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Andropause and psychopathology: minor symptoms rather than pathological ones

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Abstract

This study examined the psychological symptomatology of men diagnosed with andropause and the association between calculated free testosterone (T) and depressed mood, anxiety and quality of life. Subjects were 153 men, aged 50-70 years, who participated in a screening of andropause. Total testosterone, FSH, LH and SHBG levels were measured. Depressed mood was assessed with the Carroll Rating Scale, anxiety with the "anxiety-insomnia" dimension of the General Health Questionnaire, and quality of life with the World Health Organisation Quality of Life questionnaire. The results showed that levels of free T decreased with age, whereas FSH and LH increased. Carroll Rating Scale scores were higher among hypogonadal subjects, but the mean score was low and not pathological. A negative correlation was observed between severity of depression as assessed by the Carroll Rating Scale and free T levels. However, subjects with a significant score on this scale did not exhibit different free T levels compared to subjects with a non-significant depressive score. Anxiety and quality of life did not differ between hypogonadal and eugonadal subjects. The present study therefore suggests that andropause is not characterised by specific psychological symptoms, but may be associated with "depressive symptoms" that are not considered as pathological.

Keywords: Testosterone ; depression ; mood ; quality of life ; andropause ; hypogonadism

1. Introduction

Although the concept of andropause is far from clear in endocrinology, media widely use this term to refer to general psychoneuroendocrine modifications in ageing males. Even though gonadal function declines with age in both men and women, several lines of evidence suggest that andropause, as an equivalent to menopause, does not exist (Skolnick, 1992; Tenover, 1998; Vermeulen, 2000). Middle-aged men are however characterised by clinical symptoms such as insomnia, decreased libido, reduced sexual activity, decreased mineral bone density and a development of abdominal obesity, similar to the symptoms occurring during menopause, although less intense (Shimokata et al., 1989; Vermeulen et al., 1989, 1999a; Murphy et al., 1993; Meacham and Murray, 1994; Schiavi and Rehman, 1995; Schow et al., 1997). The clinical delimitation and diagnosis of andropause are matters of controversy because of the inter-individual variability of its expression and the lack of specific symptoms. Vermeulen (2000) stressed the fact that the etiology of these signs and symptoms is often multifactorial, and that few significant correlations have been found between symptoms and testosterone levels.

A reduced feeling of well being with unusual anxiety and irritability, nervousness, mood swings and a depressive state are often mentioned as the psychological symptoms of age-related hypogonadism (Burns-Cox and Gingell, 1997; Morley et al., 1997b; Show et al., 1997; Sternbach, 1998; Wu et al., 2000). Difficulty in concentrating, lack of motivation and lower psychological vitality are also reported in the ageing male (Metz and Miner, 1995). However, psychological aspects of andropause have not yet been specifically studied and most data on psychological symptoms come from researchers' clinical impressions rather than from systematic studies. Therefore, it seems premature to assign them to the age-associated decline in testosterone levels.

The implication of testosterone in psychological state has yielded mixed results, mostly due to the heterogeneity of samples like age, health state and different methodological aspects (i.e. androgen assays, subtypes of testosterone used, time and number of blood samples used). Among elderly men, lower testosterone levels were associated with depressive symptoms (Beck Depression Inventory scores, Barrett-Connor et al., 1999) or dysthymic disorder (Seidman et al., 2002). Moreover, lower testosterone levels were reported in men with depression independently of age (Vogel et al., 1978; Yesavage et al., 1985; Rupprecht et al., 1988; Unden et al., 1988; Steiger et al., 1991; Davies et al., 1992; Schweiger et al., 1999). In contrast, some studies did not observe any significant difference in testosterone levels between depressed men and controls (Sachar et al., 1973; Amsterdam et al., 1981; Levitt and Joffe, 1988; Mason et al., 1988; Rubin et al., 1989; Davies et al., 1992). Furthermore, several studies have suggested that testosterone replacement improved mood in hypo-gonadal men (Skakkebaeck et al., 1981; O'Carroll et al., 1985; Burris et al., 1992; Wang et al., 2000), but others did not (Wu et al., 1982; Morales et al., 1994), as in studies on eugonadal men (Anderson et al., 1992; Bhasin et al., 1998).

