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Association of Specific Symptoms and Metabolic Risks with Serum Testosterone in Older Men

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Context: Although attention and concern about health disorders in aging men have been growing, the structure of psychological and somatic complaints of actual patients, not population-based cohorts, has not been elucidated in relation to sex hormone patterns and metabolism.

Objective: The objective of the study was investigation of factors influencing complaint structures in aging male patients.

Design: This was a cross-sectional cohort study.

Setting: The study was conducted in an andrological outpatient department.

Patients: Subjects included 434 consecutive male patients aged 50–86 yr.

Main Outcome Measures: The following hypotheses were measured: 1) psychosomatic complaints and metabolic factors in aging male patients are related to sex hormone levels in a symptom-specific manner, and 2) patients form subcohorts.

Results: A clear-cut threshold for late-onset hypogonadism was not found; rather, prevalence of psychosomatic symptoms and metabolic risk factors accumulated with decreasing androgen levels. For example, androgen-induced prevalence of loss of libido or vigor increased below testosterone concentrations of 15 nmol/liter ($P < 0.001$), whereas depression and diabetes mellitus type 2 (also in nonobese men) were significantly more present in men with testosterone concentrations below 10 nmol/liter ($P < 0.001$). Erectile dysfunction was identified as a composite pathology of metabolic risk factors, smoking, and depressivity, whereas only testosterone concentrations below 8 nmol/liter contributed to that symptom ($P = 0.003$). Cluster analysis revealed aging men to present within three independent groups characterized by psychosomatic complaints, metabolic disorders, and sexual health problems. These subgroups of patients exhibit distinct features in terms of androgen levels, age, and body mass index.

Conclusions: There is no evidence that a uniform structure of testosterone concentrations and complaints exists within the cohort of elderly male patients. Rather, in aging male patients, psychosomatic complaints and metabolic risk relate to testosterone in a symptom-specific manner. **(*J Clin Endocrinol Metab* 91: 4335–4343, 2006)**

THERE IS GROWING attention and concern in regard to health disorders in aging men. The high prevalence of gender-related complaints and associated metabolic as well as psychosomatic impairments demands appropriate care services specifically directed to improving health in these men (1, 2).

Physicians treating elderly men encounter patient cohorts exhibiting differential profiles of complaints of gradual onset and ambiguous nature. To provide proper investigation and treatment, these men must be assessed by trained physicians following systematic techniques. The putative pathologies require an approach that, however, implies assessment beyond specifically male topics: multiple organ systems and metabolic factors, *e.g.* diabetes mellitus type 2, have to be considered (2, 3).

Within the group of aging males, late-onset hypogonadism (LOH) is a clinical and biochemical syndrome associated with advancing age. It may result in a significant detriment of psychosocial function and adversely affect multiple organ systems (3). Studies surveying population-based cohorts, *e.g.* the Men in Australia Telephone Survey (MATeS) (1) or the Massachusetts Male Aging Study (MMAS; *e.g.* Ref. 4), provide useful information about the prevalence and incidence of nosologies in elderly, community-dwelling men. However, these cohorts do not represent patients, *i.e.* not the persons actually seeking diagnosis and possible treatment. Consequently, it is of paramount importance to assess the nosological profiles of elderly male patients to provide physicians with necessary tools for adequate treatment.

Clinical evaluations of elderly men may point toward androgen-related complaints, hence symptoms of LOH, as described in the International Society of Andrology/International Society for the Study of the Aging Male/European Association of Urology recommendation 2 (3), such as decreased sexual desire, erectile quality, cognitive functions, and mood as well as sleep disturbances and changes of body composition. The designation of a reliable testosterone threshold below which hypogonadism-related symptoms start is, to date, at best arbitrary. No pathognomonic findings exist in relation to specific androgen concentrations for clinically relevant subsets of older men (International Society of Andrology/International Society for the Study of the Aging Male/European Association of Urology recommendation 3 sentence 2) (2, 3).

In fact, dose-titrating studies as well as cross-sectional observations suggest a nonlinearity of testosterone effects, which is most likely also tissue specific. This nonlinearity is

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Abbreviations: BMI, Body mass index; CV, coefficient of variation; LOH, late-onset hypogonadism; LUTS, lower urinary tract symptoms; MATeS, Men in Australia Telephone Survey; MMAS, Massachusetts Male Aging Study; PSA, prostate-specific antigen; ROC, receiver operating characteristics; TT, total testosterone.

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probably caused by saturation effects at the androgen receptor level and may be the reason for marked effects of testosterone treatment being caused by small changes within the low range of testosterone concentrations, whereas within the normal range, marked increases of testosterone levels are needed to cause only limited effects (5–7).

Here we describe a patient-oriented and clinically practical approach based on individuals and symptoms and provide novel insights into complaints of these patients, who suffer to a degree that causes them to seek specialists' advice. The notion that common and uniform concentrations of androgen levels can be applied to describe the increasing prevalence of testosterone-related symptoms in elderly men will be challenged in this paper.

