ORIGINAL RESEARCH
General Urology

Doi: 10.4274/jus.galenos.2023.2022.0094
J Urol Surg, 2023

A Pilot Study on Sex Hormones and Cognition Men with Multiple Sclerosis

Bilge Piri Çınar[1], Mustafa Açıkgöz[2], Önder Çınar[1], Ulufer Çelebi[1], Sibel Çekiç[1], Esra Acıman Demirel[1], H. Tuğrul Atasoy[1], Serkan Özakbaş[3]

[1]Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Neurology, Zonguldak, Turkiye
[2]Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Urology, Zonguldak, Turkiye
[3]Dokuz Eylül University Faculty of Medicine, Department of Neurology, İzmir, Turkiye

What's known on the subject? and What does the study add?

xxxxxxxxx

Abstract

Objective: The presence of sexual dysfunction in male patients further exacerbates the adverse impressions of Multiple sclerosis (MS) on the quality of life. The goal of our study was to evaluate the relationship between sex hormons and disease severity, sexual dysfunction, and cognition in male MS patients.

Materials and Methods: Twenty-eight MS patients and 14 age- and education-matched healthy controls were included in the study. To assess the cognitive status: California verbal learning test, symbol digit modalities test, revised brief visuospatial memory test, trail-making test, and to evaluate sexual function, male sexuel healt questinore (MSHQ) and international index of erectile function (IIEF) scales were used. Serum Anti-Mullerian hormone level, FSH, LH, and total testosterone levels were evaluated.

Results: Serum testosterone levels were significantly lower in the MS group than in the healthy group (4.28±1.20 and 4.50±2.24, respectively; p=0.012). Sexual functions were evaluated using the MSHQ and IIEF, and the MSHQ-ejaculation function scores were statistically significantly lower in the patient group than in the control group (p=0.014). Erectile function was assessed using the IIEF. Erectile dysfunction (ED) was detected in 11 (39%) patients, and four patients could not provide semen analysis specimens due to severe ED. BVMT and CVLT scores were statistically significantly lower in the ED group than in non-ED group (p=0.008, p=0.008, and p=0.026).

Conclusion: The importance of sexual functions and hormones during MS has been demonstrated by both laboratory and cognitive tests.

Keywords: Multiple sclerosis, testosterone, cognition

Introduction

Multiple sclerosis (MS) is a chronic autoimmune central nervous system disease that causes cognitive problems along with physical impairment and is often detected in young adults. As with many autoimmune diseases, it is more common in women, but tends to have a more severe course in men. MS harms the quality of life for several reasons. (1) The presence of sexual dysfunction, adding to physical problems in male patients in early adulthood, further exacerbates the adverse impact of MS on the quality of life. Sexual dysfunction can assume various forms in male patients, such as reduced libidoand erectile/ejaculatory dysfunction, and it is frequently correlated with decreased serum testosterone (2-4). Sexual dysfunction

Correspondence: Assoc. Prof. Bilge Piri Çınar, Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Neurology, Zonguldak, Turkiye
Phone: +90 xxxxxxxxxxxx **E-mail:** bilge.cinarpiri@gmail.com **ORCID-ID:** orcid.org/0000-0002-4884-0717
Received: 27.12.2022 **Accepted:** 05.03.2023

Cite this article as: Piri Çınar B, Açıkgöz M, Çınar Ö, Çelebi U, Çekiç S, Acıman Demirel E, Atasoy HT, Özakbaş S. A Pilot Study on Sex Hormones and Cognition Men with Multiple Sclerosis.

correlate with urinary problems in MS, and sexual functions correlate with both motor and emotional symptoms (5).

An association between low testosterone and high expanded disability status scale (EDSS) scores has previously been shown in MS (6). Studies have reported that testosterone possesses anti-inflammatory and neuroprotective properties, can protect against glutamate toxicity through neurons and is an antioxidant (6,7). Anti-Mullerian hormone (AMH) is a dimeric glycoprotein and is involved in growth and differentiation. AMH released from Sertoli cells from the intrauterine eighth gestational week causes the regression of Mullerian structures in males, while in females, it is released from birth from the granulosa cells in the small antral follicles to both the follicular fluid and the systemic circulation (8).

AMH levels in males are regulated by intratesticular testosterone (9). After puberty, it is released into the seminiferous tubule lumen and is restricted within the testis-blood barrier. Hence, it is detected at higher levels in the seminal plasma than in serum (10,11). Although the relationship between spermatogenesis, testosterone, and AMH remains partially understood, seminal AMH can be a potential non-invasive marker of permanent hypospermatogenesis (12). In women, AMH levels are closely related to follicular reserves (13). The purpose of this study was to examine the relationship between serum testosterone, serum AMH levels, spermiogram features, and severity of disease, sexual dysfunction, cognition, fatigue, and depression in patients with male MS patients.

