Increased frequency of anxiety, depression, quality of life and sexual life in young hypogonadotropic hypogonadal males and impacts of testosterone replacement therapy on these conditions


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Abstract. Hypogonadotropic hypogonadism is defined as the failure in production of gonadal hormones, thus resulting in lower amounts of testosterone. Depression, anxiety and decreased quality of life are the most common psychopathological conditions in young hypogonadal men. The aim of the present study was to assess the still debated relationship with testosterone levels and psychological symptoms in young male patients with congenital hypogonadotropic hypogonadism (CHH). Thirty-nine young male patients with CHH and 40 age-matched healthy males were enrolled in the present study. The impact of testosterone replacement treatment (TRT) on the patients' anxiety and depression levels, sexual function and quality of life were assessed before and after 6 months of treatment using valid and reliable scales, including the Short Form-36 (SF-36), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and Arizona Sexual Experiences (ASEX). Patients with CHH had significantly higher scores for BDI, BAI, and ASEX than the control subjects at baseline ($p=0.011$, $p=0.036$, $p<0.001$, respectively). The ASEX and BDI scores significantly improved after the TRT ($p<0.001$ for both), while the improvement in the BAI score was not statistically significant ($p=0.135$). When compared to the control group, treatment naïve hypogonadal patients had more severe symptoms of sexual dysfunction, anxiety, depression, and worse quality of life. After 6 months of TRT, we observed improvements in the above parameters, suggesting that low endogenous levels of testosterone might be related to the increased incidence of psychological symptoms.

Key words: Hypogonadism, Testosterone, Anxiety, Depression, Quality of life

HYPOGONADISM manifests itself with specific symptoms and signs of testosterone deficiency that can occur at any age. Early diagnosis and treatment of hypogonadism is crucial as it can improve the quality of life and prevents disease related complications. The most prominent symptoms of hypogonadism are loss of libido and erectile dysfunction [1-3]. Sexuality is not mandatory for maintaining the individual's life, but it is a necessity to sustain the species. If this requirement is not met for any reason, it can have a negative impact on psychological profile and the quality of life. Anxiety and depression are the most common and frequently undiagnosed psychological problems associated with male hypogonadism. The most important reason for this situation is that clinicians are more interested in a patient’s somatic symptoms [4-6]. Defining the psychological variables of the disease is essential to improve our understanding of this complex disorder, and can be useful for directing therapy. Furthermore, differential diagnosis of conditions that may result in a psychological distress (delayed puberty, primary hypogonadism etc.) should always be kept in mind to arrive at a definite diagnosis.

TRT restores normal sexual functions and improves libido, fatigue, sense of well being, bone density, mus-
cle mass, body composition, mood status and cognition. Overall, the restoration of the above parameters is expected to improve the quality of life [7-9]. However, few studies so far have reported positive effects of TRT on psychological well-being and quality of life [10, 11].

Therefore, we aimed to search the frequency of anxiety, depression, sexual dysfunction and impaired quality of life, and the effect of TRT on these disorders in naïve young subjects with CHH.

**Materials and Methods**

**Participants**

Thirty-nine young men with newly diagnosed CHH (mean age: 21.87±2.04 years) were included in the study between May 2009 and January 2011 at the Department of Endocrinology and Metabolism, Gulhane School of Medicine. The control group consisted of 40 age-matched healthy eugonadal males (mean age: 23.42±2.47 years). The patient group had decreased sexual function, manifested by lack of libido and inability to maintain erection, and impaired secondary sexual characteristics. All of the study participants had at least 8 years of education. The study protocols were approved by the Ethics Committee of Gulhane School of Medicine, Ankara, Turkey. At the beginning, after describing the purpose and scope of the study to all patients, a written, informed consent was obtained from each one. The diagnosis of CHH was based on a failure to undergo spontaneous puberty before 18 years of age and was confirmed by low serum total testosterone levels and normal or low gonadotropin levels. Additional criteria included the individuals in Tanner stages 1 to 2, absence of a pituitary or hypothalamic mass lesion on an MRI, presence of a gonadotropin response to repetitive doses of GnRH, and a normal karyotype (46, XY). Subjects with a recent or previous history of receiving TRT, those with metabolic, malignant or inflammatory diseases, and those with constitutional delay of puberty or other hormonal imbalances were excluded from the study. None of the patients had previously suffered from any psychiatric disorder or have ever been treated by a psychologist or psychiatrist. Patients previously diagnosed with such conditions or those on any related medications were not enrolled in the present study.