Patients and Methods

Patients

The Institute of Reproductive Medicine of the University Clinics (Muenster, Germany) is an endocrinological and andrological unit caring for male patients for more than 30 yr. A standardized procedure for the assessment of elderly male patients has been applied since the beginning of our outpatient department and consists of a structured interview (see *Methods*).

Although no defined age threshold exists for LOH, only male patients with an age of at least 50 yr who attended the institute between 1995 and 2005 were primarily eligible for this study (n = 616 of a total 9715 men attending the institute during this time period). The screening procedures were designed to select either eugonadal men or patients with LOH, which is an exclusion diagnosis (2, 3), to assess the effects of both testosterone and aging on the complaints of elderly men. Thus, all other causes for hypogonadism have been excluded in the patients of this study. Such cases are likely to act as confounders in regard to the above named purpose of the study because the classical forms of primary or secondary hypogonadism in older men are likely to have been present for a number of years and have, in most instances, already been treated by various means.

Hence, in a second screening step, subjects with previous external treatment exposure to androgens (n = 120) as well as Klinefelter patients (n = 41) were excluded. Persons with classical primary or secondary hypogonadism were excluded after appropriate assessment of history and endocrine diagnostics including GnRH-stimulation tests and prolactin determination and exclusion of pituitary adenomas by magnetic resonance tomography in case of decreased gonadotropin levels or elevated prolactin levels (n = 14). To stratify the cohort in regard to sexual symptoms, only men living within a partnership were included. This led to exclusion of men living alone (n = 7). Altogether 434 men aged between 50 and 86 yr were included for evaluation and data collection was comprehensive. All of them attended the clinic for at least one of the complaints mentioned in this study. The upper and lower limits for LH levels were set between 1 and 15 IU/liter by adding/subtracting 50% to/from the normal range values (the normal range of the assay is 2–10 IU/liter) to confine the cohort to men with the most likely diagnosis of LOH should they exhibit low androgen levels. This was performed to assure further that no men with classical primary or secondary hypogonadism were included because LH concentrations are most likely to be found out of this range in such cases. Indeed, this procedure led to no further exclusions, corroborating the screening procedures to select appropriate patients.

Analysis of patient data were performed by extraction of our electronic database (8). All patients gave written informed consent for the use of their data for scientific evaluation as approved by the Ethics Committee of the Medical Faculty, University of Muenster, Muenster, Germany, and the state medical board. There is no conflict of interest for any author.

Methods

Interview. The structured interview items applied to all patients were as follows:

1. Do you sometimes feel sad or depressed?
2. Do you experience a loss of sex drive/libido?
3. Do you feel a loss of vigor or energy?
4. Do you lack concentration?
5. Do you experience hot flushes?
6. Do you experience sleep disturbances?
7. Alcohol consumption.*
8. Diabetes mellitus type 2.*
9. Erectile dysfunction/impotence.*
10. Problems voiding urine.*
11. Cigarette consumption.*

Questions marked with an *asterisk* are detailed below.

This approach provides the physician with an easy, reliable and consistent means of patient assessment, simultaneously allowing close interaction between patient and doctor Interobserver stability is demonstrated by Cohen's kappa for the specific items ranging from 0.87 to 0.93 in 98 randomly selected patients being reassessed after 3 months without therapy, with $P < 0.001$ for each item. The questions were kept as simple as possible to provide feasible tools for daily practice, and answers were possible only in the form of yes or no.

Biochemical analyses. All venous blood samples were obtained in a fasting state under standardized conditions between 0800 and 1200 h after a 30-min rest. Serum or plasma were separated at 800 × *g*. Samples were immediately stored at −20 C. Serum testosterone levels were measured with a commercial ELISA kit (DRG Instruments GmbH, Marburg, Germany) and concentrations of LH, SHBG, and estradiol by highly specific time-resolved fluoroimmunoassays (Autodelfia, Freiburg, Germany). Mean intraassay coefficients of variation (CVs) were less than 5% and mean interassay CVs less than 10%. Levels of free testosterone were calculated from levels of SHBG and total serum testosterone according to previously published calculations (9). Prostate-specific antigen (PSA) was determined with highly specific time-resolved fluoroimmunoassay (Autodelfia), with a normal limit of less than 4 μg/liter. Mean intra- and interassay CVs were less than 2 and 5%, respectively. Sampling was performed before prostate palpation and transrectal ultrasonography. Hemoglobin determination was performed on an SE 9500 system (Sysmex Europe, Hamburg, Germany).