Several researchers have also suggested the potential use of testosterone as an antidepressant or adjutant to current treatments in depressed hypogonadal men (i.e. Rinieris et al., 1979; Rabkin et al., 1995, 1999; Seidman and Rabkin, 1998).

Against this background, the aim of the present study was to assess whether men diagnosed with andropause exhibit a depressive and/or anxiety symptomatology and a diminution of well being compared to men without andropause as assessed by objective and well-validated scales. The study also examined the relationship between testosterone levels and these psychological variables.

2. Method

2.1. Subjects

The study was conducted with 153 men, aged between 50 and 70 years (mean age of 59.9 years, SD=5.6). A letter explaining the symptoms of andropause and prostate cancer was sent to all men, aged 50-70, living in the province of Liège, to announce the andropause screening campaign organised by the province of Liège (Belgium) (Legros, 2001; Legros and Delhez, 2002). Our subjects were recruited from this campaign between September and November 2000. Because hypothalamic-pituitary-gonadal axis and testosterone could be influenced by psychotropic medication (Heindrick et al., 2000), subjects had been free of antidepressant and anxiolytic medication for at least three months. Moreover, subjects received no sex hormone therapy for at least three months. All subjects received oral and written information about andropause and the study and gave their informed consent. The protocol was approved by the ethics committee of the University of Liège Medical School.

2.2. Hormonal assessment

A single blood sample was obtained in the morning, between 0900 and 1200 h. Free testosterone (free T, ng/l) was determined by an equation developed by Sodergard et al. (1982) similar to that of Vermeulen et al. (1999b) using total testosterone (total T, µg/l) and sex hormones binding globulin (SHBG, nmol/l). These hormones were determined by radioimmunoassay (IMMUNOTECH, France and BIOCODE S.A., Belgium, respectively). Harman et al. (2001) have shown a high reliability of free T to predict the presence of hypogonadism. Luteinising hormone (LH, mIU/ml) and folliculo-stimuline hormone (FSH, mIU/ml) were obtained by ECLIA (ADVIA Centaur, Bayer). For LH, the interassay coefficient of variation (CV) varied from 4 to 5%, with values ranging from 1.8 to 55.4. For FSH, the interassay CV varied from 7 to 8%, with values ranging from 5.1 to 64.6. For SHBG, the interassay CV was 12% at mean value of 40.6. For total T, the interassay CV varied from 11 to 17%, with values ranging from 0.3 to 11.1. These assays were performed by the Clinical Biology department of Liège University Hospital.

2.3. Diagnosis of andropause

Andropause was diagnosed as hypogonadism (free T<70 ng/l). Similar values have already been mentioned (Mahmoud et al., 2000; Harman et al., 2001; Vermeulen, 2001).

2.4. Psychological assessment

The subjects were asked to answer three questionnaires during the same week as the hormonal dosage.

Depressive symptomatology was assessed by the Carroll Rating Scale (CRS; Carroll et al., 1981). This 52-item self-administrated scale was used to assess the presence and severity of a depressive state in our subjects. The cut-off score used was 15, from which the subject presents a significant depressive symptomatology.

Anxiety symptomatology was assessed by the General Health Questionnaire (GHQ-28; Goldberg and Hillier, 1979). This questionnaire is an abbreviated version of GHQ-60. It provides a measure of mental health and is relevant to detect psychiatric symptoms in medical affections. This self-report questionnaire consists of 28 items assessing four dimensions: somatic symptoms, anxiety-insomnia, social dysfunction and severe depression. For each item, subjects were instructed to rate the unusual symptoms experienced during the last past weeks on a scale ranging from "not at all" or "less than usual" to "much more than usual", scored from 0 to 3. Each domain has a maximum score of 21 with a cut-off score of 10. The total score is calculated by summing the score for each domain. The maximum score is 84 and the cut-off score is 22/23, higher scores reflect a probability of psychiatric comorbidity.

