Does Late-Onset Hypogonadism Occur by Aging? The Evaluation of IIEF, Ams-Q and Biochemical Parameters

Yaşlanmayla Geç Başlayan Hipogonadizm Oluşuyor mu? IIEF, Ams-Q ve Biyokimyasal Değerlendirilmesi

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ABSTRACT Objective: The aim of this study is to investigate whether biochemical (hormonal) hypogonadism occurs by aging and whether AMS-Q (Aging Male Symptoms-Questionnaire) and IIEF (International Index of Erectile Function) forms are adequate in order to evaluate its presence in case it occurs. **Material and Methods:** A total of 182 males who applied to the outpatient clinics of Urology Department and whose ages were between 45-90 years were included in the study. Those who had diabetes mellitus, hypertension, coronary artery disease, dyslipidemia, any psychiatric disorder and any malignancy were excluded. The patients were classified into three groups (Group 1; 45-54, Group 2; 55-64 and Group 3; over 65 years). All participants were asked to complete IIEF and AMS-Q forms and serum levels of total testosterone, free testosterone, LH, DHEA-S, SHBG and prolactin were measured. **Results:** Total testosterone and prolactin levels did not change with aging. Although free testosterone, bio-available testosterone and DHEA-S levels decreased with age, it was detected that LH and SHBG levels were increased. While IIEF scores decreased with age, however AMS-Q scores did not change. When subgroups of AMS-Q were taken into consideration, sexual scores increased, and a decrease in somatic and psychological scores was detected. There was a strong relationship between IIEF-EF (erectile function) and AMS-Sexual forms. **Conclusion:** All of the data indicate that secondary hypogonadism occurs by aging and consequent symptoms (especially sexual ones) can be evaluated with IIEF and AMS-Sexual forms.

Key Words: Aging; hypogonadism; testosterone

ÖZET Amaç: Bu çalışmanın amacı, yaşlanmayla birlikte biyokimyasal (hormonal) hipogonadizm gelişip gelişmediğini ve gelişiyorsa bunun değerlendirilmesinde AMS-SF (Yaşlanan erkek semptom sorgulama formu) ve IIEF (Uluslararası erektil fonksiyon indeksi) formlarının yeterli olup olmadığını araştırmaktır. **Gereç ve Yöntemler:** Çalışmaya, Üroloji polikliniğine başvuran yaşları 45 ile 90 arasında değişen 182 erkek alındı. Şeker hastalığı, hipertansiyon, koroner arter hastalığı, hiperlipidemi, psikiyatrik bozukluğu ve malignensisi olanlar çalışma dışı bırakıldı. Kişiler üç gruba ayrıldı (1. grup; 45-54 yaş arası, 2. grup; 55-64 yaş arası ve 3. grup; 65 yaş üzeri). Çalışmaya katılan tüm kişilere IIEF ve AMS-SF formları doldurtuldu ve serumlarından total testosteron, serbest testosteron, LH (luteinize edici hormon), DHEA-S (Dihidroepiandrostenedion sülfat), SHBG (seks hormon bağlayıcı globulin) ve prolaktin çalışıldı. **Bulgular:** Yaşlanmayla birlikte total testosteron ve prolaktin değerlerinde değişiklik olmamaktadır. Serbest testosteron, bioavailable testosteron ve DHEA-S değerleri yaşlanmayla birlikte azalırken, LH ve SHBG değerleri artmaktadır. Yine benzer şekilde yaşlanmayla IIEF skorları azalırken, AMS-SF skorları değişmemektedir. AMS-SF'nin alt gruplarında; yaşlanmayla seksüel skorlar artarken, somatik ve psikolojik skorlar azalmaktadır. IIEF-EF (Erektil fonksiyon alt grubu) ile AMS-Seksüel formları arasında güçlü bir ilişki bulunmaktadır. **Sonuç:** Tüm veriler yaşlanmayla birlikte sekonder hipogonadizm olduğunu ve bunun sonucunda oluşan semptomların (özellikle cinsel) IIEF ve AMS-Seksüel formlarıyla değerlendirilebileceğini göstermektedir.

