Testosterone and Gonadotropins in Infertile Men with Sertoli Cell Only Syndrome from Gaza Strip

MAGED M. YASSIN,1 ABDEL MONEM H. LUBBAD,1 AHMED Z TAHA,2 MOHAMMED M. LAQQAN1, SAMAR M. ABU JAMIEA1

Abstract

Aim: To assess serum testosterone and gonadotropins in Sertoli cell only syndrome patients from Gaza Strip.

Methods: Based on testicular biopsy, a cross section of 74 Sertoli cell only syndrome patients were enrolled in the study. Age matched 44 fertile men were served as controls. Patients and controls were questioned for their medical history. Blood samples were drawn and serum testosterone, luteinizing hormone (LH), and follicle stimulating hormone (FSH) were determined by enzyme-linked immunosorbent assay. Data were computer analyzed using SPSS/PC, version 18.0.

Results: Varicocele and hormonal problems were significantly more frequent among patients than controls (P<0.05). Serum testosterone was significantly lower in patients compared to controls (1.7±1.3 versus 5.0±2.2 ng/ml, P=0.000). In contrast, LH and FSH were significantly higher in patients than controls (12.8±9.7 and 20.8±14.8 mIU/ml versus 6.3±3.1 and 7.7±3.9 mIU/ml, P=0.000, respectively). Hypergonadotrophic hypogonadism and hypogonadotrophic hypogonadism patients showed lower levels of testosterone compared to the normal reference value (0.9±0.5 and 0.5±0.4 ng/ml versus 2.0-7.0 ng/ml). Higher levels of LH and FSH were recorded in hypergonadotrophic hypogonadism (24.5±2.6 and 37.4±6.7 mIU/ml) compared to the reference values of 2.0-13.0 and 2.5-10.0 mIU/ml, respectively whereas LH and FSH levels were lower in hypogonadotrophic hypogonadism (0.6±0.4 and 0.6±0.5 mIU/ml, respectively). In this context, all hypergonadotrophic hypogonadism and hypogonadotrophic hypogonadism patients showed abnormal levels of testosterone, LH and FSH.

Conclusions: Abnormal levels of serum testosterone, LH and FSH, particularly in hypergonadotrophic hypogonadism and hypogonadotrophic hypogonadism were identified in infertile men with Sertoli cell only syndrome from Gaza Strip.

Keywords: Infertility, Sertoli cell only, testosterone, gonadotropins, Gaza Strip.

Introduction

One of the important issues contributing to male infertility is azoospermia which is defined as the absence of sperm in at least two different ejaculate samples, including the centrifuged sediment.1 The etiology of azoospermia may be attributed to 1) pre-testicular causes e.g. endocrine abnormalities causing secondary testicular failure, 2) testicular causes e.g. primary testicular failure due to intrinsic disorders of spermatogenesis within the testis, including maturation arrest and complete absence of germ cells or Sertoli cell only syndrome or 3) post testicular causes e.g. ejaculatory dysfunction or ductal obstruction that prevent sperm transport.2

Sertoli cell only syndrome or germ cell aplasia is one of the etiologic categories of non-obstructive azoospermia that applies to a testicle in which germ cells at any stage of maturation are absent, but the tubular architecture is not effaced by fibrosis and supporting cells continue to be present.3 Examples of causes of Sertoli cell only syndrome may include genetic factors, hormonal factors, idiopathic factors, varicocele, toxin exposure, history of radiation therapy, and history of severe trauma.4-6

Endocrine malfunctions are more prevalent in infertile men than in the general population, but still quite uncommon. Abnormalities of the hypothalamic-pituitary-testicular axis at the testicular level cause primary testicular failure, whereas central defects of the hypothalamus or pituitary cause secondary testicular failure. Hypergonadotrophic hypogonadism results in low testosterone levels, impairment of spermatogenesis and elevated gonadotropin levels.

1. Faculty of Medicine, The Islamic University of Gaza, Gaza Strip, Palestine.
2. Department of Medical Technology, Faculty of Science, The Islamic University of Gaza, Gaza Strip, Palestine.

