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Clinico-hormonal correlation of oligospermic patients in the below sea level environment (Jordan Valley)

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ORIGINAL ARTICLE

Abstract

A correlation between serum levels of luteinizing hormone (LH), total testosterone (T), free T and sex-hormone binding globulin (SHBG) in normospermic and in oligospermic male people was done. This study was designed to measure serum levels of these hormones and of SHBG in people living at different altitude environments relative to sea level: at 209–408 meters below (the Jordan Valley, JV) and at 620 meters above (Irbid city, IC). In addition, a clinical awareness study of oligospermia was done in the North of Jordan (IC). Seminal analysis in 287 male people (age range, 18 to 40 years old) during the period between12/6/1999 and 12/2/2002 showed an oligospermia of 31.4%. Serum levels of LH, total T, free T and SHBG in normospermic subjects in IC were similar to those in normospermic of the JV (3.4 ± 1.2 vs. 4.0 ± 1.7 MIU/ml, 19.9 ± 4.0 vs. 20.4 ± 5.6 ng/ml, 53.9 ± 15.6 vs. 47.9 ± 10.7 pg/ml, 19.5 ± 3.2 vs. 18.6 ± 2.16 nmol/l, respectively). Oligospermia was associated with increase in total T at both IC (27.5 ± 4.6 vs. 19.9 ± 4.0 ng/ml) and the JV (30.7 ± 3.4 vs. 20.5 ± 5.6). The higher serum level of total T in oligospermic people in both IC and the JV was associated with higher levels of SHBG compared to those levels in normospermic subjects. On the other hand, oligospermic subjects have lower serum level of free T than in normospermic males (41.5 ± 10.0 vs. 53.9 ± 15.6) only in IC, while in the JV, serum free T level was similar (46.5 ± 6.1 vs. 47.9 ± 10.7). Taken together data for both locations, IC and the JV, suggest a clear correlation between total T and SHBG levels in both groups' normospermic and oligospermic subjects.

Introduction

There are some genetic as well as environmental (e.g. barometric pressure, temperature, culture, nutrition) differences between the people living in the JV (280–360 meters below sea level) compared to those of IC and other towns (560–620 meters above sea level) in the Hashemite Kingdom of Jordan. For instance, people of the JV are Arabs with some Negroid features such as a dark skin and Negroid-like facial features. The barometric pressure of the JV is higher than that in

IC. The average monthly temperature throughout the Late Spring, Summer and early Autumn are higher than those recorded in IC. People of the JV have higher (and younger) marriage rate with higher birth rates than those in other areas above sea level. Additionally, there are significant nutritional differences between the people of the JV and those of IC; the socio-economic conditions, including sanitary, are worse than those in other areas of the Kingdom.

Carbohydrate, lipid and protein metabolism as well as hormonal homeostasis were studied in people living in the JV by El-Migdadi and his group [1–3]. In these experiments, controls were taken from people of IC and of another nearby town that is also located at above sea level (Ramtha). A group of pituitary hormones (adrenocortitropin (ACTH), growth hormone (GH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH) and other hormones as well, such as cortisol, thyroid hormones, insulin and sex hormones (e.g. progesterone (P) and testosterone (T)), were investigated using this experimental model. These studies suggested a differential expression and/or serum level of some of these hormones and some metabolites, such as glucose and lactate, under different stress conditions [1]. Exercise caused a significant increase in serum levels of both LH and T only in athletes of North and South Shouna in the JV. It seems likely that the higher secretion of LH contributes, at least in part, for the higher serum levels of T following exercise. These data suggest that exercise has an effect on LH and T secretion that is similar to that of Ramadan (daytime)-fasting. The below sea level environmental factors, such as the high barometric pressure, as well as the genetic background of the athletes affect the pituitary and adrenal cortex as well as testicular tissue, resulting in the secretion of more LH and T [2]. In males and females of the JV, serum levels of LH, FSH and P were all higher than those of IC throughout the year. Additionally, peaks of LH and T in male and FSH and P in female subjects in the JV were observed from March through September. The high levels of these hormones and the extension of their peaks are suggested to be due to effects of the environmental factors of the JV (high temperature, high barometric pressure) compared to those in IC and other areas located at above sea level altitude [3].

