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Depression Improvement Among Patients with HIV and Endocrine Dysfunction After hormone Therapy

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Abstract

Endocrine diseases, known as a curable etiology for depression, are common among men living with HIV (MLWH); while depression impedes the adherence to treatment and the perceived quality of life. We evaluated the changes in the depressive symptoms after the medical treatment of the underlying endocrine diseases among Iranian MLWH. Since April 2013 to March 2014, a convenience sample of 296 MLWH was recruited. We interviewed all the patients using the beck depression inventory (BDI- II) questionnaire. Participants with moderate to severe depression (n = 110, scores $\geq$ 21) were evaluated for endocrine diseases (evaluations: total testosterone, triiodothyronine, thyroxine, thyroid stimulating hormone, luteinizing hormone, follicle stimulating hormone, and serum cortisol). Eleven patients diagnosed with hypogonadism were, finally, considered for hormone replacement therapy. We re-evaluated the changes in the depressive symptoms with BDI- II. Out of 237 participants, 136 (75%) had BDI scores $\geq$ 21; 110 participated in the endocrine evaluations. Secondary hypogonadism was the only observed abnormality in 10% (n = 11) of the patients. Significant improvements were observed in BDI-II scores after 3 months of treatment (P = 0.027). The evaluation and the treatment of hypogonadism can help clinicians to properly address depression among people living with HIV; hence, improve the treatment compliance and the patient outcomes.

Keywords: Depression, Endocrine Diseases, HIV, Hypogonadism

1. Background

In the era of antiretroviral treatment (ART), HIV/AIDS has turned into a chronic illness (1), while patient outcomes largely depend on adherence to treatment. Neurocognitive disorders including depression are among the influential factors impeding adherence and the quality of life (1, 2). Hence, addressing mood disorders with appropriate medical and behavioral interventions can improve the adherence to treatment and ameliorate the negative outcomes of HIV infection (2).

Major depressive disorders have been reported among 10.2% of the Iranian men, while moderate to severe depressions have been documented among 68.8% of the people living with HIV (PLWH) (3, 4). Disease stage, co-morbid psychiatric disorders, deranged social/family functioning, and unfavorable immunologic response to ART are known attributes of the higher prevalence of depression in the PLWH. Moreover, the need for long-term therapy, the side effects of antidepressant agents, and drug reactions to antiretrovirals complicate the treatment of depression in the PLWH (5-7).

Among various disorders leading to or presenting with depression, endocrine diseases are among the modifiable causes (8). HIV infection may directly or indirectly involve thyroid, adrenal glands, gonads, or bones (9). A recent study indicates hypogonadism, thyroid disease, and adrenal dysfunction as common disorders among ART-naive patients (10). Gonadal dysfunction is frequently observed (25% to 68%) even among the patients whose viral replication is undetectable, while depression may be their only presenting symptom (4, 5, 10-12).

There is a paucity of data regarding endocrine diseases among ART-treated PLWH with depressive symptoms.

2. Objectives

The purpose of this study was to evaluate the prevalence of endocrine dysfunction among Iranian patients who are diagnosed with depression, and potentially assess the effects of hormone replacement on depressive symptoms among those diagnosed with endocrine diseases.

3. Methods

3.1. Study Design

To achieve the main objectives of the current research, we designed a two-phase study (cross-sectional evaluation): In Phase I, a convenience sample of MLWH (n = 296) was recruited and 237 were interviewed using the beck depression inventory (BDI-II); in Phase II, the patients with moderate to severe depressions (110 out of 136 participants) were evaluated regarding their endocrine function. All patients diagnosed with endocrine dysfunction were re-evaluated with regards to depressive symptoms after the standard medical treatment of underlying diseases in a single-arm experiment.

3.2. Setting and Participants

A sample size of 104 was calculated with precision of 0.9 and alpha level of 0.05 to evaluate the prevalence of endocrine diseases. To envisage loss to follow up, a convenience sample of 296 MLWH was recruited in 12 months (April 2013 - June 2014). Patients had been registered at a referral HIV clinic located in a 1000-bed academic hospital in the capital city of Tehran, affiliated with Tehran University of Medical Sciences (TUMS). The long duration of the study as well as the heterogeneity of the consulting patients led us to consider a convenience sample of MLWH being representative of the target population.