Corresponding author: Dr. Maged M. Yassin, Professor of Physiology, Department of Physiology, Faculty of Medicine, The Islamic University of Gaza, P.O. Box 108, Remal, Gaza Strip, Palestine. Tel: +970 (8) 2860700. Fax: +970 (8) 2860800. E-mail: myassin@jugaza.edu.ps
Hypogonadotropic hypogonadism results in low testosterone levels, impairment of spermatogenesis and low or low-normal gonadotropin levels.\textsuperscript{7,8}

Research carried out on azoospermia in Gaza strip is very limited. To our knowledge, only two recent studies published; one addressing screening for Y chromosome microdeletions in a population of infertile males\textsuperscript{9} and the other study handled hormonal and histological aspects among infertile men in Gaza strip.\textsuperscript{10} However, the present study focused specifically on testosterone and gonadotropin hormones in infertile men with Sertoli cell only syndrome from Gaza Strip. Therefore, the present study provided more information on endocrine profile of Sertoli cell only syndrome and highlighted an extraordinary public health problem of high concern for couples seeking children in Gaza Strip.

**Subjects and Methodology**

**Subjects**

Based on testicular biopsy, a cross section of 74 infertile men with Sertoli cell only syndrome (patients) visiting the Specialized Medical Centers in Gaza strip were enrolled in the present study. They have the history of at least 3 years duration of infertility.\textsuperscript{11} Semen analysis was also performed to confirm azoospermia based on World Health Organization criteria.\textsuperscript{1} A total number of 44 controls were selected at the basis of being married with at least one child and sperm count >20 million sperm/ml. Patients and controls were age matched. Ethical approval was provided by Helsinki committee at the Palestinian Ministry of Health and all participants gave an informed consent. Patients and controls were questioned for their medical history.

**Testicular biopsy**

Incision biopsy was taken by physician, from bilateral testes, then pre solved in Bouin’s solution as a fixative reagent.\textsuperscript{12} Following fixation, dehydration of fixed tissues was done through ascending grades of ethyl alcohol (50%, 70%, 90%, 95% and absolute alcohol). Tissues were then cleared with xylene. This was followed by impregnation with paraffin wax. Having been completely impregnated, the tissues were embedded in paraffin wax, sectioned by a rotary microtome at a thickness of 3 μm, mounted and affixed to slides. Sections were then stained as a routine in harris’s alum haematoxylin and eosin.

**Blood sampling and processing**

Venous blood samples were drawn by a well-trained medical technologist into vacutainer tubes from patients and controls. Blood was left for a while without anticoagulant to allow blood to clot. Then, serum samples were obtained by centrifugation at room temperature at 3000 rpm/10 minutes for hormonal assay. Testosterone, LH and FSH levels were determined by enzyme-linked immunosorbent assay, TECO kit, USA.

**Statistical analysis**

Data were computer analyzed using SPSS/PC (Statistical Package for the Social Science Inc. Chicago, Illinois USA, version 18.0) statistical package. Simple distribution of the study variables and the cross tabulation were applied. Yates’s continuity correction test, $\chi^2$ (corrected) was used as not more than 20% of the cells had an expected frequency of less than five and the expected numbers were small. The independent sample t-test procedure was used to compare means of quantitative variables by the separated cases into two qualitative groups such as the relationship between patients and controls hormones. Percent difference $= ((V1 - V2) / ((V1 + V2)/2)) \times 100$. The one-way ANOVA test was applied. The results were accepted as statistical significant when the p-value was less than 5% (P<0.05).

**Results**

Medical history of the study population

The mean age of patients (n=74) and controls (n=44) were 29.8±5.9 and 30.2±5.7 years, respectively. Medical history revealed that varicocele was significantly more prevalent among patients compared to controls 12 (16.2%) versus 1 (2.3%), $\chi^2$ (corrected)=4.142 and P=0.042. Similarly, hormonal problems were significantly higher in patients than controls 19 (25.7%) versus 2 (4.5%), $\chi^2$ (corrected)=7.039 and P=0.008. Although trauma was more frequent among patients, the difference between patients and controls was not significant 9 (12.2%) versus 2 (4.5%), $\chi^2$ (corrected)=1.120 and P=0.294.

Testosterone and gonadotropins levels of the study population

As illustrated in Table I, the mean level of testosterone was significantly lower in patients compared to controls with percentage difference of 98.5% (1.7±1.3 versus 5.0±2.2 ng/ml, t=10.054, P=0.000). In contrast, the mean levels of LH and FSH were significantly higher in patients compared to controls showing percentage differences of 68.1% and 91.9%, respectively (12.8±9.7 and 20.8±14.8 mIU/ml versus 6.3±3.1 and 7.7±3.9 mIU/ml, t=4.352 and t=5.708, P=0.000, respectively).
As indicated in Table II, ANOVA test showed significant change among different diagnostic aspects of Sertoli cell only syndrome for each particular hormone (P=0.000).