The incidence of oligospermic male infertility in the JV and IC had not been investigated yet. Additionally, hormonal evaluation in infertile men may have some valuable clinical implication. Our hypothesis was designed to utilize the experimental model of people living in the below sea level environment in the JV to address the hormonal status of fertile and infertile male humans. It is proposed that clinical awareness (incidence) of male infertility in the JV is different than that in IC. Additionally, it is hypothesized that LH, total and free testosterone and SHBG profile(s) is not the same among peoples in the JV and in IC.

The objectives for this study are:

Investigate the awareness of oligospermic male infertility in people of below sea level environment in the Jordan Valley (JV) and in those living at above sea level in Irbid City (IC).

Hormonal assessment of LH, testosterone (free and total) and sex hormone binding globulin (SHBG) in oligospermic infertile men in the two locations (JV and IC).

Expereimental Design, Materials And Methods

I. Description of Research location

IC is located in Northwestern Jordan. Its altitude is about 620 meters above sea level. Summer temperatures in IC are between 20 °C and 35 °C. Winter temperatures fluctuate mainly between 5 °C and 20 °C. The JV has an altitude of about 209 meters below sea level in the area of Lake Tabaria and 408 meters below sea level at the lowest point on earth, the Dead Sea. The climate is mild in Winter with temperatures between 5 °C and 20 °C and it is hot and dry in the Summer (25 °C – 40 °C).

II. Selection of Human Subjects

Selection of individuals included in the Clinical Awareness Study. For a Clinical Awareness Study of male infertility in the IC and the JV, a retrospective analysis of seminal fluid analyses records was done. The records from the Clinical Laboratories at Princess Basma Teaching Hospital were used. Data from 12/6/1999 to 12/2/2002 were analyzed and randomly selected. A total number of 287 males with age range from 18 to 40 years old were included in this analysis. Seminal fluid analysis were documented as described by DY, Liu and HWG, Baker (1992) and grouped into 3 subgroups (Fertile, Oligospermic and Azoospermic) depending on their sperm count and sperm morphology and motility.

Selection of individuals for hormonal evaluation. Over a period of 6 months, selection of male individuals for hormonal assessment was done at the Clinical Laboratories in Princess Basma Teaching Hospital in IC. A random selection of these individuals was performed, every third individual was chosen on different days of the week over 24 weeks. These individuals, of only 18–40 years old, were referred from the Outpatient Clinics of Princess Basma Teaching Hospitals for seminal fluid analysis. Those who were selected were informed of our intention of their inclusion in this study and a signed consent was taken. They also filled a questionnaire. In addition to their seminal fluid taken for analysis, a blood sample was taken for hormonal assessment. A group of 20 individuals living in IC, with a normal seminal analysis (fertile) were selected for serum LH, total T, free T and SHBG measurements. Another group of 20 people from IC with sperm count < 10 millions / ml and with abnormal morphology in their seminal fluid analysis (infertile) were selected for hormonal measurements.

A similar selection procedure was done to select 20 fertile and another 20 infertile individuals from the JV. These individuals were referred from the Outpatient

Clinics of the JV to the Clinical Laboratories at Princess Basma Teaching Hospital for seminal fluid analysis. Only those, who are originally from the JV and still living in the JV area were selected.

Experimental groups are summarized in Table 1.

III. Blood sample collection and handling

Venous blood samples were collected in the morning between 8.00–11.00 O'clock. Precautions for venipuncture procedure were observed. Nonoxalated vacutainer tubes, plain tubes, (9ml) were used for obtaining blood serum samples. Plain tubes were set at room temperature for 15 minutes to allow blood clotting. Samples were separated by centrifugation at 4000 rpm for 3 minutes. Serum samples were frozen at –20 °C.