The height, weight and waist circumferences of all participants wearing underwear only, were measured. Body mass index (BMI) was computed as the ratio of weight to the square of height (kg/m²). BMI was categorized as follows: underweight (<18.5 kg/m²), normal (18.5-24.9 kg/m²), overweight (25-29.9 kg/m²), and obese (>30 kg/m²).

**Testosterone replacement therapy**

Following enrolment into the study, the patients were given replacement therapy using an oil-based injectable blend of four esterized testosterone compounds (Sustanon 250 mg; 30 mg testosterone propionate, 60 mg testosterone phenylpropionate, 60 mg testosterone isocaproate and 100 mg testosterone decanoate) administered every 3-weeks for 6 months. Blood samples were taken just before the first testosterone injection for the evaluation of the baseline parameters. The patients were followed-up for 6 months and then a final examination was conducted. The follow-up visits were arranged on days just before the next testosterone administration. Therefore, the time points for taking the blood samples were the same for all participants. The mean age of the patients was 21 and none of them were married. Because fertilization was not required, we did not have any subjects having an indication of LH + FSH therapy.

**Laboratory measurements**

For biochemical analyses, all blood samples were collected at around 0800 AM after an overnight fast from an antecubital vein. The samples were centrifuged at 4,000 rpm for 15 minutes, aliquot and immediately stored at a temperature of -80 °C prior to use. Total testosterone, FSH, and LH levels were determined by a chemiluminescence immunoassay method using a Unicell Beckman & Coulter DXI 800 model device. After the calibration of the weighing equipment, anthropometric measurements of patients (weight and height) were performed in the morning, while they were standing in an upright position on an empty stomach, wearing no clothing or shoes.

**Instruments**

Prior to and following TRT, all participants underwent a psychological and sexual assessment. Anxiety, depression, quality of life and sexual function of patients were evaluated using valid and reliable scales. The scales shown below were used for the patients and participants in the control group.

1. **Short Form-36 (SF-36)**

SF-36 is a self-evaluation scale designed to assess the quality of life. It contains 36 items that calculate 8 dimensions including, physical functioning, physical
role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. For each dimension, scores of related items are coded according to the responses. Zero represents the worst quality of physical and mental life, while the best possible overall score one can receive is 100 points. SF-36 was originally developed by Ware and Sherbourne, and has been standardized for the Turkish culture by Kocyigit and colleagues [12, 13].

2. The Beck Depression Inventory (BDI)
BDI is a self-report scale with 21 items. The objective of the scale is not to establish depression, but to objectively define the severity of depressive symptoms. Possible scores range between 0 and 63 points. Individuals having a score of 16 or greater are classified as depressed. BDI was developed by Beck, and has been modified to Turkish by Hisli [14, 15].

3. The Beck Anxiety Inventory (BAI)
BAI is a self-report scale with 21 items. Total BAI scores range between 0 and 63 points. Increasing scores indicate severity of the intensity of anxiety symptoms. BAI was designed by Beck and colleagues, and the Turkish version was developed by Ulusoy [16, 17].

4. Arizona Sexual Experiences Scale (ASEX)
ASEX is a brief, five-item scale designed to evaluate the core elements of sexual functioning: drive, arousal, penile erection/vaginal lubrication, ability to reach orgasm, and satisfaction with orgasm. Each item is rated with a six-point Likert system. Total scores range between 5 and 30 points, and higher scores reflect sexual dysfunction. A total ASEX score of 19 or greater, any one item with a score of 5 or greater, or any three items with a score of 4 or greater have all been found to be correlated with impaired sexual function [18]. The reliability and validity of ASEX in Turkish patients have already been validated by Soykan [19].

### Statistical analysis
Statistical evaluations were performed by running the SPSS 11.0 package program (SPSS, Inc., Chicago, IL, USA). While defining the data, number, percentage, median, mean, and standard deviation (SD) values were used. The normality of distribution of continuous variables was evaluated using the Kolmogorov-Smirnov test. For between-group comparisons, if continuous variables were acceptable with normal distribution, we used Student’s t-test, if not, we used the Mann-Whitney U test. For intra-group comparisons, if variables were acceptable with normal distribution, the t-test was used, if not, the Wilcoxon test was used. For comparisons of discrete variables, the chi-square and Fisher’s exact test were used between independent groups, and the McNemar test between dependent groups. A $p \leq 0.05$ was considered statistically significant.