Materials and Methods

Patient Enrollment

Male patients aged 18-65 diagnosed with progressive MS (PMS) or relapsing-remitting MS (RRMS) based on the McDonald 2017 MS diagnostic criteria and age-and education level-matched healthy individuals representing the control group were included in this study. The control group were healthy volunteers who applied to the neurology outpatient clinic with complaints such as headache or dizziness and had no chronic disease. The patient group without erectile dysfunction (ED) and the healthy control group were sexually active.

Patients lacking sufficient cognitive levels to provide information about their past histories, using drugs capable of affecting clinical evaluations (antipsychotic medicine use, corticosteroid use in the previous three months, and other neurological/autoimmune or urological diseases), were excluded from this study. Verbal informed consent forms were obtained from all patients and the healthy control group, and ethical approval for this study was granted by the university's ethical committee to which the clinic belonged.

Clinical Assessment

The main aim of our study was to define the tie between the clinical status of patients with MS patients and AMH levels. Therefore, a detailed cognitive evaluation was performed. BICAMS was used because it was validated in Turkish (14); it was easy to use, including the essential cognitive domains retained in MS. Three tests of BICAMS, the California verbal learning test II, the symbol digit modalities test (SDMT), and the revised brief visuospatial memory test, were administered by the same person trained in the administration of neuropsychological tests. Adding to BICAMS, trail-making testing was also implemented to further evaluate executive functions. The presence of depression was evaluated using the Beck depression inventory (BDI), whereas fatigue levels were assessed using the fatigue impact scale (FIS). To achieve standardization, whole cognitive tests were carried out in the same order, in a quiet room and in the morning.

The male sexual health questionnaire (MSHQ) and the international index of erectile function (IIEF) were used to assess sexual functions in the study group. Because serum AMH levels, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), and total testosterone levels exhibit a diurnal rhythm, they were measured before 10:00 am to ensure standard and accurate measurement. Routinely investigated serum glucose, complete blood count, and TSH levels were also included in the analysis. Study group semen analysis, sperm quality, and numbers were also investigated. Semen analysis data were assessed in compliance with the World Health Organization criteria of a semen volume of 1.5 mL, sperm concentration 15 million/mL, total sperm count 39 million/ejaculate, total motility 40%, normal morphology 4%, and vitality 58%. Serum FSH levels of 1.5-12.4 mIU/mL, LH levels of 1.7-8.6 mIU/mL, PRL levels of 4.6-21.4 ng/mL, and testosterone levels of 2.5-8.4 ng/mL were evaluated as reference ranges. Patients' erectile functions were assessed using the validated, six-question Turkish-language version of the IIEF (15). Each question was scored from 1 (never or seldom) to 5 (always or almost always), and the total scores were recorded. The severity of ED was assessed as severe (total score=0-6), moderate (total score=7-12), mild-moderate (total score=13-18), mild (total score=19-25), or no ED (total score =26-30). The ejaculation function was classified using the Turkish-language version of the short form of the MSHQ, comprising four questions scored between 0 and 5. The first three questions assessed ejaculatory function, frequency, and force (MSHQ-123) (0-15), while the fourth evaluated ejaculation bother (MSHQ-EjD) (0-5) (16). A higher total score for the first three questions was relevant with better ejaculatory function, whereas higher scores on the fourth question were associated with poor ejaculation bother.

Statisticsal Analysis

The study data were analyzed using the SPSS 22.0 software. The normality of the distribution of continuous variables was assessed both visually and using normal distribution tests. The independent sample t-test was applied to two-group comparisons of normally distributed variables, and the Mann-Whitney U test was applied to two-group comparisons of non-normally distributed variables. Categorical variables were compared using the chi-square tests. This was evaluated using Spearman's correlation analysis since the relationship between continuous variables was not normally distributed. P-values of less than 0.05 were considered statistically significant for all analyses.

Results

Twenty-eight male patients with RRMS-PMS diagnosed with MS based on the McDonald criteria, aged 40.89±10.93 years, and 14 men with no additional disease, aged 36.27±4.86, representing the control group, were included in the study. No difference was determined between the two groups concerning age or education levels (p=0.085 and p=0.262, respectively). The mean age at MS onset was 33.39±1.55 (18-49), and the mean EDSS score was 2.35±1.55 (0-5.5).

The patient and control groups' serum glucose, TSH, FSH, LH total testosterone, and PRL levels were investigated. Serum testosterone levels were statistically significantly lower in the MS group than in the control group (4.28±1.20 and 4.50±2.24, respectively; p=0.012) (Table 1). Testosterone levels were at the lower limit of the normal value in 3 patients in the study group and 1 participant in the control group. The presence of depression in the study group was investigated using the BDI, and no significant difference was observed between the two groups (p=0.152). Fatigue levels were assessed by the FIS, with both subscores and total fatigue levels being compared. The total FIS scores and the physical and social subscores were statistically higher in the MS patient group than in the control group (p=0.037, p=0.008, and p=0.014) (Table 2).