IV. Hormonal measurements

Total T, LH, Free T and SHBG were measured in all serum samples from groups 1, 2, 3 and 4 at the same time. The DSL– 4600 ACTIVE Coated–tube Immunoradiometric Assay (IRMA) kits were used for hormonal measurements. The Automatic Gamma Counter (LKB-Wallac Clini Gamma 1272–001) located at the Clinical Laboratories in Princess Basma Teaching Hospital was the device used to measure the radioactivity of samples and to calculate their concentrations. The results were obtained in MIU / ml for LH, ng / ml for total T, pg / ml for free T, and nmol / l for SHBG.

V. Data Assessment and Statistical Analysis

Data from the Clinical Awareness Study were analyzed and sub grouped into Fertile, Oligospermic and Azoospermic. The total number for each subgroup was represented as % of the total number of individuals, who were included in this study.

Raw Data for serum levels of LH, total T, free T and SHBG were averaged and expressed as mean ± standard deviation (SD). Differences in the values of means were subjected to unpaired Student t-test. P values were considered significant where P is less than 0.03.

Results

Table 2 shows data from the Clinical Awareness Study. During the period from 12/6/1999 to 12/2/2002, there were 167 individuals with normal seminal fluid. The clinical awareness of male fertility in the North of Jordan (IC) represents 68.6%. The rest of individuals (111) were classified as either oligospermic (97) or azoospermic (14), representing 26.5% and 4.9% respectively. Consequently, clinical awareness of male infertility in the North of Jordan (IC) represents 31.4%.

In IC, serum levels of LH in fertile male subjects are similar to those in infertile men (3.4 vs. 3.6 MIU/ml) (table 3 and figure 1). On the other hand, the mean value of serum levels of LH in fertile males of the JV is lower than that in infertile people (4.0 vs. 7.1 MIU/ml). However, there is no statistical significance between the two groups. Serum level of LH in fertile males of IC is lower than that in fertile male subjects of the JV (3.0 vs. 4.0 MIU/ml); but when subjected to statistical analysis, there was no significant difference between the two groups. Similarly, serum levels of LH in infertile males of IC are lower than those in infertile men of the JV (3.4 vs. 7.1 MIU/ml) with no statistical significance.

Table 1: Male groups selected for hormonal evaluation.

Group Symbol	Group type	Number of members in group	Location
1	Adult fertile males	20	IC
2	Adult fertile males	20	JV
3	Adult infertile males	20	IC
4	Adult infertile males	20	JV

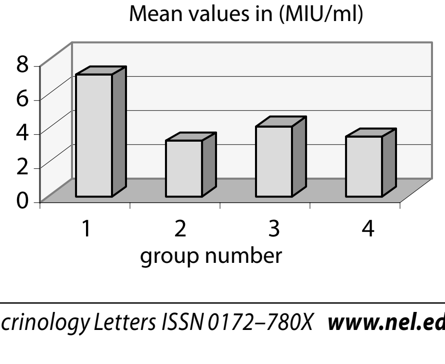
Table 2: Data from Clinical Awareness Study

Sperm count	Clinical aspect	%
>20million	Fertile	68.6%
<20million	Oligospermic	26.5%
No sperms	Azoospermic	4.9%

Table 3: Raw Data and their Mean ± Standard Deviation for Serum Levels of LH in Male subjects of IC and the JV.

Fertile males (IC)	Fertile males (JV)	Infertile males (IC)	Infertile males (JV)
1.872	1.57	1.312	5.253
2.191	1.728	1.567	5.913
2.284	2.171	1.7	8.153
2.522	2.931	2.34	8.831
2.65	4.076	3.364	7.673
3.099	4.242	3.504	6.765
3.564	4.648	3.847	8.909
3.638	5.299	4.05	8.25
4.295	5.412	4.867	5.651
4.882	5.744	6.345	6.08
6.488	6.793	7.116	6.231
3.407	5.235	3.652	8.1
4.013	3.256	3.9	6.854
2.399	5.424	2.9	5.214
5.114	2.568	5.624	6.58
1.584	4.025	2.489	8.979
3.77	4.8	6.365	7.865
3.325	2.012	1.9	7.075
4.312	1.9	3.24	8.36
2.701	6.9	2.311	4.455
Mean 3.4055	4.0367	3.61965	7.05955
SD 1.217	1.68750	1.69564	1.36519

Figure 1: Mean values of serum LH in (MIU/ml).