Quality of life was assessed by the World Health Organisation Quality of Life questionnaire (WHOQOL-Bref; The WHOQOL Group, 1998). This 26-item self-report questionnaire is organised in four domains: physical symptoms, psychological symptoms, social relationships and environment. For the summary scores, item scores are transformed to a scale from 0 (worst possible quality of life) to 100 (best possible quality of life). The cut-off score is 50.

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2.5. Statistical analysis

The statistical analysis was performed using Statistica (version 5; Statsoft, Tulsa, USA). The relationships between psychological and hormonal variables were examined by partial correlation coefficients controlling for age, to avoid potential confounding, as testosterone levels are known to decline with age. Multivariate analysis of variance (Mancovas) with age as cofactor were performed to assess differences for the psychological scales between subjects with a positive diagnosis of andropause and those with a negative diagnosis. A two-tailed level of significance of 5% was adopted.

3. Results

Using the calculation of free T and a threshold of 70 ng/l, 107 subjects (69.9%) were hypogonadal, whereas 46 subjects (30.1%) were eugonadal. The mean age was statistically different between the two groups; the hypogonadal subjects were older (60.9±5.5 vs. 57.9±5.2 years, t_{151}=3.06, p=0.003).

LH and FSH levels were not significantly different among the groups. Free T levels were significantly correlated with FSH levels (r=–0.17, p=0.03), but not with LH levels. LH levels were positively associated with FSH levels (r=0.53, p<0.0001). Age was negatively correlated with free T (r= –0.26, p<0.001) and positively with LH (r=0.19, p=0.016) and FSH levels (r=0.17, p=0.029).

The mean scores, standard deviations for each questionnaire and mancovas are reported in Table 1. Carroll rating scores were higher among hypogonadal subjects (p=0.016).

Table 1 *Means and standard deviations of the Carroll Rating Scale (CRS), the General Health Questionnaire (GHQ-28) and the World Health Organisation Quality of life questionnaire (WHOQOL) among hypogonadal (H) (n=101) and eugonadal (E) (n=46) men. Group differences are shown by analysis of variance (MANCOVA)*

Questionnaires	Sub scores	H	E	*F* value (1.150) (1.148*)	*P* value
CRS	_	8.9 (5.5)	6.6 (6.5)	5.94	0.016
GHQ-28	Somatic	4.9 (3.4)	4.2 (3.5)	3.11*	0.08
	Anxiety	5.2 (3.9)	5.3 (4.8)	0.25*	0.61
	Social dysfunction	7.7 (1.7)	7.6 (1.7)	0.28*	0.59
	Severe depression	1.9 (3.1)	1.8 (2.9)	0.01*	0.91
	TOTAL	19.8 (8.9)	18.9 (10.6)	1*	0.32
WHOQOL	Q1: overall quality of life perception	3.8 (0.7)	3.8 (0.65)	0.73	0.39
	Q2: general health perception	3.7 (0.7)	3.8 (0.8)	1.91	0.17
	Physical symptoms	75.4 (12.5)	79.1 (14.1)	2.88	0.09
	Psychological symptoms	69.3 (14.5)	68 .8 (15.2)	0.04	0.83
	Social relationships	62.9 (15.6)	67.7 (17.7)	2.49	0.12
	Environment	76.4 (14.9)	77.2 (16.2)	0.67	0.42
	TOTAL	71.1 (9.9)	73.2 (12.02)	2.14	0.15

However, in both groups, mean scores did not reflect a significant depressive state (8.9±5.5 vs. 6.6±6.5). A negative partial correlation was showed between CRS scores and free T levels (r= –0.17, p=0.04). Age was not significantly associated with CRS scores. In the sample, 25 subjects had a CRS score of 15 or more. When these subjects were removed from the analysis, the negative partial correlation between CRS scores and free T levels was higher (r= –0.33, p<0.01). The T levels for these 25 subjects did not differ from those observed among the subjects with a score below 15 on CRS (61.8±19.4 ng/l vs. 61.2±19.2 ng/l, respectively; $F_{1.150}$=0.0005, p=0.98).