Sexual functions were analyzed using the MSHQ and IIEF, and the MSHQ-ejaculation function scores were statistically significantly lower in the patient group than in the control group (p=0.014) (Table 2). Erectile function was assessed using the IIEF. ED was detected in 11 (39%) patients, and four patients could not provide semen analysis specimens due to severe ED (Figure 1). Sperm counts were 30±9.4 million in the MS group and 24±6.5 million in the healthy control group; the difference was not statistically significant (p=0.452). Sperm motility was 42.50±18.67 in the MS group and 45.87±15.52 in the control group. The difference was insignificant (p=0.362).

The patients with and without ED in the MS group were compared regarding clinical characteristics, cognitive involvement, and other features. Mean EDSS scores were 2.7±2.03 in the ED group and 1.62±0.80 in the non-ED group (p=0.001). BVMT and CVLT scores were significantly lower in the ED group than in the

Table 1. Sex hormone levels, glucose, and TSH levels of the study group

	MS group	Healthy group	p-value
FSH level Mean ± SD median, range (min-max)	5.43±3.23	5.52±4.67	0.426
LH level Mean ± SD median, range (min-max)	5.01±2.21	5.65±3.14	0.068
Prolactin level Mean ± SD median, range (min-max)	7.77±3.88	10.85±3.87	0.841
Total testosterone level Mean ± SD median, range (min-max)	4.28±1.20	4.50±2.24	**0.012**
Plasma AMH level Mean ± SD median, range (min-max)	8.86±5.29	10.02±2.74	0.215
Serum glucose level Mean ± SD median, range (min-max)	95.32±8.60	92.22±5.06	0.319
Serum TSH level Mean ± SD median, range (min-max)	1.80±1.26	1.96±0.60	0.264

SD: Standard deviation, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, AMH: Anti-Mullerian hormone

Table 2. MSHQ, IIEFQ, and fatigue impact scale scores of the study group

	MS group	Healthy group	p-value
FIS-total score Mean ± SD	34.7±23.33	17.67±6.57	**0.037**
FIS-cognitive subscale Mean ± SD	7.30±6.24	5.78±4.57	0.112
FIS-psychosocial subscale Mean ± SD	18.00±13.53	8.67±5.54	**0.018**
FIS-physical subscale Mean ± SD	9.57±7.63	3.22±2.38	**0.008**
MSHQ-ejaculation function score Mean ± SD	5.71±2.68	9.28±4.82	**0.014**
MSHQ-ejaculation bother score Mean ± SD	2.33±1.55	2.57±1.98	0.275
IIEFQ score mean ± SD	24.65±5.07	27.54±4.50	0.185

SD: Standard deviation, FIS: Fatigue impact scale, MSHQ: Male sexuel healt questinore, IIEF: International index of erectile function

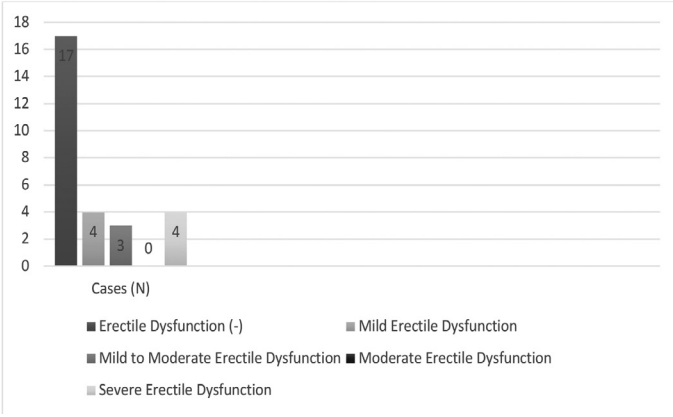

Figure 1. Erectile dysfunction status of the study group according to the IIEFQ

IIEF: International index of erectile function

Table 3. Cognitive- fatigue-depression scores and sex hormones of all study groups

	ED (+)	ED (-)	p-value
Age (years) Mean ± SD	45.60±12.88	39.00±10.07	0.191
Age of onset (years) Mean ± SD	36.00±8.71	31.75±8.85	0.27
Disease duration (years) Mean ± SD	9.6±8.00	7.5±4.31	0.082
EDSS score Mean ± SD	2.7±2.03	1.62±0.80	0.001
CVLT score Mean ± SD	41.60±14.04	52.50±13.75	0.008
BVMT-R score Mean ± SD	14±9.75	24.50±6.85	0.008
SDMT score Mean ± SD	28.55±13.83	37.83±14.40	0.15
Trail making test-A score Mean ± SD	66.01±41.80	45.26±35.55	0.234
Trail-making test-B score Mean ± SD	173.95±94.83	96.84±50.72	0.026
FIS-cognitive subscale Mean ± SD	4.43±3.82	9.64±7.47	0.101
FIS-physical subscale Mean ± SD	7.43±7.45	9.18±6.88	0.615
FIS-psychosocial subscale Mean ± SD	14.86±13.59	18.64±14.29	0.582
Depression score Mean ± SD	12.78±8.55	11.73±8.11	0.783
Total testosterone level Mean ± SD	4.77±0.91	3.75±1.46	0.07
Plasma AMH level Mean ± SD	10.32±6.08	8.35±5.12	0.59

SD: Standard deviation, AMH: Anti-Mullerian hormone, FIS: Fatigue impact scale, SDMT: Symbol digit modalities test, BVMT-R: Revised brief visuospatial memory test, EDSS: Expanded disability status scale

non-ED group, while trail-making test times were significantly longer (p=0.008, p=0.008, and p=0.026) (Table 3).