Specific assessments

Prostate measurement. Standardized procedures of this transrectal ultrasound examination were previously published (10, 11). Subjects with PSA concentrations 4 μg/liter or greater were routinely referred to the

TABLE 1. General data of 434 elderly men consulting for symptoms of suspected LOH

Parameter	Mean ± SD	Range
Anthropometrical data		
Age (yr)[a]	57.9 ± 6.6	50–86
BMI (kg/m^2)[a]	27.7 ± 4.2	19–53
Body height (cm)[a]	178.5 ± 7.0	157–198
Body weight (kg)[a]	88.2 ± 14.2	59–152
Biochemical values		
TT (nmol/liter)[a]	13.6 ± 7.0	0.5–44.8
Free testosterone (pmol/liter)[a]	257 ± 143	5–976
Estradiol (pmol/liter)[a]	80.67 ± 35.9	12.5–220
SHBG (nmol/liter)[a]	40.1 ± 19.0	8.7–138.8
LH (IU/liter)[a]	2.8 ± 3.7	1.5–14.8
PSA (μg/liter)[a]	2.5 ± 1.2	0.4–8.3
Hemoglobin (g/liter)	15.6 ± 1.1	9.3–18.2
Cigarette smoking (>5/wk)	Yes, n = 71 No, n = 350 Ex-smokers for less than 2 yr, n = 13	
Alcohol consumption (>40 g/d)	Yes, n = 136 No, n = 298	
Prostate size (ml)[a]	29.3 ± 10.0	10–92

[a] Data were not normally distributed and were log-transformed for parametric analyses when required.

TABLE 2. Symptomatology of 434 elderly male patients in relation to TT concentrations (nmol/liter)

Symptom	Yes	No	Mann-Whitney *U* test (*P*)	Percent yes
Loss of libido	10.5 ± 5.3	15.1 ± 7.3	0.0001	34
Erectile dysfunction	12.6 ± 7.1	14.9 ± 6.9	0.004	59
Feeling depressed	10.8 ± 6.5	14.0 ± 7.0	0.0001	15
Lacking vigor	9.9 ± 5.1	14.5 ± 7.2	0.0001	21
Lacking concentration	11.1 ± 7.2	13.9 ± 6.9	0.002	11
Hot flushes	10.9 ± 7.5	14.0 ± 6.9	0.0001	15
Disturbed sleep	10.9 ± 6.5	14.0 ± 7.0	0.002	14
Diabetes mellitus type 2 (ADA criteria)				
All patients	11.2 ± 8.0	14.1 ± 6.7	0.0001	18
Nonobese patients (n = 318)[a]	12.8 ± 9.4	14.5 ± 6.9	0.009	12
Arterial hypertension[a]	12.3 ± 6.1	14.1 ± 7.4	0.03	31
Overweight (BMI > 30 kg/m^2)	10.7 ± 5.3	14.6 ± 7.3	0.0001	27
LUTS[a]	16.8 ± 7.7	13.0 ± 6.8	0.0001	15

Data are expressed as mean ± SD. The percentage of all patients (n = 434) with a respective complaint or symptom and the TT concentration is given for patients with or without the complaint. The statistically significant difference between the testosterone concentrations is given by the *P* value of the Mann-Whitney *U* test. ADA, American Diabetes Association.

[a] See *Methods* for definitions of overweight, arterial hypertension, and LUTS.

urological department for further investigations. No malignancy was detected.

Diagnosis of diabetes mellitus type 2. The subjects were diagnosed according to the American Diabetes Association criteria by specialists.

Obesity. Patients with a body mass index (BMI) greater than 30 kg × m^{-2} were considered obese.

Lower urinary tract symptoms (LUTS). The patient was categorized LUTS positive if any question derived from the International Prostate Symptom Score questionnaire was answered with yes. This is a rather simplified approach that, however, reflects the clinical experience with our patients. Indeed, only 15% of all men were LUTS positive according to this definition (see *Results*). Urologists dealing with aging men may find a higher rate of LUTS because their specialty attracts such patients. Other institutions, especially urological ones, may find it meaningful to either use International Prostate Symptom Score scores as a continuous variable or define LUTS as the occurrence of a standardized score above some rational threshold.

Erectile dysfunction. The specific question was: did you have problems achieving an erection during the last 6 months, which caused you subjective disturbances in general sexual well-being? The patient was categorized with erectile dysfunction if this question was answered with yes. This is in good agreement with the one-question procedure applied in the MMAS (12) and the Australian MATeS study (1).

Alcohol consumption. Significant alcohol consumption was diagnosed as regular intake of more than 40 g of pure alcohol per day.

Cigarette smoking. Consumption of more than five cigarettes per week was determined as significant abuse of nicotine. Cigarette smoking was coded as follows: nonsmoker or ex-smoker for more than 2 yr = 0, smoker = 1, ex-smoker for less than 2 yr = 2.

