzyme and prolactin (ng/ml) R factor0.136.

Table7: Shows correlation between SRD5A2enzymeand hormonal levels of the infertile males

Parameter	Hormones	R factor	*P* value
SRD5A2enzyme	Testosterone (ng/ml)	0.288	0.025 *
	FSH (mμ/ml)	-0.328	0.010 *
	LH (mμ/ml)	-0.088	0.503
	Prolactin (ng/ml)	0.136	0.3

*Significant at p≤0.05. (- indicates negative correlation).

There was a typical germ cells population in 5 alpha-reductase-deficient males, but a lack of primary biopsy spermatocytes was identified the reduced number of germ cells and evidence of primary spermatocytes appeared to be present in men with isolated cryptorchidism. This indicates that DHT plays a part in spermatocyte growth and differentiation. Subfertility in males with 5 alpha-reductase-2 deficiency has also been suggested to be a consequence of an intrinsic failure of the Sertoli cell to reach full fertility (32). This lead to couse increase level of the FSH in infertile men that which confirm the significant negative correlation between SRD5A2 and FSH with R factor -0.328 as shown in the table 7.

In conclusion this study revealed significantly decrease in the levels of SRD5A2 and in the Azoospermic and oligospermic infertile men, and significant negative correlation (P<0.05) between SRD5A2 pg/ml and FSH (mIu/ml) R factor-0.328. Therefore, SRD5A2 has important role in the diagnosis of idiopathic male infertility and its one of the important markers in diagnosis of normal spermatogenesis.

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