The healthy control group exhibited a negative correlation between FSH and testosterone (r=-0.783) and a positive correlation between FSH and AMH (r=0.400). A negative correlation was observed between AMH and testosterone (r=-0.500, p=0.004). Serum testosterone levels were well negatively correlated with SDMT scores and were well positively correlated with trail-making test times (A-B) [r=-0.582 (p=0.025), r=0.567 (p=0.017), and r=0.683 (p=0.036)]. The patient group exhibited a negative correlation between age and BVMT and SDMT [r=-0.461 (p=0.015), and r=-0.436 (p=0.026)]. A moderate negative correlation was also observed between serum total testosterone levels and SDMT scores (r=-0.498; p=0.034). Evaluation of erectile function in the MS group revealed a negative correlation between the IIEF and EDSS (r=-0.415, p=0.048), a positive correlation with the CVLT, one of the cognitive tests (r=0.503, p=0.011), and a negative correlation with trail-making test time (B form) (r=-0.521, p=0.015).

Discussion

FSH and LH released from the pituitary gland are gonadotropic hormones LH stimulates the production of testosterone by stimulating Leydig cells in the testicular tissue, while the target of FSH is Sertoli cells involved in spermatogenesis. Also, FSH functions with testosterone in regulating Sertoli cell functions. Although decreased Sertoli cells, sperm counts, and testis volumes are detected in some individuals, normal sexual development and fertilization can still occur. However, full germ cell maturation independently of testosterone is impossible. FSH, LH, and testosterone levels are parameters for determining the roles in both fertility and erectile functions (17). Both FSH and LH levels increase in primary testicular insufficiency in infertile men with testicular insufficiency. However, it should be remembered that FSH and LH levels are variable in infertile men (18,19).

While sex hormones are generally known for their roles in sexual development and maturation during adolescence, sex steroids can act as trophic factors affecting brain development and neuron plasticity, and because of this effect, they can stimulate neurite outgrowth, synapse numbers, and myelination with their direct effects on glial cells (20-22). Regarding its capability of crossing the blood-brain barrier and directly affecting neuronal cells, the neuroprotective impacts of testosterone have been described in many studies (21,22). The detection of lower testosterone levels at the onset of disease in male patients with autoimmune disease has hypothesized that low testosterone levels may be a risk factor for autoimmune diseases (23). Low testosterone values have previously been notified in men with

MS (24,25). However, the fact that no comparison was made with healthy controls should be remembered as a limitation of this study and evaluated accordingly.

The prodromal stage of MS has recently attracted significant attention. This is when many subjective complaints, such as depression, anxiety, decreased academic performance, and dermatological symptoms, appear before the clinical onset of MS. One study reported that low testosterone may also be a prodromal marker (26). However, further studies involving more significant patient numbers and different clinical characteristics are needed on this subject. Mobile male MS patients not receiving pulse steroids for at least three months, not in the attack period, and without very high EDSS scores were evaluated in this study. The erectile functions of the patient group and the profiles of hormones capable of affecting these were compared with those of healthy controls. Serum glucose, TSH, FSH, LH, total testosterone, and PRL levels were normal in the patient and healthy control groups. A previous study determined central hypogonadism at a rate of 40% at all ages in patients with MS and reported that low testosterone values were related to increased EDSS values (6). However, no hypogonadism was detected in the MS group in this study, but serum testosterone levels were statistically significantly lower in the patient group compared with healthy controls. No significant correlation was observed between EDSS and serum total testosterone levels in this study. The absence of any association between EDSS and testosterone may be related to the low number of patients, the group having relatively low EDSS values, or other potential factors affecting testosterone levels. In addition, no abnormality was detected in FSH, LH, TSH, or PRL levels in the MS group, and there was no statistically significant difference between the groups. As expected, a statistically significant negative correlation showing negative feedback was observed between FSH and testosterone, indicating a normally functioning hypothalamic-pituitary-gonadal axis in the healthy group. However, there was no similar correlation in the MS group. Evaluated together with the relatively lower testosterone levels determined compared with the healthy group, this suggests that the hypothalamic-pituitary-gonadal axis may be affected at any level in the MS group. However, the data from this study were insufficient to pinpoint the effect.