Eligible participants had to: 1) be male, 2) have BDI-II scores $\geq$ 21, and 3) consent to further participation in the study. Patients were excluded from the study if: 1) using immunosuppressive agents, 2) having fever/opportunistic infections, 3) using hormonal agents or antidepressants, 4) having a history of substance use, 5) having suicidal thoughts, and 6) having lost a close relative or divorced a month prior to the study.

3.3. Measurements

3.3.1. Beck Depression Inventory-Second Edition (BDI-II)

To screen the participants regarding depressive symptoms in Phase I, all the candidates were interviewed by a primary care physician to complete the BDI-II questionnaire. BDI-II consists of 21 items and is widely used for the assessment of depressive symptoms based on the fourth edition of diagnostic and statistical manual of mental disorders (13). Internal consistency (α = 0.92) and test-retest reliability (r = 0.93) are known to be satisfactory. A significant correlation between BDI-II and Hamilton depression rating scale (r = 0.71) indicates good convergent validity for the measure (16). The Persian version of the BDI-II has shown proper internal consistency (α = 0.91) and convergent validity (correlation coefficient of 0.87 between BDI-II and the depression sub-scale of the Brief Symptoms Inventory) (14). This questionnaire has been proved to be reliable and valid to assess depression among PLWH (15).

3.4. Laboratory Tests

Venous blood samples were collected after an overnight fast. For serum preparation, 5 mL of blood from a vein of the left arm in a fasting state was collected and incubated for 5 minutes at room temperature to let it clot, then, it was centrifuged at 3000 rpm for 10 minutes. Free thyroxine (FT4) and thyroid stimulating hormones (TSH) were determined on -70°C stored serum samples by electro-chemiluminescence immunoassay (ECLIA) method, using Roche diagnostics kits and Roche/Hitachi Cobas e- 411 analyzer (GmbH, Mannheim, Germany). Luteinizing hormone (LH) and FSH levels were assessed in the serum by the ECLIA (Cobas, England). Total Testosterone levels were determined by standard radioimmunoassay in accordance with manufacturer guidelines (Abbott Laboratories S.A.; Dubai, UAE).

3.5. The Definition of Endocrine Diseases

Primary hypogonadism: Low total testosterone with high gonadotropins.

Secondary hypogonadism: Low total testosterone and low gonadotropins.

Primary hypothyroidism: Low free triiodothyronine (T3) with normal or increased Thyroid Stimulating Hormone (TSH).

Secondary hypothyroidism: Low free T3 and free thyroxine (T4); normal or decreased TSH.

Adrenal insufficiency: 8:00 A.M. cortisol level lower than the lower limit of reference range.

Hypercortisolemia: 8:00 A.M. cortisol level higher than the upper limit of reference range.

3.6. Intervention

Test results were interpreted based on the reference ranges: T3 (80 - 200 ng/dL), T4 (4.5 - 12 μg/dL), TSH (0.3 - 4 mIU/L), LH (1.8 - 12 1.8 - 12 mIU/L), FSH (1.5 - 12.4 mIU/mL), Cortisol (5-25 μg/dL), and Total Testosterone (2.8 - 8.8 ng/mL). Table 1 shows the definition of various endocrine diseases considered based on the laboratory tests. Participants diagnosed with endocrine dysfunction (hypogonadism) and accepted to participate in the pilot study received three monthly intra-muscular injections of testosterone (250 mg) by a blinded nurse. Testosterone levels and BDI-II scores were re-evaluated to assess the effects of testosterone therapy.