In IC, the mean value of serum total T in fertile males subjects is lower than that in infertile people (19.9 vs. 27.5 ng/ml) (table 4 and figure 2). Similarly, in the JV, the mean value of serum levels of total T in fertile males is also lower than that in infertile people (20.5 vs. 30.7 ng/ml). In both fertile and infertile male subjects, serum levels of total T in IC are similar to those in the JV (19.9 vs. 20.5 ng/ml, 27.5 vs. 30.7 ng/ml, respectively).

The mean value of serum free T in fertile male people in IC is higher than that infertile subjects (53.9 vs. 10.0 pg/ml), as seen in table 5 and figure 3. In a similar fashion, serum levels of free T in fertile males in the JV are also higher than those in infertile subjects (47.9 vs. 6.1 pg/ml). On the other hand, at both locations, IC and the JV, serum levels of free T in fertile people are similar to those in infertile subjects (53.9 vs. 47.9 pg/ml and 10.0 vs. 6.1 pg/ml, respectively).

The mean value of serum SHBG in fertile subjects in IC is lower than that infertile (19.5 vs. 46.6 nmol/l), as seen in table 6 and figure 4. Similarly, serum levels of SHBG in fertile males in the JV are also lower than those in infertile people (18.6 vs. 45.3 nmol/l). On the other hand, when one compares IC to the JV, serum levels of SHBG in fertile male subjects and in infertile male subjects are similar (19.5 vs. 18.6 nmol/l, 46.6 vs. 45.3 nmol/l, respectively).

Discussion

The study reported here was designed to investigate a possible correlation between serum levels of three hormones, LH, total T, free T and SHBG for people living at different altitude environment relative to sea level (below, the JV and above, IC). Additionally, a correlation between hormone (LH, total T and free T) levels and SHBG levels in normospermic and in oligospermic male subjects was done.

Mean values of both LH and SHBG in male subjects of IC and the JV were similar to what is reported in the literature [4]. On the other hand, mean values of serum levels for total T and free T in male population of the north of Jordan (IC and the JV) were higher than what is reported elsewhere [4]. The high basal serum levels of total T in people of the north of Jordan were

Table 4: Raw Data and their Mean ± Standard Deviation for Serum Levels of Total T in Male subjects of IC and the JV.

Fertile males (IC)	Fertile males (JV)	Infertile males (IC)	Infertile males (JV)
15.155	14.345	23.335	27.501
17.331	12.678	32.866	28.34
14.092	13.399	19.579	30.57
21.787	19.576	25.26	32.81
11.945	20.816	22.713	33.579
20.553	21.827	23.335	25.245
29.313	22.866	27.296	33.579
25.331	23.764	27.57	39.57
25.816	26.786	31.847	27.713
18.145	28.787	39.849	29.045
19.958	20.525	27.45	28.101
18.456	28.121	25.25	30.754
20.753	12.225	29.743	32.878
21.348	15.124	27.554	25.478
17.693	23.249	22.994	33.744
19.001	27.451	31.332	33.313
20.253	13.298	32.22	29.847
21.223	16.408	25.74	30.656
19.562	21.784	25.749	28.241
20.868	26.245	27.654	32.875
Mean 19.9292	20.4637	27.4668	30.692
SD 3.97225	5.57823	4.58335	3.42832

Tale 5: Raw Data and their Mean ± Standard Deviation for Serum Levels of Free T in Male subjects of IC and the JV.