AMH can inhibit aromatase in Sertoli cells and act locally in Leydig cells to control steroidogenesis (19,20). In mice with *AMH* gene overexpression, decreased Leydig cell functions have also been shown (21-23). Leydig cells regulate testosterone production in testicular cells. Since testosterone production decreases as the capacity of Leydig cells decreases with aging, serum testosterone levels decline (27). There was a positive correlation between FSH and AMH and a negative correlation between AMH and testosterone in the MS group in this study. Accordingly, we concluded that either testosterone decreased following inhibition in the Leydig cells line with increasing AMH or that a negative correlation at any level exists between AMH and testosterone. One study examining the effect of inhibin B and AMH on sperm determined high serum FSH and low inhibin B and AMH levels in subfertile males (28). The authors of that study also reported that this hormone may represent a valuable marker of spermatogenesis due to the broad overlap between the control and subfertile males. The decrease in AMH production indicates increased intratesticular androgen concentration, and low AMH levels have been reported in azoospermia. The previously shown negative relationship between testosterone and AMH was also been demonstrated in our study (9). There are few published data regarding the possible role of AMH in male fertilization and sexual function. Additionally, investigating the relationship between AMH, FSH, and testosterone in both healthy and sexually dysfunctional individuals may help clarify the issue. Also, AMH levels in the seminal fluid can yield more effective results. However, both collection and measurement entail technical problems (29).

The increased frequency of ED in neurodegenerative diseases of the central nervous system can be explained by both lesion localization and the global effect on the central nervous system. Past studies have demonstrated the presence of ED in patients with MS (30-32). ED was also detected at a rate of approximately 40% in the MS group in this study. When we evaluated sexual functions in the patient and healthy groups using the MSHQ, the ejaculatory function was statistically significantly poorer in the patient group by comparison with the healthy. Consistent with this study, a previous study also observed dysejaculation in patients with MS patients, although no comparison with healthy controls was performed (33). In this study, a negative correlation was shown between IIEF and EDSS. Because low IIEF scores indicate poor erectile function, we evaluated low IIEF scores in patients with high EDSS as compatible with the usual course of the disease. When individuals with and without ED in the patient group were compared, EDSS scores were statistically significantly higher in the ED group. Another study comparing the erectile functions of MS patients with those of healthy controls obtained similar findings to ours, with IIEF scores being significantly lower in patients with high EDSS scores (34).

There has been minimal investigation of the hypothalamus-pituitary-testis axis and sperm parameter activity in patients with MS (24). In-depth evaluation of inflammation is important since it can impact fertility by affecting hormone production. Whether or not sperm counts and characteristics in MS patients were affected by high-dose cortisone use over many years, drugs with immunosuppressive characteristics or drugs secondary to autoimmunity were assessed using semen analysis. There was no difference between the MS group and healthy controls in terms

of sperm count and motility. Also, no significant difference was observed in the healthy control group regarding sperm parameters. The few studies on this subject have investigated the impact of disease-modifying therapies on sperm parameters and have reported no change in sperm parameters or the association between clinical and radiological variables (35,36). In conclusion, this study has shown that although erectile dysfunction and low testosterone levels are determined in patients with MS patients, fertility is not impaired.

The impairment of cognitive function is seen in approximately half of the people with MS, and numerous factors impact cognition, such as age, sex, and disease severity (37,38). Following a previous study, a negative correlation was shown between age and information processing speed and visuospatial memory scores in this study (39,40). Studies showing a relationship between cognitive tests and testosterone have found that high testosterone levels are correlated with better cognitive functions (6). Also, studies are reporting an improvement in cognition with testosterone therapies, or testosterone does not affect cognition (41-44). This study determined a negative correlation between information processing speed and testosterone in the healthy control group. Concurrently, a positive correlation was determined between executive function and testosterone levels. There was also a negative correlation between testosterone and information processing speed in the MS group. That is to say, a negative correlation, although weak, was observed between testosterone and cognition in both the healthy and MS groups. This observation of a negative connection between testosterone and cognition in both groups, unlike a previous study, may be associated with the low number of patients or suggests that the relationship between these two parameters is more complex than currently thought. Additionally, in a previous study, it was reported that testosterone may damage cognitive function (45). Some observational studies have suggested that testosterone is related to better verbal memory or higher mini-mental state examination scores (46,47).

Study Limitations

The low number of patients may be considered as the principal limitation of this study. However, sex hormones in male MS patients have been investigated in several previous studies, and we think that this study's results, which evaluated sexual function disorder, cognitive functions, and sperm characteristics, may contribute to illuminating the function of sex hormones in MS.

Conclusion

The effect of androgens on cognition remains unclear. Erectile function disturbance in the MS group was associated with low verbal memory scores and low executive functions. Cognitive scores (verbal memory, executive functions, and visuospatial memory) were statistically significantly weaker in the group with ED than in the non-ED group. Higher EDSS scores and cognitive impairment in patients with MS patients with ED were regarded as consistent with both cognitive impairment and erectile function disorder, indicating a poor prognosis for MS.

Ethics

Ethics Committee Approval: Ethical approval for this study was granted by the university's ethical committee to which the clinic belonged.