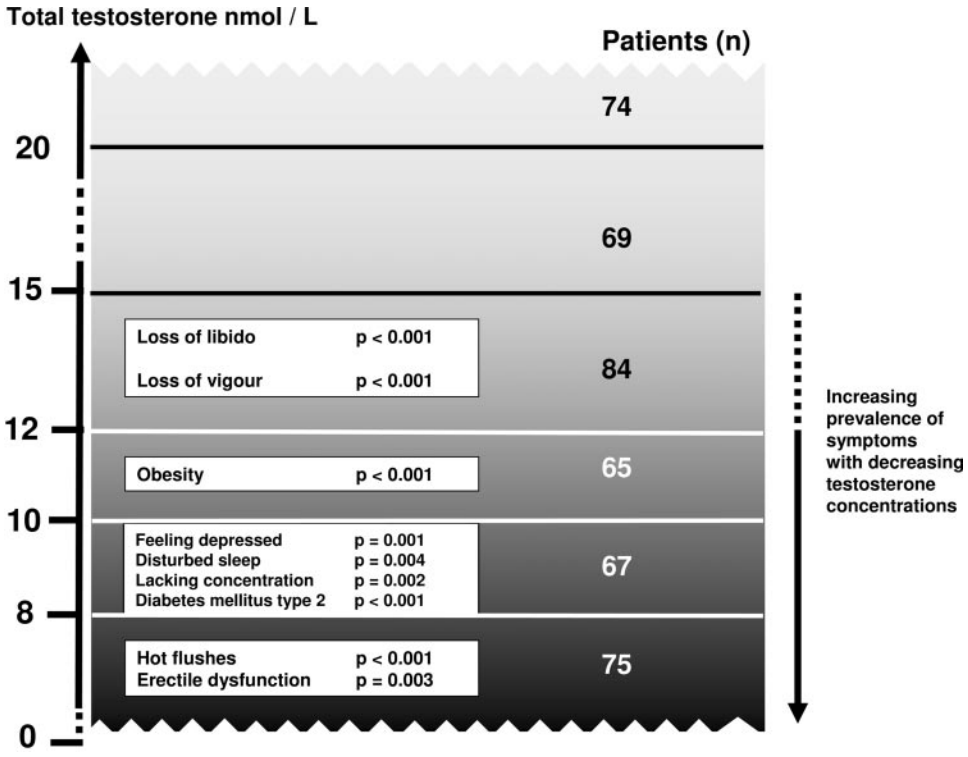


FIG. 1. Overview of symptom-specific concentrations of TT levels below which the prevalence of the respective symptom starts to increase, hence, a lack of androgens exerts influence. The levels were determined by a stepwise backward Somer's D test, a result confirmed by binomial regression analyses (Table 3) in which TT sextiles and other covariates are used. Also see Table 4 for clinical relevance. The *lines* indicate the sextiles of testosterone concentrations used for analyses. Also the number of patients within each sextile is given. Note that the scale has been broken.

TABLE 3. Stepwise backward binomial regression models (complaints with psychological and somatic components in 434 older male patients)

Symptom	Predictor	*P*	Excluded
Psychological components			
Loss of libido	Sextile 1: TT < 8 nmol/liter	<0.0001	Age, BMI, LUTS, TT sextiles 5 and 6, and alcohol consumption
	Sextile 2: 8 ≤ TT < 10 nmol/liter	<0.0001	
	Sextile 3: 10 ≤ TT < 12 nmol/liter	0.003	
	Sextile 4: 12 ≤ TT < 15 nmol/liter	0.04	
	Feeling depressed	<0.0001	
	Lacking vigor	<0.0001	
Erectile dysfunction (n = 421)	Sextile 1: TT < 8 nmol/liter	0.04	Age, BMI, LUTS TT sextiles 2–6, and alcohol consumption
	Cigarette consumption	0.003	
	Diabetes mellitus type 2	0.005	
	Feeling depressed	0.02	
	Disturbed sleep	0.03	
	Arterial hypertension	0.07 (trend)	
Feeling depressed	Sextile 1: TT < 8 nmol/liter	0.02	Age and TT sextiles 3–6
	Sextile 2: 8 ≤ TT < 10 nmol/liter	0.06 (trend)	
	Disturbed sleep	<0.0001	
	Excessive alcohol consumption	0.009	
Lacking vigor	Sextile 1: TT < 8 nmol/liter	<0.0001	Age, TT sextiles 5+6, and alcohol consumption
	Sextile 2: 8 ≤ TT < 10 nmol/liter	0.002	
	Sextile 3: 10 ≤ TT < 12 nmol/liter	0.01	
	Sextile 4: 12 ≤ TT < 15 nmol/liter	0.03	
	Feeling depressed	<0.0001	
	Disturbed sleep	<0.0001	
Lacking concentration	Sextile 1: TT < 8 nmol/liter	0.02	Age, TT sextiles 3–6, and alcohol consumption
	Sextile 2: 8 ≤ TT < 10 nmol/liter	0.03	
	Feeling depressed	<0.0001	
	Disturbed sleep	<0.0001	
Hot flushes	Sextile 1 (TT < 8 nmol/liter)	0.01	Age, BMI, and TT sextiles 2–6
	Feeling depressed	0.002	
	Disturbed sleep	0.03	
	Diabetes mellitus type 2	0.01	
Disturbed sleep	Sextile 1 (TT < 8 nmol/liter)	0.04	Age, TT sextiles 3–6, and alcohol consumption
	Sextile 2 (8 ≤ TT < 10 nmol/liter)	0.06 (Trend)	
	Feeling depressed	<0.0001	
	Higher BMI	0.03	
Somatic components			
Diabetes mellitus type 2			
All patients	Sextile 1: TT < 8 nmol/liter	0.003	Age and TT sextiles 3–6
	Sextile 2: 8 ≤ TT < 10 nmol/liter	0.04	
	Higher BMI	<0.0001	
Only nonobese men, n = 318 (BMI < 30 kg/m^2)	Sextile 1: TT < 8 nmol/liter	0.02	Age and TT sextiles 3–6
	Sextile 2: 8 ≤ TT < 10 nmol/liter	0.04	
	Higher BMI	0.001	
Arterial hypertension (n = 421)	Sextile 1: TT < 8 nmol/liter	0.009	Cigarette smoking and TT sextile 6
	Sextile 2: 8 ≤ TT < 10 nmol/liter	0.01	
	Sextile 3: 10 ≤ TT < 12 nmol/liter	0.008	
	Sextile 4: 12 ≤ TT < 15 nmol/liter	0.01	
	Sextile 5: 15 ≤ TT < 20 nmol/liter	0.003	
	Advanced age	0.02	
	Higher BMI	<0.0001	
LUTS	Sextile 5: 15 ≤ TT < 20 nmol/liter	0.03	TT sextiles 1–4 and alcohol consumption
	Sextile 6: TT ≥ 20 nmol/liter	0.004	
	Advanced age	0.04	
	Higher prostate size	<0.0001	
	Diabetes mellitus type 2	0.02	