Table 1. Descriptive Characteristics of the Depressed Patients Participated in Endocrine Testing (n = 110)

Variables	Mean ± SD	Normal range
Age (year)	39.65 ± 8.79	
Duration of therapy (year)	5.13 ± 3.81	
CD4 (n/mL)	281 ± 191	
T3 (ng/dL)	139.17 ± 27.11	80 - 200
T4 (μg/dL)	8.15 ± 1.32	4.5 - 12.5
TSH (mlU/L)	1.70 ± .94	0.3 - 4
LH (mlU/mL)	4.39 ± 1.80	1.8 - 12
FSH (mlU/mL)	4.69 ± 1.51	1.5 - 12.4
Cortisol (μg/dL)	18.62 ± 5.11	5 - 25
Testosterone	**Median**[a]	
Before treatment	2 ng/mL (0.6 -2.7)	2.8 - 8.8

Abbreviations: FSH, follicle stimulating hormone; LH, luteinizing hormone; SD, standard deviation; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone.
[a]Based on median IQR.

3.7. Study Outcomes

In Phase I, the objective was to screen MLWH for moderate to severe depressions. The main outcome of the experimental part of the study was to observe the changes in the mean BDI scores of the patients who had undergone treatment.

3.8. Ethical Considerations

The study protocol was approved by the ethics board of TUMS. All the participants were competent to take part in the interviews, none of them suffered from compromised mental capacity and all of them provided written consent forms that were developed according to the Helsinki Declaration. They were assured about their right to discontinue the study course upon their wish. The protocol of the study was also registered at the Iranian registry of clinical trials (registration number: IRCT2013071914054N1).

3.9. Data Analysis

The acquired data were analyzed using the statistical package for the social sciences (SPSS version 16.0). Mean and SD (standard deviation) were reported for continuous variables. To investigate the change in BDI-II scores and testosterone levels before and after the treatment, Wilcoxon rank test was performed. Due to the negative results of the Kolmogorov Smirnov test, a non-parametric test was utilized.

4. Results

Out of 237 MLWH (Mean age = 39.65; SD = 8.79) in Phase I, 136 had BDI-II scores $\geq$ 21; a total number of 26 patients declined further participation and 110 patients participated in Phase II (participation rate: 80%). The only endocrine abnormality was secondary hypogonadism with low testosterone levels ($\leq$ 2.8 nmol/L; normal: 2.8 to 8.8 nmol/L) (Table 1). Four participants declined further participation and the final sample that received hormonal therapy included 7 MLWH (Figure 1).

Median testosterone level significantly increased after hormonal replacement (2 vs. 4 ng/mL, interquartile range (IQR): 0.6 - 2.7 vs. 2 - 5) (P = 0.012); and the patients' median BDI-II scores significantly decreased from 40 (IQR: 27 - 50) to 19.5 (IQR: 7 - 40) 9 (P = 0.027).