Anahtar Kelimeler: Yaşlanma; hipogonadizm; testosteron

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Aging is the condition of progressive impairment in physical, social, sexual, psychological and cognitive functions due to genetic factors, nutritional habits, lifestyle and other additional pathologies. Although the age limit for aging is controversial, general consideration in the literature is 65 years.[1]

Psychological, somato-vegetative and sexual complaints that were the consequences of the decline in androgen levels with aging were denominated as andropause, male climacterium, ADAM (Androgen Decline in the Aging Male) and PADAM (Partial Androgen Deficiency in the Aging Male).[2-5] Recently, the term "late-onset hypogonadism in males" is used more frequently in the literature and is recommended.[6,7]

AMS-Q (Questionnaire for the symptoms of aging males) was considered to be sufficient to evaluate male late-onset hypogonadism and to determine the type and severity of the symptoms.[8] It was assumed that the symptoms that were due to the reduced sex steroids could be evaluated by using this form in aging males.[9] However there is no data in the literature about the timing and the rate of this decrease in sex steroids and whether it occurred in all males.

MATERIAL AND METHODS

A total of 182 males who applied to outpatient clinics of Urology Department between 2005 and 2006 with the ages between 45-90 years and who fulfilled the inclusion criteria were included in the study. Before participation, all patients were informed about the study and their written consents were obtained. The patients were classified into three groups according their ages; those who were between 45 and 54 years constituted Group 1, those who were between 55 and 64 years constituted Group 2 and those who were over 65 years constituted Group 3.

Inclusion criteria were determined as being or above 45 years of age, being mentally capable to give a consent, absence of any known psychiatric disease and/or any previous therapies for this reason, absence of any active cardiovascular disease, diabetes mellitus, hypertension, dyslipidemia or a malignancy.

Total testosterone (TT), prolactin and luteinizing hormone (LH) levels were measured using ROCHE E170 (Germany) device with the method of electrochemiluminescence immunoassay (ECLIA); dihydroepiandrostenedion-sulphate (DHEA-S) and sex hormone binding globulin (SHBG) levels were measured using IMMULITE 2000 (Diagnostic Products Corporation, Los Angeles, USA) device with the method of competitive chemiluminescent enzyme immunoassay; free testosterone levels were measured using Diagnostic Systems Laboratories Inc. (lot no: 02176, USA) device with the method of Radioimmunoassay (RIA). Blood samples of the participants were obtained between 8-11 am. In order to calculate bioavailable testosterone values, total testosterone and SHBG levels were applied to the calculator page of the official site of International Society for the Study of Aging Male (www.issam.ch).

All participants were asked to complete validated IIEF (International Index of Erectile Functions) and AMS-Q scales with face-to-face interviews. The study protocol was approved by the Ethics Committee of the Celal Bayar University.

STATISTICAL ANALYSIS

The results of the study were analyzed with SPSS 10.0 software. One-Way ANOVA analysis was employed in comparison of AMS-Q subgroups, IIEF, serum hormone (LH, Prolactin, TT, FT, SHBG and DHEA-S) levels and bioavailable testosterone values of three groups. Pearson correlation analysis was employed to analyse the relation between the two variants. In evaluation of the results of the analyses, p levels below 0.05 ($p< 0.05$) were considered as significant.

RESULTS

Mean age of the participants was 58.95 ± 9.33 years (45-90). Mean ages and the number of participants according to the groups were presented in Table 1. Comparisons between groups according to mean serum values of total testosterone, free testosterone, DHEA-S, LH, prolactin, SHBG and bioavailab-

TABLE 1: Patient groups and their mean ages.

Groups	Age interval	Mean age
Group 1 (n= 67)	45-54	50.23 ± 2.85
Group 2 (n= 65)	55-65	58.35 ± 2.77
Group 3 (n= 50)	65 and over	71.40 ± 6.10

le testosterone are presented in Table 2 and Figure 1. Comparisons between groups according to IIEF-EF and IIEF-total score values are presented in Figure 2.