Lower levels of testosterone were found in hypergonadotrophic hypogonadism and hypogonadotrophic hypogonadism compared to the normal reference value (0.9±0.5 and 0.5±0.4 versus 2.0-7.0 ng/ml). In primary testicular failure and idiopathy testosterone levels were in the range of normal reference value.

Higher levels of LH and FSH were recorded in primary testicular failure (17.3±6.1 and 28.9±6.3 mIU/ml, respectively) as well as in hypergonadotrophic hypogonadism (24.5±2.6 and 37.4±6.7 mIU/ml, respectively) compared to the reference values of 2.0-13.0 and 2.5-10.0 mIU/ml, respectively. In contrast, LH and FSH levels were lower in hypogonadotrophic hypogonadism (0.6±0.4 and 0.6±0.5 mIU/ml, respectively).

In idiopathy, LH and FSH levels were in the range of normal reference values.

As indicated in Table III, the number of primary testicular failure, hypergonadotrophic hypogonadism, hypogonadotrophic hypogonadism and idiopathic patients showing normal levels of testosterone were 18 (45.0%), 9 (100%), 14 (100%) and 3 (27.3%), respectively compared to 22 (55.0%), 0 (0.0%), 0 (0.0%) and 8 (72.7%) patients with normal levels of the hormone ($\chi^2_{(corrected)}=18.890$ and $P=0.000$).

Abnormal levels of LH were exhibited by 30 (75.0%), 9 (100%) and 14 (100%) and 4 (36.4%) patients, respectively versus 10 (25.0%), 0 (0.0%), 0 (0.0%) and 7 (63.6%) patients with normal levels ($\chi^2_{(corrected)}=12.644$ and $P=0.005$). For FSH, all primary testicular failure, hypergonadotrophic hypogonadism, hypogonadotrophic hypogonadism patients as well as 4 (36.4%) idiopathic patients showed abnormal levels of the hormone ($\chi^2_{(corrected)}=35.512$ and $P=0.000$).

### Table-I

**Testosterone and gonadotropins levels of the study population**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Patients (n=74)</th>
<th>Controls (n=44)</th>
<th>% Difference</th>
<th>t value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone (ng/ml)</td>
<td>1.7±1.3</td>
<td>5.0±2.2</td>
<td>98.5</td>
<td>10.054</td>
<td>0.000</td>
</tr>
<tr>
<td>Range (min-max)</td>
<td>(0.03-6.1)</td>
<td>(1.9-11.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*LH (mIU/ml)</td>
<td>12.8±9.7</td>
<td>6.3±3.1</td>
<td>68.1</td>
<td>4.352</td>
<td>0.000</td>
</tr>
<tr>
<td>Range (min-max)</td>
<td>(0.1-31.2)</td>
<td>(1.1-11.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>**FSH (mIU/ml)</td>
<td>20.8±14.8</td>
<td>7.7±3.9</td>
<td>91.9</td>
<td>5.708</td>
<td>0.000</td>
</tr>
<tr>
<td>Range (min-max)</td>
<td>(0.1-48.0)</td>
<td>(2.5-16.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*LH: Luteinizing hormone, **FSH: Follicle stimulating hormone. Reference values: Testosterone 2.0-7.0 ng/ml, LH 2.0-13.0 mIU/ml, FSH 2.5-10.0 mIU/ml. All values are expressed as mean±SD. P<0.05: Significant.

### Table-II

**Testosterone and gonadotropins levels of different aspects of Sertoli cell only patients**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>1ry TF (n=40)</th>
<th>Hyper hypo (n=9)</th>
<th>Hypo hypo (n=14)</th>
<th>Idiopathy (n=11)</th>
<th>F</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone (ng/ml)</td>
<td>2.2±1.3</td>
<td>0.9±0.5</td>
<td>0.5±0.4</td>
<td>2.4±1.0</td>
<td>12.135</td>
<td>0.000</td>
</tr>
<tr>
<td>*LH (mIU/ml)</td>
<td>17.3±6.1</td>
<td>24.5±2.6</td>
<td>0.6±0.4</td>
<td>2.6±1.5</td>
<td>79.794</td>
<td>0.000</td>
</tr>
<tr>
<td>**FSH (mIU/ml)</td>
<td>28.9±6.3</td>
<td>37.4±6.7</td>
<td>0.6±0.5</td>
<td>3.5±1.6</td>
<td>167.415</td>
<td>0.000</td>
</tr>
</tbody>
</table>