5. Discussion

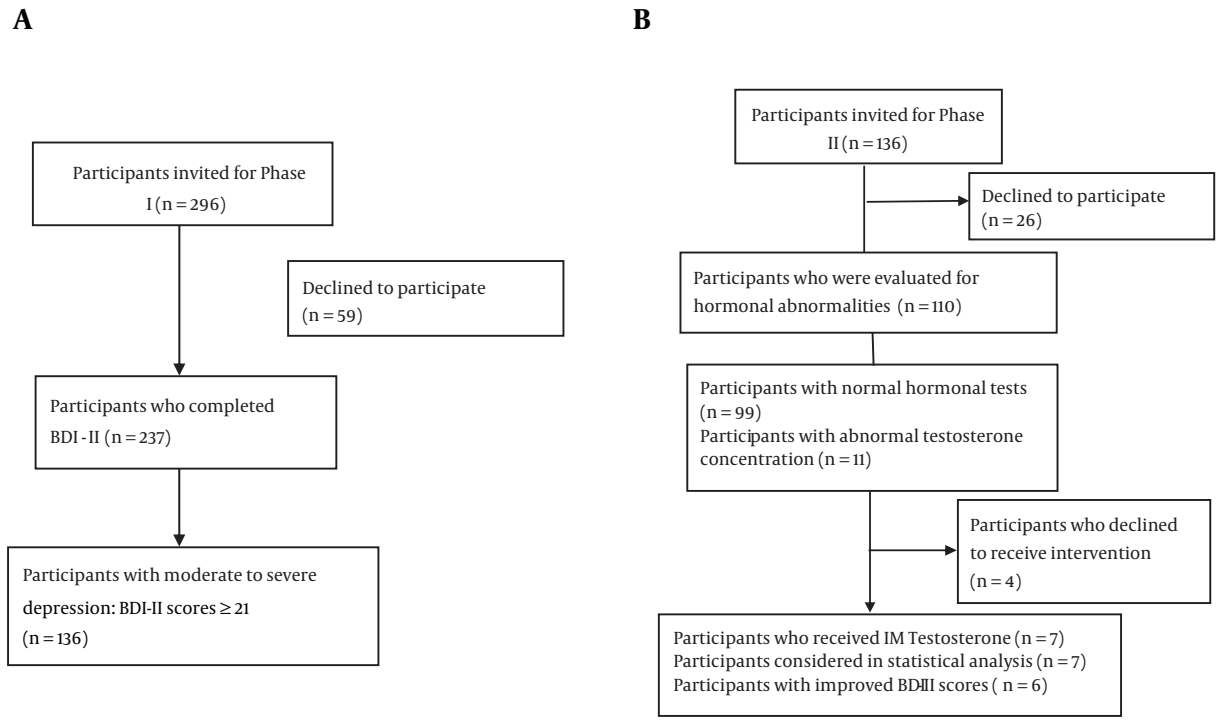
The findings of the present study suggest that hypogonadism is the most common endocrine disease among the MLWH and is, also, the most common depressive symptom. Despite the small number of patients in the experiment, treatment with hormone replacement did improve BDI-II scores. Hence, the assessment and the treatment of underlying endocrine dysfunction improve patient outcomes.

Endocrine diseases such as hypothyroidism, hypogonadism, and adrenal insufficiency have been reported among the PLWH; one of the most common being primary or secondary hypogonadism (10, 16, 17). After the introduction of antiretroviral agents, the prevalence of hypogonadism has decreased from 50% to 15% among the PLWH (10), suggesting that systemic inflammation, itself, contributes to endocrine morbidity (17).

The present study showed that 10% of the MLWH with moderate to severe depression have hypogonadism, similar to another study in 2007 which found that 17% of 300 MLWH had secondary hypogonadism (11). However, the findings contrast with an earlier study in Iran that reported a considerably higher rate (68%) (4). We suggest that the inconsistent use of antivirals and simultaneous treatment with methadone in that study contributed to higher rates.

Although we found no thyroid disease in our patients, a previous study found the rates of sick euthyroid syndrome and hypotestoteronemia to be relatively high (16 vs. 29%) in MLWH; they, also, demonstrated that the defects in the hypothalamic-pituitary axis correlate with the stage of the disease and CD4+ counts (18). Based on the difference, we suggest that hypogonadism among PLWH who receive ART, represents a subset of patients with depression. Thus,

Figure 1. Participants' Flow Diagram



A, Phase I; B, Phase II.

while social factors are to be considered, endocrine tests should be run after observing the classic signs of hypogonadism as a possible cause of depression.

Via a before-after experiment, we confirmed the positive effects of testosterone to ameliorate depression in hypogonadal patients. This confirms the results of previous studies which showed that therapeutic interventions to address the endocrine dysfunction also help to ameliorate depression (16, 17, 19). A meta-analysis also confirms the positive effect of testosterone on depressed patients and in subpopulations with hypogonadism and HIV (20).

Although the present study shows the improvement of depressive symptoms among a small sample of HIV patients with hypogonadism after testosterone treatment, the generalizability of the findings are limited because of the final sample size in the experiment. Hence, a large cohort of HIV patients to evaluate other potential endocrine abnormalities and treatment outcomes is recommended.

5.1. Conclusion

In summary, although endocrine diseases were not a major cause of depression in our patient population, a short course of hormonal treatment among the patients with hypogonadism produced a marked improvement in BDI scores. Thus screening the MLWH for endocrine diseases could improve the depressive symptoms and lead to positive consequences regarding the adherence to ART and the happening of long-term outcomes.

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Footnotes

Conflict of Interest: The authors declare no conflict of interest.

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