AMS-Q was made up of three subgroups. Psychological, somatic and sexual subgroups were evaluated separately. The sum of three subgroups was also evaluated separately as AMS-Q. Comparisons between groups according to AMS-Q, AMS-PSY, AMS-SOM and AMS-SEX scores are presented in Figure 3 and mean scores and p-values of groups in AMS-Q, IIEF and subgroups are presented in Table 3.

There was a statistically significant positive relationship between IIEF-EF scores and DHEA-S and bioavailable testosterone values (p= 0.000 and p= 0.01, respectively). Similarly, there was a statistically significant positive relationship between IIEF-total scores and DHEA-S and bioavailable testosterone values (p= 0.000 and p= 0.008, respectively).

The relationships between AMS-Q, AMS-PSY, AMS-SOM and hormone levels were not statistically significant. There was a statistically significant inverse relationship between AMS-SEX scores and free testosterone, and DHEA-S and bioavailable testosterone values (p= 0.001, p= 0.004 and p= 0.01, respectively). There was a positive relationship with serum LH levels (p= 0.000).

IIEF-EF and IIEF total scores were lower while AMS-SEX scores were higher.

DISCUSSION

Late-onset hypogonadism should be defined clinically and biochemically. There are more than one questionnaires used for clinical diagnosis. Most commonly used form is AMS-Q. AMS-Q is a form that evaluates somatic, psychological and sexual changes that occur with aging and separates them into subgroups. Late-onset hypogonadism is not diagnosed solely by AMS-Q. If there is a clinical suspicion, the form is completed first, and then hormonal profile is checked.[10,11] The hormonal profile that is outlined in the literature includes total testosterone, free testosterone and bioavailable testosterone. The lower limits of these values are 319 ng/dL, 6.5 ng/dL and 110 ng/dL, respectively.[12] These values may change with aging. In 2006, Yoshiji et al reported that while free testosterone and DHEA-S decreased with aging total testosterone levels did not change.[13] No change was observed in total testosterone levels with aging in our study (Table 2). On the other hand, we found that free testosterone and bioavailable testosterone levels decreased with aging. It was reported in the literature that SHBG levels increased significantly by aging and our results were in parallel with this finding.[13] The results confirmed the presence of hypogonadism with aging however they also revealed

TABLE 2: Mean hormone values of the groups.

Hormone	Group 1	Group 2	Group 3	p vaule
T. testosterone	4.52 (1.84-10.37)	4.49 (1.81-10.61)	4.13(1.64-10.23)	0.418
F. testosterone	11.83 (0.33-29.14)	11.75 (0.01-30.71)	8.79 (1.52-21.08)	0.000*
Bio. testosterone	230.16 (30.70-654.00)	206.40 (80.30-433.00)	176.90 (51.50-367.00)	0.002*
SHBG	30.53 (8.79-56.50)	36.47 (11.60-115.00)	40.65 (11.80-119.00)	0.004*
LH	5.39 (0.31-12.15)	6.60 (2.13-25.17)	8.62 (0.13-34.35)	0.001*
DHEA-S	180.87 (31.70-455.00)	157.22 (32.40-416.00)	74.12 (15.00-216.00)	0.000*
Prolaction	11.70 (2.97-60.94)	12.58 (1.36-07.80)	18.75 (6.46-176.30)	0.054

* Statistically significant (p< 0.05).

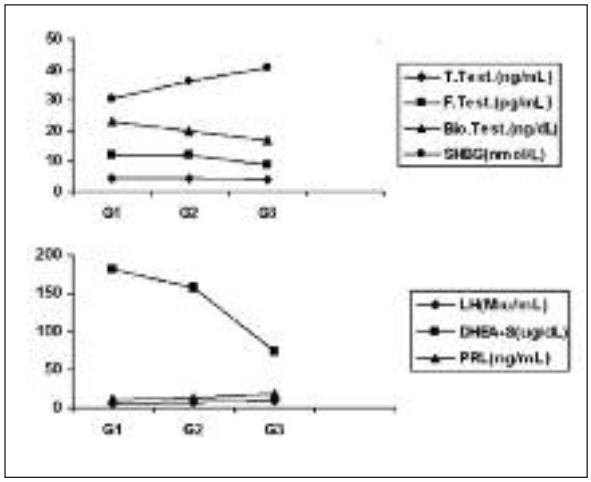

FIGURE 1: The changes in hormones with aging.