Informed Consent: Verbal informed consent forms were obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.P.Ç., M.A., Ö.Ç., S.Ö., Design: B.P.Ç., Ö.Ç., S.Ö., Data Collection or Processing: B.P.Ç., M.A., Ö.Ç., U.Ç., S.Ç., E.A.D., H.T.A., Analysis or Interpretation: M.A., Ö.Ç., U.Ç., E.A.D., H.T.A., Literature Search: B.P.Ç., M.A., Ö.Ç., U.Ç., S.Ç., E.A.D., H.T.A., Writing: B.P.Ç., Ö.Ç., U.Ç., S.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This study was funded by the Multiple Sclerosis Research Society.

References

1. Berrigan L.I., Fisk J.D., Patten S.B., Tremlett H., Wolfson C., Warren S., Fiest K.M., McKay K.A., Marrie R.A., CIHR Team in the Epidemiology and Impact of Comorbidity on Multiple Sclerosis (ECoMS) Health-related quality of life in multiple sclerosis: Direct and indirect effects of comorbidity. Neurology. 2016;86:1417–1424. doi: 10.1212/WNL.0000000000002564. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
2. Luo H, Jiang R. [Multiple sclerosis and erectile dysfunction]. Zhonghua Nan Ke Xue. 2009 Jan;15(1):56-9. Chinese. PMID: 19288752.
3. Nabavi SM, Dastoorpoor M, Majdinasab N, Khodadadi N, Khanjani N, Sekhavatpour Z, Zamanian M, Kazemian S, Eftekhari AE, Ashtari F, Abolfazli R, Jalili M, Ghaedi G, Ghalianchi HR. Prevalence of Sexual Dysfunction and Related Risk Factors in Men with Multiple Sclerosis in Iran: A Multicenter Study. Neurol Ther. 2021 May 18. doi: 10.1007/s40120-021-00257-0. Epub ahead of print. PMID: 34008168.
4. Abdulla FA, Albagmi FM, Al-Khamis FA. Factors that influence quality of life in patients with multiple sclerosis in Saudi Arabia. Disabil Rehabil. 2021 May 9:1-9. doi: 10.1080/09638288.2021.1919929. Epub ahead of print. PMID: 33966564.
5. Pakpoor J, Goldacre R, Schmierer K, Giovannoni G, Goldacre MJ. Testicular hypofunction and multiple sclerosis risk: a record-linkage study. Ann Neurol. 2014 Oct;76(4):625-8. doi: 10.1002/ana.24250. Epub 2014 Aug 30. PMID: 25131454.
6. Bove R, Musallam A, Healy BC, Raghavan K, Glanz BI, Bakshi R, Weiner H, De Jager PL, Miller KK, Chitnis T. Low testosterone is associated with disability in men with multiple sclerosis. Mult Scler. 2014 Oct;20(12):1584-92. doi:

10.1177/1352458514527864. Epub 2014 Apr 7. PMID: 24710799; PMCID: PMC4188801.

7. Gold SM, Voskuhl RR. Estrogen and testosterone therapies in multiple sclerosis. Progress in brain research. 2009; 175:239–51

8. Crisosto N, Codner E, Maliqueo M, et al. Anti-Mullerian hormone levels in peripubertal daughters of women with polycystic ovary syndrome. J Clin Endocrinol Metab 2007; 92:2739–2743.

9. Xu HY, Zhang HX, Xiao Z, Qiao J, Li R. Regulation of anti-Müllerian hormone (AMH) in males and the associations of serum AMH with the disorders of male fertility. Asian J Androl. 2019 Mar-Apr;21(2):109-114. doi: 10.4103/aja.aja_83_18. PMID: 30381580; PMCID: PMC6413543.

10. Barranco I, Fernandez-Fuertes B, Padilla L, Delgado-Bermúdez A, Tvarijonaviciute A, Yeste M. Seminal Plasma Anti-Müllerian Hormone: A Potential AI-Boar Fertility Biomarker? Biology (Basel). 2020 Apr 10;9(4):78. doi: 10.3390/biology9040078. PMID: 32290279; PMCID: PMC7236007.

11. Fénichel P, Rey R, Poggioli S, Donzeau M, Chevallier D, Pointis G. Anti-Müllerian hormone as a seminal marker for spermatogenesis in non-obstructive azoospermia. Hum Reprod. 1999 Aug;14(8):2020-4. doi: 10.1093/humrep/14.8.2020. PMID: 10438420.

12. La Marca A., Sighinolfi G., Radi D., Argento C., Baraldi E., Artenisio A.C., Stabile G., Volpe A. Anti-Mullerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART) Hum. Reprod. Update. 2010;16:113–130. doi: 10.1093/humupd/dmp036.

13. Tal R, Tal O, Seifer BJ, Seifer DB. Antimullerian hormone as predictor of implantation and clinical pregnancy after assisted conception: a systematic review and meta-analysis. Fertil Steril. 2015;103:119–130. doi: 10.1016/j.fertnstert.2014.09.041.

14. Ozakbas S, Yigit P, Cinar BP, Limoncu H, Kahraman T, Kösehasanoğulları G. The Turkish validation of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery. BMC Neurol. 2017 Dec 6;17(1):208. doi: 10.1186/s12883-017-0993-0. PMID: 29207954; PMCID: PMC5717821.