Anxiety as assessed by the "anxiety-insomnia" scores from the GHQ-28 did not differ between hypogonadal and eugonadal subjects.

Similarly, no significant difference between both groups was observed for the other dimensions of the GHQ-28. Nevertheless, "somatic symptoms" scores were higher in hypogonadal men, but the difference did not reach statistical significance (p=0.08). Furthermore, free T levels were negatively correlated with "somatic symptoms"

(r= –0.16, p=0.04).

Age was negatively correlated with "somatic symptoms" (r= –0.16, p=0.05), "anxiety-insomnia" scores (r= –0.21, p=0.008) and with the total score of GHQ-28 (r= –0.16, p=0.04).

Quality of life as assessed by the WHOQOL-Bref did not differ between hypogonadal and eugonadal subjects. However, the "physical symptoms" domain was lower in hypogonadal subjects, but the difference did not reach statistical significance (p=0.09). Correlations between testosterone and each domain score showed that the "social relationships" domain was associated with free T levels (r=0.17, p=0.004). Age was correlated with question 1 ("Are you satisfied with your quality of life?") (r=0.19, p=0.02). The other correlations were not significant.

In a supplementary statistical analysis, the diagnosis of andropause was restricted to the presence of a hypergonadotrophic hypogonadism (free T<70 ng/l combined with LH>10 mIU/ml and/or FSH>8 mIU/ml) (Legros and Delmotte, 1997). This allowed us to compare 35 subjects (22.9%) with a hypergonadotrophic hypogonadism to 39 controls (25.5%) with levels of free T, LH and FSH within the normal range. The hypergonadotrophic hypogonadal subjects were significantly older than the control subjects (62.4±5.2 vs. 57.5±5.1 yr, t_{72}=4.12, p=0.0001).

Mean levels of free T, LH and FSH were respectively 49.29±12.48 ng/l, 8.89±3.32 mIU/ml and 13.58±6.68 mIU/ml in the group of hypergonadotrophic hypogonadal subjects and 85.97±11.69 ng/1, 5.06±2.02 mIU/ml and 4.8±1.54 mIU/ml in the control group.

MANCOVAs did not show any difference of mean scores for CRS and GHQ-28 between hypergonadotrophic hypogonadal subjects and controls, as indicated in Table 2.

Table 2 *Means and standard deviations of the Carroll Rating Scale (CRS), the General Health Questionnaire (GHQ-28) and the World Health Organisation Quality of life questionnaire (WHOQOL) among hypergonadotrophic hypogonadal (hH) (n=35) and controls (C) men (n=39). Group differences are shown by analysis of variance (MANCOVA)*

Questionnaires	Sub scores	hH	C	*F* value (1,71) (1,70*)	*P* value
CRS		9.1 (5.3)	7.5 (6.8)	1.45	0.23
GHQ-28	Somatic	5 (3.6)	4.2 (3.67)	2.19*	0.14
	Anxiety	4.9 (3.3)	5.7 (4.9)	0.02*	0.88
	Social dysfunction	7.9 (1.9)	7.8 (1.8)	0.12*	0.72
	Severe depression	1.7 (3.1)	1.9 (3.1)	0.4*	0.52
	TOTAL	19.5 (7.7)	19.6 (11.2)	0.12*	0.73
WHOQOL	Q1: overall quality of life perception	3.9 (0.6)	3.7 (0.7)	0.6	0.42
	Q2: general health perception	3.7 (0.8)	3.7 (0.8)	0.03	0.87
	Physical symptoms	75.6 (15.1)	78.5 (14.6)	0.28	0.59
	Psychological symptoms	68.4 (16.2)	67.1 (15.1)	0.04	0.84
	Social relationships	62.1 (15.1)	66.9 (17.6)	1.58	0.21
	Environment	75.1 (16.3)	75.5 (16.8)	0.07	0.78
	TOTAL	70.3 (11.3)	72.1 (12.1)	0.6	0.44

Furthermore, quality of life evaluated by the WHOQOL-Bref was not significantly different between hypergonadotrophic hypogonadal subjects and controls (Table 2).