The symptom or complaint (column 1) is analyzed in regard to factors associated with it (column 2: predictor). Factors significantly associated with the symptom are given in column 2 along with the *P* value (column 3). Factors that were clinically possible to be associated, but excluded by analysis, are given in column 4. For loss of libido, *e.g.* it is demonstrated that TT levels < 15 nmol/liter are associated with this symptom, as well as depression and lacking vigor, whereas age, BMI, alcohol consumption, TT levels greater than 15 nmol/liter, and LUTS do not influence the prevalence of loss of libido. The sextiles of TT levels are analyzed separately and in most cases, the lowest concentration of testosterone exhibits the strongest association. The sextile with the highest testosterone level still significantly associated with the symptom is in agreement with the results of the nonparametric Somers D test (see Fig. 1 and Table 4 for clinical relevance). In case cigarette smoking was included as a potential variable, patients with a history of quitting cigarette consumption for less than 2 yr were not included and n = 421 applies.

Arterial hypertension. Diagnosis was made using an automated cuff device applied after 30 min of rest. Systolic blood pressure greater than 140 mm Hg and/or diastolic blood pressure greater than 95 mm Hg was considered as arterial hypertension. Antihypertensive premedication was considered similarly.

Statistics

Primary statistics as comparisons between presence of complaints and testosterone levels were performed as nonparametric tests (Mann-Whitney *U* test).

To assess potentially nonlinear effects of testosterone levels, it was necessary to form statistically independent subgroups according to testosterone concentrations. Power estimation indicated that with a total number of 434 men, sextiles of testosterone levels would be appropriate to obtain patient group sizes to achieve a power of 80% to detect differences at $P < 0.05$. The sextile ranges were chosen both to obtain sample sizes of 60–90 men per sextile and represent clinically useful thresholds of total testosterone (TT) levels of round numbers (*i.e.* not 8.4 nmol/liter but rather 8.0 nmol/liter as a threshold). The sextiles and numbers of patients are as follows: TT less than 8 nmol/liter (n = 75), TT 8 or greater and TT less than 10 nmol/liter (n = 67), TT 10 or greater and TT less than 12 nmol/liter (n = 65), TT 12 or greater and TT less than 15 nmol/liter (n = 84), TT 15 or greater and TT less than 20 nmol/liter (n = 69), and TT 20 or greater (n = 74).

For nonobese men (n = 318), the sextiles were maintained for reasons of consistency in regard to the other analyses, although this created more variation in terms of sample size. Thus, patient numbers are respectively modified: TT less than 8 nmol/liter (n = 47), TT 8 or greater and TT less than 10 nmol/liter (n = 39), TT 10 or greater and TT less than 12 nmol/liter (n = 46), TT 12 or greater and TT less than 15 nmol/liter (n = 70), TT 15 or greater and TT less than 20 nmol/liter (n = 55), and TT 20 or greater (n = 61).

Both nonparametric and parametric procedures were used to describe the potential relation of testosterone levels to symptoms (stepwise backward Somer's D test and stepwise backward binomial regression).

To detect complaint structures as well as patient profiles and describe these in relation to age, BMI, and testosterone levels, cluster analyses were performed.

To provide the reader with more information on the clinical relevance of the observed results, receiver operating characteristics (ROC) were calculated, given specificity and sensitivity for testosterone-related thresholds of symptom-prevalence.