*LH: Luteinizing hormone, **FSH: Follicle stimulating hormone, 1ry TF: Primary testicular failure, Hyper hypo: Hypergonadotrophic hypogonadism, Hypo hypo: Hypogonadotrophic hypogonadism. Reference values: Testosterone 2.0-7.0 ng/ml, Luteinizing hormone 2.0-13.0 mIU/ml, Follicle stimulating hormone 2.5-10.0 mIU/ml. All values expressed as mean±SD, P<0.05: Significant.
Male infertility is a reproductive health problem that is poorly studied and understood. Worldwide, male infertility contributes to more than half of all cases of childlessness and it is argued that male infertility may be particularly problematic for Middle Eastern men in their societies; there, both virility and fertility are typically tied to manhood. Thus, male infertility is a potentially emasculating condition, surrounded by secrecy and stigma.

In this context, there are under-reporting or even no real figures on male infertility in Gaza Strip. Therefore, the present study targeted Sertoli cell only syndrome as one of the etiologies of azoospermia focusing on testosterone and gonadotropins in infertile men from Gaza Strip.

The mean age of the patients in the present study (29.8 years) was lower than that reported from Nigerian (35.7 years) and Kenyan (36.1 years) studies. The younger age of our patient sample could be explained on the basis that most men seeking out to have children at young age immediately after marriage. Medical history showed that varicocele was significantly more prevalent among patients compared to controls. This coincides with the idea that varicocele contributes to male infertility.

The proposed pathophysiologic mechanisms by which varicocele impairs male fertility may include hypoxia and stasis, elevated testicular temperature, reflux of adrenal catecholamines, and increased oxidative stress. Hormonal problems were also significantly higher in patients than controls implying that Sertoli cell only syndrome is associated with hormonal disturbances.

Hormonal profile of the study population showed that the mean level of testosterone was significantly lower in patients compared to controls. Such decline in testosterone levels in patients may be explained on the basis of hypogonadism which is characterized by a deficiency or absence of Leydig cell function in production of testosterone. In contrast, the mean levels of LH and FSH were significantly elevated in patients compared to controls. Such result is in accordance with other studies. In the infertile men, higher concentration of FSH is considered to be a reliable indicator of germinal epithelial damage, and was shown to be associated with azoospermia and severe oligozoospermia.

The clinical picture of Sertoli cell only syndrome aspects in infertile men in Gaza Strip showed marked lower levels of testosterone in hypergonadotrophic hypogonadism and hypogonadotrophic hypogonadism compared to the normal reference value. Similar results were previously reported. Higher levels of LH and FSH were recorded in primary testicular failure and hypergonadotrophic hypogonadism whereas their levels were obviously lower in hypogonadotrophic hypogonadism compared to the reference values. Male hypergonadotrophic hypogonadism is characterized by hypogonadism due to an impaired response of the testes to LH and FSH, and in turn a lack of testosterone production and elevated gonadotropin levels as an attempt of compensation by the body. In male hypergonadotropic hypogonadism, the levels of LH and FSH were significantly elevated in patients compared to controls. Such result is in accordance with other studies. In the infertile men, higher concentration of FSH is considered to be a reliable indicator of germinal epithelial damage, and was shown to be associated with azoospermia and severe oligozoospermia.
hypogonadism there is inadequate secretion of hypothalamic gonadotropin releasing hormone and lack of production of pituitary gonadotropins and in turn lack of testosterone production.22,28

As depicted from data presented in this study, all infertile men with hypergonadotrophic hypogonadism and hypogonadotrophic hypogonadism showed abnormal levels of testosterone, LH and FSH in comparison with their normal reference values. Such findings supported the above mentioned results that abnormal low levels of testosterone were recorded in both hypergonadotrophic hypogonadism and hypogonadotrophic hypogonadism as well as high and low abnormal levels of LH and FSH were found in hypergonadotrophic hypogonadism and hypogonadotrophic hypogonadism respectively, and coincided with that previously reported.16,29

Conclusion
Serum testosterone was significantly lower in patients than controls, whereas LH and FSH were significantly higher in patients. Abnormal lower levels of testosterone were found in hypergonadotrophic hypogonadism and hypogonadotrophic hypogonadism compared to the normal reference value. Higher levels of LH and FSH were recorded in hypergonadotrophic hypogonadism, whereas LH and FSH levels were lower in hypogonadotrophic hypogonadism compared to the reference values.

Conflict of interest: None.

References