4. Discussion

The prevalence of hypogonadism is particularly high in our sample (69.9%). The variability of the values and subtypes of testosterone used in different studies makes it difficult to compare our results to existing epidemiological data. However, a well-conducted longitudinal study showed that 9% of men aged from 50 to 59 years and 34% of men aged between 60 and 69 years presented reduced levels of free T (Harman et al., 2001). The high percentage of hypogonadism in our sample is presumably due to the selection bias. Firstly, some of our subjects were retired, and probably not comparable to a population of professionally involved men. Secondly,

our subjects all lived in Seraing, which is a mixed rural and industrial town. It is not excluded that environmental factors such as pesticides slow down the gonadal axis (Bouillon et al., 2001). In a larger sample of the andropause detection of the province of Liège, 45.7% among 745 men were hypogonadal. Thirdly, we have no demographic data, which might have explained this high percentage.

In the present study, FSH and LH are positively correlated. The same finding was previously demonstrated by Morley et al. (1997a). According to these authors, the association between FSH and LH is not surprising since they are liberated by a common hormone, the gonadotropin releasing hormone. The lack of correlation between LH and free T, together with the weak negative correlation between FSH and free T, might be puzzling. However it is known that the demonstration of a negative correlation LH-T is found only in large populations suffering from clear-cut genetic or organic testicular damage leading to variable decrease of steroidogenic activity. Indeed, due to LH spontaneous peaks fluctuations (Legros et al., 1974) the demonstration of a preserved LH-free T (positive) relationship in normal or "sub normal" men would need serial, 10-20 min interval blood samplings and statistical methods that take into account the different half lives of the two hormones and the delay between hypophyseal LH and testicular T release. Interestingly, since plasma FSH is quite stable (Legros et al., 1974) and its level is related to the quality of the spermatogenesis (Franchimont et al., 1972) it is not too surprising that its plasma level is related to another aspect of testicular function, which is T production. Moreover, this is a negative relationship, which suggests that at least part of the androgen deficiency in ageing male might be of testicular origin, as previously suspected through the demonstration of an increased release of LRH-induced LH release as of age 50 (Legros and Bruwier, 1979) and a decreased HCG-induced testosterone release (Harman and Tsitouras, 1980). However an increase in gonostat sensitivity, leading to a partial central androgen deficiency differing from one individual to another, has also been demonstrated (Deslypere et al., 1987; Winters et al., 1997) and has also been postulated as the cause of the lack of LH-free T correlation (Morley et al., 1997a).

The age-associated decline of free T and increase of LH and FSH were consistent with previous studies (Morley et al., 1997a; Harman et al., 2001). The present study also confirms that free T is a more representative indicator of testosterone decline with age than total T, which was not correlated with age in our sample (Gray et al., 1991). In hypergonadotrophic hypogonadal subjects, 9 (23%) presented high levels of LH, whereas 34 (87.2%) had high levels of FSH. The same observation was reported by Morley et al. (1997a). Several authors consider that the increase of LH levels linked to age-associated testosterone decline is rare (Tenover, 1998; Vermeulen, 2000).

In the main analysis, higher depressive symptomatology in hypogonadal subjects than in eugonadal subjects was observed, but the CRS scores were not pathological. In contrast, no difference in CRS scores was observed in the supplementary analysis between hypergonadotrophic hypogonadal subjects and controls. Taken together, these findings suggest that depressive state does not appear to be a psychological symptom of andropause syndrome.