Fertile males (IC)	**Fertile males (JV)**	**Infertile males (IC)**	**Infertile males (JV)**
24.04	34.76	21.2	35.42
32	37.731	26.78	35.68
32	28.387	31.56	45.04
32.48	33.03	31.98	45.56
34.68	34.32	35.68	46.5
40.04	40	36.88	46.54
53.24	41.2	37.94	47.44
54.68	42.22	39.04	49.42
54.36	44.65	40.46	56
56	45.86	41.84	57.72
58.98	48.9	43.3	46.532
60.06	50.66	44.1	44.654
60.1	52.2	44.12	48.89
60.2	52.68	47.8	36.235
64.4	54.8	47.8	56.453
66.82	58.08	48.52	45.763
68.02	60.26	48.86	47.932
72.68	60.59	55.96	42.675
74.88	66.4	65.62	48.121
78.48	70.841.6	41.516	46.4513
Mean 53.907	47.8764	41.5494	46.4513
SD 15.6401	10.6592	9.95742	6.07741

Figure 2:Mean values of serum total T in (ng/ml).

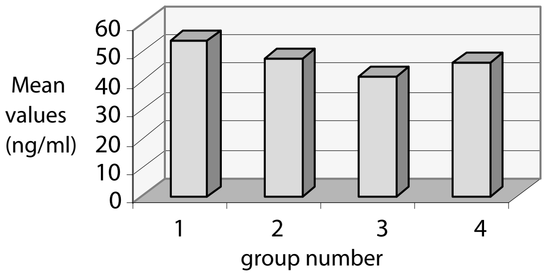
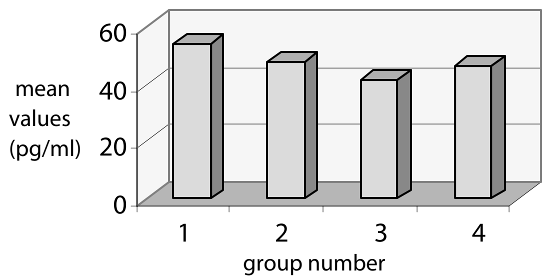


Figure 3: Mean values of serum free T in (pg/ml).

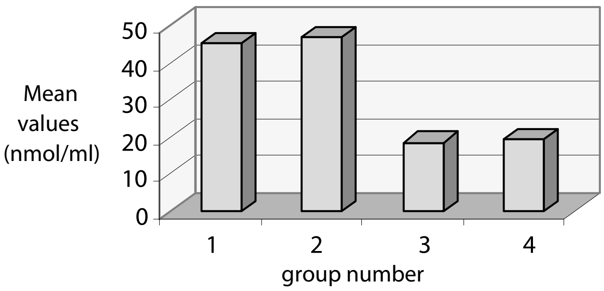


also reported by Banihani *et al.* [2]. It is unclear, however, the reason for such discrepancy between what is reported in the literature for serum levels of total T and free T and our data. Mohler *et al.* [5] reported that black and white men had similar T and dihydrotestosterone (DHT). However, black men had higher SHBG. Racial differences do not seem to be the lone major contributor to the differences between our data from Jordan and others done elsewhere. Blood measurements of basal total and free T in a large-scale (1000 randomly-selected) experiment of male subjects from the North of Jordan is advised before making any vivid conclusion regarding this issue. Finally, environmental factors including temperature, barometric pressure and human diet and consumed food may play a role in the differences between blood levels of male sex hormones measured among different human groups in different parts of the world. Niskanen *et al.* [6] reported significant changes in sex hormone-binding globulin and testosterone during weight loss and weight maintenance using very low calorie diets.

Table 6: Raw Data and their Mean ± Standard Deviation for Serum Levels of SHBG in Male subjects of IC and the JV.