15. Turunç T, Deveci S, Güvel S, Peşkircioğlu L. The assessment of Turkish validation with 5 question version of international index of erectile function (IIEF-5). Turk J Urol 2007;33:45-9.

16. Kendirci M, Asci R, Yaman O, Cayan S, Orhan I, Usta MF, Ekmekcioglu O, Kadioglu A. Prevalence of male pelvic dysfunction: results from the Turkish society of andrology male sexual health study group. Andrology. 2014 Mar;2(2):219-24. doi: 10.1111/j.2047-2927.2013.00176.x. Epub 2013 Dec 19. PMID: 24357639.

17. Babu SR, Sadhnani MD, Swarna M, Padmavathi P, Reddy PP. Evaluation of FSH, LH and testosterone levels in different subgroups of infertile males. Indian J Clin Biochem. 2004 Jan;19(1):45-9. doi: 10.1007/BF02872388. PMID: 23105425; PMCID: PMC3453920.

18. Bergmann, M., Behre, H. and Nieschlag, E. (1994) Serum FSH and testicular morphology in male infertility. Clin. Endocrinol. 40, 133-136.

19. de Kretser, D.M. (1974) Clin. Obstet. Gynaecol. 1, 409-427.

20. van Honk J, Pruessner JC. Psychoneuroendocrine Imaging: a special issue of psychoneuroendocrinology. Psychoneuroendocrinology. 2010; 35:1–4. [PubMed: 19945797

21. Cerghet M, Skoff RP, Bessert D, Zhang Z, Mullins C, Ghandour MS. Proliferation and death of oligodendrocytes and myelin proteins are differentially regulated in male and female rodents. J Neurosci. 2006; 26:1439–1447. [PubMed: 16452667.

22. Romeo RD, Waters EM, McEwen BS. Steroid-induced hippocampal synaptic plasticity: sex differences and similarities. Neuron Glia Biol. 2004; 1:219–229. [PubMed: 18634599

23. Bove RM. Autoimmune diseases and reproductive aging. Clinical Immunology. 2013

24. Safarinejad MR. Evaluation of endocrine profile, hypothalamic-pituitary-testis axis and semen quality in multiple sclerosis. Journal of neuroendocrinology. 2008; 20:1368–75. PubMed: 19094084.

25. Wei T, Lightman SL. The neuroendocrine axis in patients with multiple sclerosis. Brain. 1997; 120(Pt 6):1067–76.

26. Marrie RA, Yu N, Wei Y, Elliott L, Blanchard J. High rates of physician services utilization at least five years before multiple sclerosis diagnosis. Mult Scler. 2012.

27. Chen H, Hardy MP, Zirkin BR. Age-related decreases in Leydig cell testosterone production are not restored by exposure to LH in vitro. Endocrinology. 2002 May;143(5):1637-42. doi: 10.1210/endo.143.5.8802. PMID: 11956144.

28. Muttukrishna S, Yussoff H, Naidu M, Barua J, Arambage K, Suharjono H, et al. Serum anti-Müllerian hormone and inhibin B in disorders of spermatogenesis. Fertil Steril. 2007;88:516–8. doi: 10.1016/j.fertnstert.2006.11.110.

29. Dimitrios G Goulis 1, Christos Tsametis, Paschalia K Iliadou, Paris Polychronou, Persefoni-Dimitra Kantartzi, Basil C Tarlatzis, Ioannis N Bontis, Ioannis Papadimas. Serum inhibin B and anti-Müllerian hormone are not superior to follicle-stimulating hormone as predictors of the presence of sperm in testicular fine-needle aspiration in men with azoospermia.

30. Ludwig W, Phillips M. Organic causes of erectile dysfunction in men under 40. Urol Int. 2014;92(1):1-6. doi: 10.1159/000354931. Epub 2013 Nov 21. PMID: 24281298.

31. Lew-Starowicz M, Gianotten WL. Sexual dysfunction in patients with multiple sclerosis. Handb Clin Neurol. 2015;130:357-70. doi: 10.1016/B978-0-444-63247-0.00020-1. PMID: 26003254.

32. Li V, Haslam C, Pakzad M, Brownlee WJ, Panicker JN. A practical approach to assessing and managing sexual dysfunction in multiple sclerosis. Pract Neurol. 2020 Apr;20(2):122-131. doi: 10.1136/practneurol-2019-002321. Epub 2019 Nov 21. PMID: 31753860.

33. Blum C, Chesnel C, Hentzen C, Turmel N, Lacroix P, Manceau P, Amarenco G. Troubles de l'éjaculation et sclérose en plaques : étude prospective de 44 patients [Ejaculation disorders in multiple sclerosis: Prospective study of 44 patients]. Prog Urol. 2019 Jul;29(7):385-390. French. doi: 10.1016/j.purol.2019.02.001. Epub 2019 Feb 25. PMID: 30819632.