A detailed and referenced *Appendix* on *Details on Statistical Analyses* is published as supplemental data on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org.

The Statistical Software SPSS (version 12.0; SPSS, Chicago, IL) was used.

Results

General patient characteristics in terms of hormone values and physical parameters are given in Table 1. Distributions of complaints according to the structured interview are given in Table 2 along with results of nonparametric tests (Mann-Whitney *U* test). Increments of symptom prevalence in men with testosterone concentrations below specific levels are given in Fig. 1 (according to patient sextiles after the stepwise backward Somer's D test). Substitution of TT by levels of free testosterone did not produce differential results.

Predictors and excluded parameters of complaints are also given as results of stepwise binomial regression analyses in Table 3: results confirm the differential strata of androgen levels associated with various symptoms and also when other influencing factors are taken into account (compare Fig. 1). The relevance of these findings for clinical application is shown by ROC analyses detailed in Table 4.

Results of the cluster analysis are displayed in Fig. 2, A–C. The relation of age, TT, and BMI to each cluster is shown in Fig. 3, A–C.

Discussion

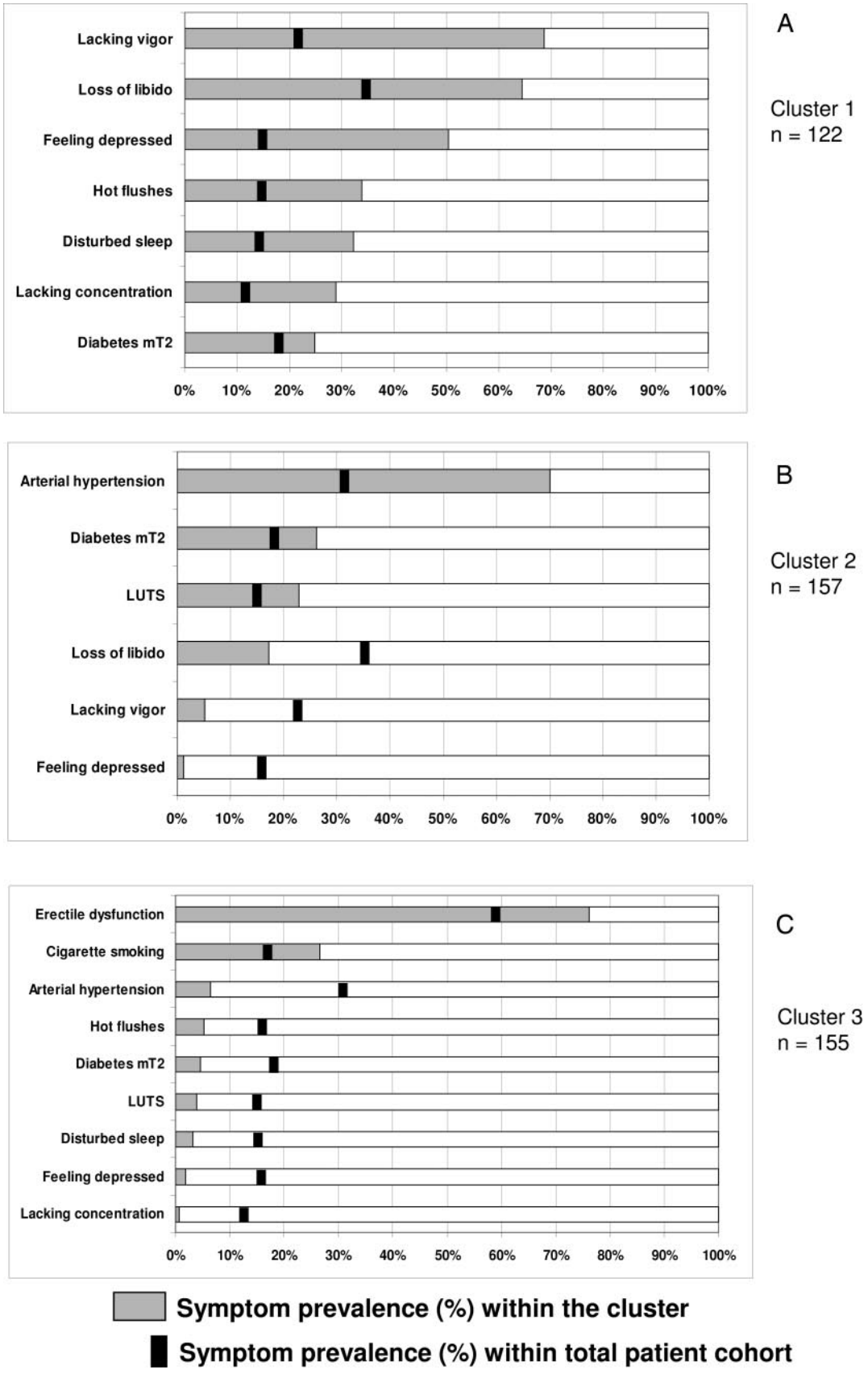
These data provide no evidence that a uniform structure of testosterone concentrations and complaints exists within the cohort of elderly male patients; rather, the practitioner encounters distinct psychosomatic, endocrinological, and