Fertile males (IC)	Fertile males (JV)	Infertile males (IC)	Infertile males (JV)
10.452	14.89	18.477	18.477
18.233	15.968	20.88	34.626
19.98	16.614	23.795	36.861
20.455	18.99	30.235	40.279
20.655	20.145	31.572	41.305
21.434	21.233	40.163	43.527
25.859	22.98	49.051	43.95
18.834	18.898	49.193	45.749
20.315	17.701	51.415	47.971
21.89	19.187	58.174	52.415
17.554	16.965	64.33	54.65
24.108	20.131	69.623	55.304
14.663	21.854	72.107	58.174
19.876	15.109	75.178	60.304
19.664	18.845	46.898	44.44
20.121	19.143	48.121	46.019
21.234	20.357	44.141	47.525
18.457	17.852	40.9	43.224
17.147	16.963	51.891	45.008
19.852	18.661	45.977	46.007
Mean 19.5392	18.6243	46.6061	45.2908
SD 3.20887	2.16429	16.3167	9.17141

Figure 4: Mean values of serum SHBG in (nmol/l).



In agreement with what is known in the physiology of hypothalamic-pituitary-gonadal axis [7], there was a clear correlation between serum levels of LH and those of total T and free T.

In IC, mean values of serum LH in fertile males are similar to those in infertile subjects and these values are in agreement to what is reported in the literature [4]. The higher serum levels of total T in infertile people living in IC was associated with higher levels of SHBG as compared to those in fertile male subjects. This may explain, at least in part, the lower serum levels of free T in oligospermic male people (Table 7). Confirmation of male hormonal insufficiency is a must before prescribing androgen replacement therapy [8]. This fact underlines the significance of hormonal measurements in oligospermic men found among people of the North of Jordan. However, when diagnosing low androgen levels in this part of the world, one should keep in mind the higher basal levels of total and free T and of SHBG (see above).

Table 7: A comparative analysis of serum levels (Mean ± SD) of LH, total T, free T and SHBG between normospermic and oligospermic males in IC.

	LH MIU/ml	Total T ng/ml	Free T Pg/ml	SHBG nmol/l
Fertile males (IC) (N=20)	3.4 ± 1.2	19.9 ± 4.0	53.9 ± 15.6	19.5 ± 3.21
Infertile males (IC) (N=20)	3.62 ± 1.66	27.5 ± 4.6	41.5 ± 10.0	46.6 ± 16.3
p-value	0.190	0.004	0.025	0.000

Data in Table 8 indicates that, in a similar fashion to IC, in the JV, there was no effect of oligospermia on the serum levels of LH in male subjects. Additionally, there was a higher serum level of total T in oligospermic men than that in normospermic subjects. Oligospermia was also associated with higher serum level of SHBG than that that in normospermia. In the JV, however, there was no significant difference between serum levels of free T in oligospermic and normospermic male people.

Table 8: A comparative analysis of serum levels (Mean ± SD) LH, total T, free T and SHBG between normospermic and oligospermic males in the JV.

	LH MIU/ml	Total T ng/ml	Free T pg/ml	SHBG nmol/l
Fertile males (JV) (N=20)	4.0 ± 1.7	20.5 ± 5.6	47.9 ± 10.7	45.29 ± 9.2
Infertile males (JV) (N=20)	7.06 ± 1.37	30.7 ± 3.4	46.5 ± 6.1	18.6 ± 2.2
p-value	0.004	0.016	0.085	0.006

Data for both locations, IC and the JV, suggest a clear correlation between serum levels of total T and SHBG in both groups of male subjects, normospermic and oligospermic (Tables 7 and 8). In oligospermic subjects, serum levels of free T were either lower (IC) or similar (the JV) to those in normospermic people. Together, these data suggest that it is, perhaps, essential to measure not only the total T, but also the free fraction of T and/or SHBG in evaluation of male infertility based on seminal analysis. Blood measurements of all total and free T and of SHBG are supported by what is reported by Christ-Crain *et al.* [9]. Free T levels have been suggested to represent more reliably the bioactive hormone at the tissue level as compared to total T levels. The best practical approach is to calculate the free testosterone level [10]. Again, measurement of serum levels of LH is also an essential component of this evaluation. American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients [11] supports the proposed, herein, clinical strategy.

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