In the present study, a significant negative correlation was observed between CRS scores and free T, indicating that declining free T was associated with more depressive symptoms. Although this correlation was weak, it is consistent with the study of Barrett-Connor et al. (1999), based on bioavailable T in elderly men and with those of Yesavage et al. (1985), based on total T among depressed men with a wide range of age and severity of depression. However, our results did not confirm the relationship between T and major depression, since lower free T levels did not characterise the subgroup composed of 25 depressed men compared to controls, as demonstrated in some studies. Moreover, the negative partial correlation between free T and depressive symptoms was higher when these subjects were removed from the analysis. On the opposite, Barrett-Connor et al. (1999) reported that elderly men who are depressed had lower testosterone levels. Other studies also showed a significant difference in mean total and free T levels between younger depressive patients and controls (Vogel et al., 1978; Schweiger et al., 1999). Nevertheless, many studies showed no difference between depressed men and controls based on salivary, free or total testosterone levels (Amsterdam et al., 1981; Levitt and Joffe, 1988; Rubin et al., 1989; Davies et al., 1992). Therefore, the conclusion of a significant relationship between testosterone and depression appears to be premature. Our results suggest only an association between testosterone and "minor depressive symptoms", which are not considered as pathological.

Concerning anxiety and mental health status as assessed by the GHQ-28, no significant difference was observed. Furthermore, no correlation exists between endocrine parameters and anxiety. It has been suggested that testosterone replacement in young hypogonadal men improves mood (Skakkebeack et al., 1981; Wang et al., 1996, 2000). In contrast, anxiety as assessed by the "Multi-component Anxiety Inventory" and testosterone were not associated in 58 teenagers aged from 15 to 17 years (Olewus et al., 1980). In the present study there was a trend with the "somatic symptoms" subscale, indicating that hypogonadal subjects may report more physical complaints than eugonadal subjects. Moreover, there was a significant correlation between that subscale and free T.

Quality of life as assessed by the WHOQOL-Bref was relatively high regardless of the group or the domain. The

first two questions, related to the subjective perception about quality of life and health, indicated a positive perception among the entire sample. Consequently, quality of life did not appear to be affected by a testosterone deficiency in our sample. However, hypogonadal subjects had a non-significant score in the "physical symptoms" domain, compared to eugonadal subjects. It should be postulated that consequences of testosterone deficiency might be more salient at a physical level than at a psychological level, as suggested also by the correlation between "somatic symptoms" scores and free T. The use of a quality of life scale more specifically oriented on vasomotor, sexual and psychosocial factors could be more adequate for assessing quality of life during andropause.

Mixed results are reported on the relationship between mood dimensions (i.e. well being and anxiety) and testosterone. A possible explanation is that the psychological measures in these studies are based on non-standardised instruments and are secondary to the measures of physiological changes that follow testosterone treatment. That is why further studies using psychological standardised instruments are warranted (i.e. Morales et al., 1994; Wang et al., 2000).

In the present study, age was significantly correlated with several psychological and quality of life measures. Overall, increasing age seemed to be associated with fewer anxiety and somatic symptoms and better mental health status and quality of life perception. This finding was also observed by Perry et al. (2001). However, CRS was not associated with age (Barrett-Connor et al., 1999; Perry et al., 2001). The oldest men in our sample exhibited a higher satisfaction with their quality of life.

In conclusion, this study shows that andropause, defined as hypogonadism or as hypergonadotrophic hypogonadism, is not characterised by specific psychological symptoms. Even if hypogonadal subjects have a higher mean score on the CRS, this score is low. This indicates that andropause could be associated with "minor depressive symptoms" that are not considered pathological. In agreement with Perry et al. (2001), free T was not an important determinant of psychological state or quality of life. The correlations between testosterone and depression should be interpreted with caution since they are weak. Moreover, this study does not demonstrate a significant difference in sex steroid between depressed males and normal controls. Taken together, the lack of convincing relationship between endocrine parameters and psychological functioning is not surprising since the clinical symptoms of andropause are not specific and probably have a multifactorial origin, as suggested by Vermeulen (2000).

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