TABLE 4. ROC for TT concentrations and complaints in 434 elderly male patients

Symptom	TT level (nmol/liter) below which prevalence of symptom increases[a]	Sensitivity at threshold TT level (%)	Specificity at threshold TT level (%)	TT level (nmol/liter) at 90% specificity	TT level (nmol/liter) at 95% specificity	Details of ROC model		
						AUC	95% CI for AUC	*P*
Loss of libido	15	82	41	7.8	5.9	0.70	0.65–0.75	<0.0001
Loss of vigor	15	88	38	7.1	4.7	0.70	0.64–0.76	<0.0001
Obesity (BMI > 30 kg/m^2)	12	68	60	6.9	4.2	0.66	0.60–0.72	<0.0001
Feeling depressed	10	54	69	7.0	4.7	0.64	0.57–0.72	<0.0001
Disturbed sleep	10	46	78	6.8	3.6	0.58	0.50–0.66	0.06
Lacking concentration	10	54	70	6.9	3.7	0.64	0.55–0.72	0.002
Diabetes mellitus type 2								
All patients	10	65	73	7.3	4.5	0.68	0.61–0.75	<0.0001
Nonobese patients	10	54	75	7.2	3.8	0.62	0.51–0.73	0.02
Hot flushes	8	35	83	7.0	4.7	0.64	0.57–0-72	<0.0001
Erectile dysfunction	8	24	86	7.8	6.3	0.56	0.51–0.61	0.04

In agreement with the results presented in Fig. 2 and Table 4, ROC models demonstrate the association of TT to complaints of elderly men, *e.g.* loss of libido. However, this means that the symptom of loss of libido will not be found in every patient with TT levels less than 15 nmol/liter and TT substitution therapy will not be successful in restoring libido in every man with TT levels less than 15 nmol/liter. The specificity of the ROC model at the TT level presenting the threshold of increased prevalence of the respective symptom indicates how strong the association of TT to the symptom is, *e.g.* although the prevalence of loss of libido increases below TT levels less than 15 nmol/liter (see Fig. 1 and Table 3), only 41% of all men with TT levels less than 15 nmol/liter have a loss of libido (whereas 90% of all men with TT levels below 7.8 nmol/liter and 95% of all men with TT levels below 5.9 nmol/liter have a loss of libido). The sensitivity indicates that, in this example, 82% of all men presenting with a loss of libido will have a TT level less than 15 nmol/liter. AUC, Area under the curve, which should be significantly different from 0.5 and ideally 1.0; CI, confidence interval.

[a] According to stepwise backward binomial regression and Somer's D models.



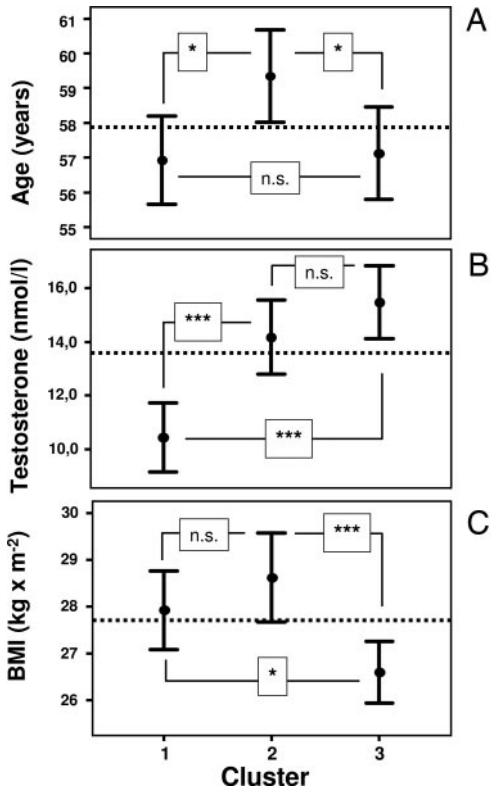


FIG. 3. A–C, For each cluster, the mean and 95% confidence intervals for the continuous parameters TT, BMI, and age were calculated and related to the total cohort (the *horizontal line* indicates the mean of all patients). When a displayed confidence interval does not cross the *horizontal line*, it indicates with a statistical significance of at least $P < 0.05$ that the cluster is different from the total cohort in this regard. Results are shown in A-C: the patients in cluster 1 had TT concentrations significantly lower than the total cohort (B), patients in cluster 2 were older (A) and had a marginally higher BMI than the total group (C), and the men of cluster 3 were slimmer and had TT levels higher than the total group (B and C). Differences between the clusters concerning age, TT concentrations, and BMI were calculated by ANOVA models, followed by *post hoc* tests. The results are given as *asterisks* (*, $P < 0.05$; ***, $P < 0.001$; n.s., not significant).

sexually impaired subgroups. These patients exhibit metabolic parameters differentially; simultaneously, various strata of serum TT concentrations are associated with specific symptoms. In addition, a multiple influence of metabolic, psychosomatic, and endocrine parameters on symptoms exists, as demonstrated by Table 3 and Figs. 2 and 3.