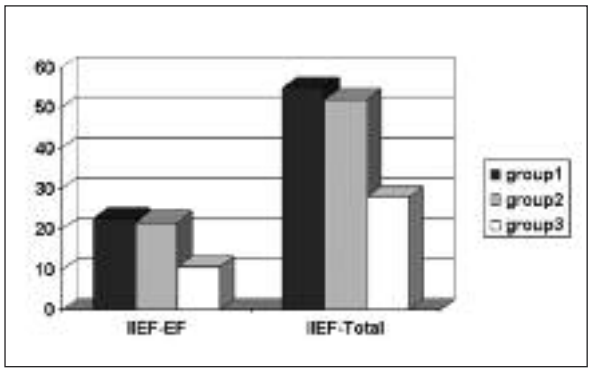

FIGURE 2: Comparisons of IIEF-EF and IIEF-Total scores between groups.

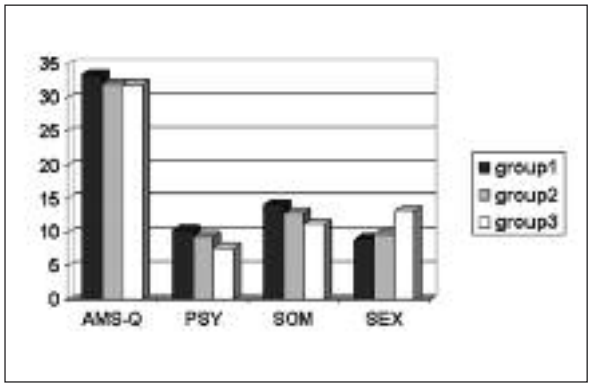

FIGURE 3: Comparisons of AMS-Q, AMS-PSY, AMS-SOM and AMS-SEX scores between groups.

that the measurement of bioavailable and/or free testosterone levels was more sensitive than total testosterone.[14] However, Morales et al suggested that testicular failure, in aging men was related to the decrease in total testosterone.[15] The findings about LH levels are controversial.[16-18] We observed a significant increase in LH levels with aging (p= 0.000). This increase might be due to primary Leydig cell deficiency as well as the inductors in hypothalamus-pineal gland axis. The studies on hormonal alteration in aging men revealed different results regarding the changes of LH and total testosterone levels with aging. Disparity of the results on this topic may be due to the differences of the number and the average age of patients enrolled in each report. There was no adequate data in the literature about prolactin levels in the elderly. We observed an increase in prolactin levels with aging, however the role of this finding in the diagnosis of hypogonadism is controversial. Further studies with greater patient populations are needed.

Somatic, psychiatric and sexual complaints occur with aging. They may be observed either alone or together.[12] There is a need for a standard form in order to evaluate these symptoms. Most commonly used form is AMS-Q and it is also accepted by ISSAM. It was reported that this form was not only useful for evaluating of symptoms related to androgen deficiency, but also beneficial for determining the effects of these symptoms on quality of life and as well as determining the efficacy of androgen replacement therapy (ART).[19]

Kentaro et al evaluated the relationship between age and AMS-Q in 2211 males in 2006 and they reported that the scores of AMS-Q (total) and sexual subgroup significantly increased with aging. They did not observe any significant correlation between age and the scores of psychological and somatic subgroups.[20] We also found that AMS-sexual scores increased significantly with aging, however there was not any significant correlation between AMS-Q (total) and aging (p= 0.77). Somatic and psychological scores significantly decreased with aging. These findings might be interpreted as follows the symptoms that occurred during aging were considered as natural consequences of aging by the participants. The reason for the absence of a considerable relation between AMS-Q (total) scores and aging might be the decrease in somatic and psychological subgroups in contrast with the incre-

TABLE 3: Mean score values of AMS-Q, IIEF and subgroups.