34. Odabaş FÖ, Gümüş H, Akkurt HE, Uca AU, Yilmaz H. The Assessment of Sexual Dysfunction in Male Patients with Multiple Sclerosis. Noro Psikiyatr Ars. 2018 Dec;55(4):349-353. doi: 10.5152/npa.2017.19335. Epub 2018 Jul 5. PMID: 30622392; PMCID: PMC6300844.

35. D'Amico E, Zanghì A, Burgio G, Chisari CG, Condorelli RA, La Vignera S, Calogero AE, Patti F. Gonadal Steroids and Sperm Quality in a Cohort of Relapsing Remitting Multiple Sclerosis: A Case-Control Study. Front Neurol. 2020 Aug 4;11:756. doi: 10.3389/fneur.2020.00756. PMID: 32849215; PMCID: PMC7417674.

36. D'Amico E, Zanghì A, Burgio G, Chisari CG, Condorelli RA, La Vignera S, Calogero AE, Patti F. Gonadal Steroids and Sperm Quality in a Cohort of Relapsing Remitting Multiple Sclerosis: A Case-Control Study. Front Neurol. 2020 Aug 4;11:756. doi: 10.3389/fneur.2020.00756. PMID: 32849215; PMCID: PMC7417674.

37. Sandi D, Rudisch T, Füvesi J, Fricska-Nagy Z, et al. The Hungarian validation of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery and the correlation of cognitive impairment with fatigue and quality of life. Multiple sclerosis and related disorders 2015;4(6): 499-504.

38. Giedraitienė N, Kizlaitienė R, Kaubrys G. The BICAMS battery for assessment of lithuanian-speaking multiple sclerosis patients: Relationship with age, education, disease disability, and duration. Medical science monitor: international medical journal of experimental and clinical research 2015;21: 3853.

39. Kouvatsou Z, Masoura E, Kiosseoglou G, Kimiskidis VK. Evaluating the relationship between working memory and information processing speed in multiple sclerosis. Appl Neuropsychol Adult. 2020 Aug 19:1-8. doi: 10.1080/23279095.2020.1804911. Epub ahead of print. PMID: 32813544.

40. Baird JF, Cederberg KLJ, Sikes EM, Jeng B, Sasaki JE, Sandroff BM, Motl RW. Changes in Cognitive Performance With Age in Adults With Multiple Sclerosis. Cogn Behav Neurol. 2019 Sep;32(3):201-207. doi: 10.1097/WNN.0000000000000200. PMID: 31517704; PMCID: PMC6750025.

41. Yalamanchi S, Dobs A. Debate position: cognition and mood are not improved in men administered exogenous testosterone therapy. Curr Opin Urol. 2017 Nov;27(6):525-531. doi: 10.1097/MOU.0000000000000435. PMID: 28863017.

42. Cinar O, Turunc T, Kazaz IO, Yildirim O, Deliktas H, Cihan A, Gudeloglu A, Ure I, Deveci S, Sahin B, Cinar BP, Ozkara H. Effects of androgen deprivation therapy on cognitive functions in patients with metastatic prostate cancer: A multicentric, prospective study of the Society of Urological Surgery Andrology group. Int J Clin Pract. 2021 Jun;75(6):e14095. doi: 10.1111/ijcp.14095. Epub 2021 Feb 28. PMID: 33619782.

43. Resnick SM, Matsumoto AM, Stephens-Shields AJ, Ellenberg SS, Gill TM, Shumaker SA, Pleasants DD, Barrett-Connor E, Bhasin S, Cauley JA, Cella D, Crandall JP, Cunningham GR, Ensrud KE, Farrar JT, Lewis CE, Molitch ME, Pahor M, Swerdloff RS, Cifelli D, Anton S, Basaria S, Diem SJ, Wang C, Hou X, Snyder PJ. Testosterone Treatment and Cognitive Function in Older Men With Low Testosterone and Age-Associated Memory Impairment. JAMA. 2017 Feb 21;317(7):717-727. doi: 10.1001/jama.2016.21044. PMID: 28241356; PMCID: PMC5433758.

44. Muller, M., Aleman, A., Grobbee, D. E., de Haan, E. H. & van der Schouw, Y. T. Endogenous sex hormone levels and cognitive function in aging men: is there an optimal level? Neurology 64, 866–871 (2005).

45. Martin, D. M., Wittert, G., Burns, N. R., Haren, M. T. & Sugarman, R. Testosterone and cognitive function in ageing men: data from the Florey Adelaide Male Ageing Study (FAMAS). Maturitas 57, 182–194 (2007).

46. Hogervorst E, Matthews FE, Brayne C. Are optimal levels of testosterone associated with better cognitive function in healthy older women and men? Biochim Biophys Acta. 2010 Oct;1800(10):1145-52. doi: 10.1016/j.bbagen.2009.12.009. Epub 2010 Jan 7. PMID: 20060437.

47. Wolf, O. T. & Kirschbaum, C. Endogenous estradiol and testosterone levels are associated with cognitive performance in older women and men. Horm. Behav. 41, 259–266 (2002).