### Results
The BMI values of the patients were similar to the control subjects and increased significantly after TRT. The low Tanner stages of the patients significantly improved after TRT (Table 1). BDI, BAI, and ASEX scores of the patients were significantly higher than those of the control group at baseline ($p=0.011$, $p=0.036$, $p<0.001$, respectively).

With a cut-off value of 16 for BDI, 23.1% of the patient group had depressive symptoms, whereas this rate was only 5% in the control group ($p=0.036)$. When the cut-off value of ASEX was accepted as 11 points, any one item with a score of 5 or greater, or any three items with a score of 4 or greater have all been found to be correlated with impaired sexual function [18]. The

### Table 1
Physical properties and hormonal profiles of study group and control groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Study Group</th>
<th>Control Group</th>
<th>$p^1$</th>
<th>$p^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-TRT (n=39)</td>
<td>Post-TRT (n=39)</td>
<td>Control (n=40)</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>21.87±2.04</td>
<td>-</td>
<td>23.42±2.47</td>
<td>0.080</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.91±2.15</td>
<td>25.8±2.11</td>
<td>24.28±2.76</td>
<td>0.064</td>
</tr>
<tr>
<td>Total testosterone (ng/dL)</td>
<td>78.09±73.03</td>
<td>261.03±186.45</td>
<td>482.70±117.50</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>0.64±0.30</td>
<td>0.91±0.47</td>
<td>5.40±1.20</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
<td>0.39±0.32</td>
<td>0.70±0.65</td>
<td>5.41±1.01</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Tanner classification (Stage)</td>
<td>1.5±0.5</td>
<td>3.5±0.5</td>
<td>5.0±0.00</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Values are given as mean ± Standard deviation. BMI, Body mass index; FSH, Follicle-stimulating hormone; LH, luteinizing hormone; TRT, Testosterone replacement therapy.

$p^1$: Pre-TRT study group versus control group, independent-samples t test; $p^2$: Pre-TRT study group versus post-TRT study group, paired-samples t test; * $p<0.05$
The results of the present study show that treatment naïve young hypogonadal patients have more sexual dysfunction, anxiety, depression, and experience poorer quality of life when compared to their healthy counterparts. The results also support that in addition to recovered sexual functions, TRT also improves anxiety and depression scores and the life qualities of these patients at 6 months.

Testosterone has neurobehavioral, somatic and metabolic effects in adult men. Patients with hypogonadism not only have loss of libido and erectile dysfunction, but also have several other problems such as fatigue, increased body fat, osteoporosis, mild anemia, gynecomastia, sleep disturbances, and hair and skin changes [1-3, 5]. All of these conditions may cause anxiety and depression in these patients. Indeed, a prospective follow-up study has shown that the incidence of depression is significantly higher in patients with hypogonadism. However, there are other studies showing that there is only a trivial relationship between the depressive symptoms and plasma testosterone levels. A meta-analysis of the previous reports also shows that the relationship between low testosterone levels

Table 2 Comparisons of scores between the study (pre- and post-TRT subgroups) and control groups

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Control Group (n=40)</th>
<th>Median (Interquartiles)</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-TRT (n=39)</td>
<td>Post-TRT (n=39)</td>
<td>p&lt;sub&gt;1&lt;/sub&gt;</td>
<td>p&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>BDI</td>
<td>9 (2.00-17.00)</td>
<td>1 (0.00-11.00)</td>
<td>2 (0.00-8.00)</td>
</tr>
<tr>
<td>BAI</td>
<td>7 (1.00-11.00)</td>
<td>4 (2.00-9.00)</td>
<td>3 (1.00-7.00)</td>
</tr>
<tr>
<td>ASEX</td>
<td>17 (14.00-21.00)</td>
<td>10 (8.00-16.00)</td>
<td>8 (4.00-11.00)</td>
</tr>
</tbody>
</table>

SF-36

| Physical function | 78.71±20.41 | 73.43±35.08 | 90.85±9.52 | 0.045* | 0.422 | 0.058 |
| Role difficulty (physical) | 60.89±36.63 | 75.01±31.41 | 82.75±36.11 | 0.032* | 0.010* | 0.023* |
| Pain | 72.69±26.74 | 83.44±17.75 | 79.57±15.00 | 0.241 | 0.048* | 0.443 |
| General health | 54.46±22.49 | 64.36±16.23 | 78.90±18.47 | 0.032* | 0.042* | 0.032* |
| Vitality (energy) | 59.10±25.38 | 66.01±17.04 | 71.62±20.03 | 0.015* | 0.059 | 0.002* |
| Social function | 70.38±20.53 | 71.10±21.38 | 76.56±21.09 | 0.167 | 0.943 | 0.502 |
| Role difficulty (emotional) | 48.71±38.87 | 62.40±38.37 | 73.33±24.44 | 0.003* | 0.025* | 0.004* |
| Mental health | 53.84±19.37 | 62.47±16.81 | 65.40±17.00 | 0.124 | 0.041* | 0.087 |

BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; ASEX (Male form), Arizona Sexual Experiences Scale Male Form; SF-36, Study 36-Item Short Form; TRT, Testosterone replacement therapy; SD, Standard deviation

p<sub>1</sub>: Pre-TRT study group versus control group; p<sub>2</sub>: Pre-TRT study group versus post-TRT study group; p<sub>3</sub>: Post-TRT study group versus control group; *, p<0.05
and the frequency of depression is not always present [6]. TRT improves sexual function, muscle strength, bone mineral density, and the secondary sex characteristics in men with symptomatic androgen deficiency [7]. However, data on the effect of TRT on improving depressive symptoms are controversial [6]. Most of the studies have been performed in patients with hypogonadism of different etiologies, having several comorbidities and taking a wide range of drugs [2, 20]. Also, the subjects in these studies were mostly middle aged or elderly [1-3, 18]. There is agreement however, that testosterone levels decline progressively with advancing age and that many of the physiological changes including anxiety and quality of life occur as people age [1, 21, 22]. Our results, which show a significant increase in depression scores of patients with CHH, are utmost important, as they are performed in a highly specific and homogeneous population of young and treatment naïve hypogonadal subjects.

We also examined the ASEX scores in our patients and found TRT having a positive impact on sexual function. Previous studies with relatively short follow-up periods have shown that the administration of different testosterone regimens improves the sexual motivation and performance scores in patients with a wide age distribution [3, 4, 23]. To our knowledge, there aren’t any studies observing the effect of testosterone treatment on ASEX scores in young patients with hypogonadotropic hypogonadism. Our study is the first one that investigated the difference between the ASEX scores of CHH patients and healthy subjects. According to our results, the ASEX scores increase in the follow-up period and become similar to those of the healthy subjects.

The quality of life in patients with hypogonadism can be impaired due to decrease in muscle mass, libido and sexual activity, or co-occurrence of metabolic disorders and emotional difficulties. The SF-36 scores of hypogonadal Japanese males, in varying ages, were found to be lower in all subcategories, when compared to those of age-matched healthy individuals. TRT significantly improved the vitality, social functioning and emotional role in these patients. Similar results on different components of SF36 scores have been reported in other studies [10, 24]. Our results are also parallel to those of the above-mentioned findings. In our study, the scores of role difficulty, pain, general health, emotional role, and mental health significantly improved, while the increase in other parameters was not significant. However, previously published literature investigating the quality of life in patients with hypogonadism, was mainly focused
on the geriatric population. We examined a population of hypogonadal patients younger than any other previously reported studies. Although post-treatment testosterone levels in the patient group increased in some degree, they were slightly below the normal range. This could be a possible reason for why some of the SF-36 scores in our subjects did not improve. There are also some reports on this subject with different conclusions [25, 26]. This contradiction with other studies might be due to our samples’ demographic profile in terms of age distribution. It might also be related to the difference between the follow up periods.

This study may have several limitations. Due to strict inclusion criteria, the study population may not be representative of the elderly hypogonadal patients with several metabolic confounders. In addition, the study period could have been longer to assess the long-term psychological effects of TRT. However, the homogeneity of our study population allows us to observe the unconfounded effects of TRT on sexual dysfunction, anxiety, depression and the quality of life. Furthermore, the significant improvement in the Tanner Stages of the patients 6 months after starting TRT may indicate that the follow-up period of the study was acceptable.

**Conclusion**

In the present study, young patients with CHH had a high incidence of sexual dysfunction, anxiety, depression, and a poorer quality of life, suggesting that low endogenous levels of testosterone might be related to the increased incidence of psychological symptoms. We observed an improvement, not only in the sexual function, but also in the mental health and quality of life in patients who were treated with TRT. Patients suffering from hypogonadism should not be evaluated by their metabolic and functional parameters alone, but a particular attention should also be paid for signs of additional psychological problems and if found, these should also be managed and followed-up. Prospective studies with a higher number of patients, focusing on hypogonadism and its relation to mental and sexual disorders, may help to identify the true long-term mental and sexual risks in these individuals.

**Acknowledgments**

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**References**