Form	Group 1	Group 2	Group 3	p value
IIEF-Total	54.89	52.07	28.04	0.000*
IIEF-EF	22.62	21.67	10.68	0.000*
AMS-Q	34.40	32.03	31.98	0.665
AMS-PSY	10.29	9.38	7.66	0.002*
AMS-SEX	9.01	9.73	13.12	0.000*
AMS-SOM	14.08	12.87	11.14	0.004*

* Statistically significant (p< 0.05).

ase in sexual subgroup scores. It was concluded that aging people overrated sexual symptoms compared to somatic or psychological complaints.

Başar et al. compared AMS-Q and IIEF scores and found a inverse correlation between IIEF-EF and sexual subgroups of AMS. The reason for this inverse correlation was the increased complaints resulted with an increase in AMS-Q scores while they caused a decrease in IIEF scores. There was not any significant relation between other subgroups and total scores of AMS and IIEF.[9] In addition, we found a strong relationship between IIEF-EF and AMS-SEX scores (p= 0.000) and this finding was consistent with the literature. As the sensitivity of IIEF was well known in evaluation of sexual complaints, the strong relationship was considered as AMS-SEX scores were reliable for the same objective. There were no statistically significant relation between IIEF-EF and somatic and psychological subgroups of AMS. This finding was also consistent with the literature. In contrast to the literature, we found that there was an increase in AMS-Q (total) scores while IIEF scores decreased. While the mean age of the cohort of Başar et al was 48 years, it was 58.95 ± 9.33 years in our study group. Our finding of the relationship between AMS-Q and IIEF might be due to older participants in our study group.

Yoshini and Başar et al did not show a significant relationship between AMS-Q and total testosterone,[9,13] however a correlation between AMS-Q and total and bioavailable testosterone was observed in some other studies.[21-24] We did not find any relationship between AMS-Q total scores and total, free and bioavailable testosterone levels (p= 0.95). On the other hand, when we evaluated subgroup scores, we found that sexual scores increased while the free and bioavailable testosterone levels decreased. The same tendency was present with the decrease in DHEA-S levels. Significant changes were observed (Group 3) in sex hormones other that total testosterone by aging. This finding supported the hypothesis that hypogonadism occurred by age. Nonetheless, total testosterone was inadequate to evaluate this change and free and bioavailable testosterone levels were more reliable. As the changes in these hormones were only related to AMS-SEX scores, it was suggested that the decreased sex steroids did not cause somatic or psychological symptoms. It was known that the changes in sex hormones during menopausal process resulted in increased somatic and psychological symptoms in females. It was reported that in order to observe these symptoms in males, the levels of sex hormones should decrase as low as seen after orchiectomy.[25]

It was reported in the literature that IIEF-EF scores decreased with aging. This decrease was especially significant after 50 years of age. Although this decrease was found to be significantly related with the decrease in free testosterone levels, no significant correlation was found between IIEF-EF scores and total testosterone levels.[26] When we evaluated the correlations between IIEF scores and hormone levels in our study, we found that IIEF-EF and IIEF-total scores decreased in parallel to the decreases in total and free testosterone levels, however the difference was not statistically significant. On the other hand, both IIEF-EF and IIEF-total scores were related to the bioavailable testosterone levels (p= 0.01 and p= 0.008, respectively). This fin-

ding revealed once more that bioavailable testosterone levels were more valuable for evaluating the symptoms of aging men. There was not any significant correlation between IIEF scores and SHBG and prolactin levels. The decreases in IIEF-EF scores showed a significant correlation with the decreases in DHEA-S levels (p= 0.000). Similarly, the decreases in IIEF-EF scores were significantly correlated to the increases in LH levels (p= 0.000). In addition, IIEF-total scores were related to both DHEA-S and LH levels (p= 0.000 and p= 0.000, respectively).

CONCLUSION

Serum bioavailable testosterone levels decrease with age. Consequently, measurement of bioavailable testosterone levels may be more beneficial in determination of late-onset hypogonadism. IIEF-EF and AMS-SEX scores support each other for evaluating sexual symptoms.

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