Erectile dysfunction may serve as an example of a composite dysfunctionality in which arterial endothelial function, testosterone concentrations, and psychological status play pivotal roles (13, 14). Our results corroborate such findings, demonstrating significant influence of vessel damaging parameters (cigarette smoking, high blood pressure, diabetes mellitus), low testosterone concentrations, and mood dysbalances (depression, disturbed sleep) on the prevalence of erectile dysfunction (Table 3).

The suspicion of LOH and, certainly, the decision for pharmacological intervention should be approached with appropriate reserve, taking the specific increment of symptom prevalence in relation to testosterone levels into account. Numerous controversies concerning TT levels and symptoms of LOH most likely originate in the application of uniform thresholds to hypogonadism (2–4, 15–17). This is reflected in the significant variation among European countries applying thresholds for hypogonadism ranging from 7.5 to 12.0 nmol/liter (18). Physicians in different countries may have different approaches to the symptoms of hypogonadism and may attribute varying values to single symptoms in regard to possible treatment. It has recently been demonstrated by application of an artificial neural network that the clinical manifestation of hypogonadism is multifactorial and that proper assessment should comprise somatic and psychological aspects (19).

First hints that symptom-specific associations of nonlinear nature might exist in regard to androgen levels are given by dose-titrating studies (5, 6) as well as observations in Klinefelter patients, in whom testosterone concentrations relate nonlinearly to androgen-dependent features (7, 20). Our study suggests that some symptoms of LOH might start at higher concentrations of androgens than other complaints (Fig. 1). Individual and symptom-oriented treatment might apply in the future if this assumption of variable hormone-symptom-strata is correct. Attempts to apply symptom-specific thresholds of androgen levels have already been made in the MMAS, a general population-based study, corroborating our results found in patients (21, 22).

Nevertheless, the ROC analyses detailed in Table 4 indicate that it is not warranted to initiate androgen substitution in men, with, *e.g.* loss of libido and TT concentrations less than 15 nmol/liter, without further consideration of the individual case. Although, in this example, the prevalence of loss of libido starts to increase below TT concentrations of 15 nmol/liter, only 41% of all men with TT levels below this threshold have a loss of libido. That means, in an individual patient, loss of libido and a testosterone concentration of, *e.g.* 13 nmol/liter, might be coincidental. The lower the testosterone level is in a man with loss of libido, the less likely is such a coincidence (see specificity columns of Table 4). Especially for such borderline cases, we recommend discussing treatment attempts with the patient individually, taking contraindications and side effects of testosterone therapy into account (3).

FIG. 2. A–C, Results of the cluster analysis resulting in three clusters of similar size (see n of patients). Symptoms characterizing the specific clusters are given. Note that a significant over- as well as underrepresentation of a complaint can contribute to such a description. Significance was accepted when the log10-likelihood was greater than 1.8 after correction according to Bonferroni (see *Appendix* in supplemental data). Cluster 1 represents a subcohort of patients with predominantly psychosomatic complaints (A). Cluster 2 consists of men with metabolic disorders and an especially low prevalence of psychological discomfort (B). Cluster 3 summarizes a patient group characterized by overrepresentation of erectile dysfunction as well as cigarette smoking and a simultaneously very low prevalence of other complaints. Note that this does not mean that patients in clusters 1 and 2 did not, *e.g.* present with erectile dysfunction. Rather, erectile dysfunction was present in some of these men but not to an extent significantly different from the overall prevalence in all patients; thus, it was not included in these clusters. Also note that the nature of each cluster constellation as a total is descriptive, although each symptom prevalence within the cluster is significantly different from the total cohort.

However, because the results pertain to a specific population of patients who consulted for various complaints at an andrological unit, the findings are not representative for the general population. It is also possible that patients consulting in a different setting (*e.g.* a nonandrological internal medicine unit or urological practice) exhibit a different profile. Thus, a certain specificity of the study population exists.

Obviously physicians also encounter patients with limited complaint profiles restricted to disturbances of sexual function. These men especially (cluster 3) will not report symptoms otherwise associated with advancing age but present in relatively good health with normal BMI and testosterone levels above the average of andrological patients, such as found within the general aging male population (23). It is important to acknowledge these men as persons deserving help. The overrepresentation of erectile dysfunction and cigarette smoking as possible indicators of a generally affected arterial endothelium should especially induce further cardiovascular assessments. Such patients are at increased cardiovascular risk (24).

A key question in regard to this investigation is the relation of our patients to the large population-based studies. Men assessed in the MMAS as well as the Australian MATeS exhibit the same age profile and BMI as our patients. However, patients show a higher prevalence of erectile dysfunction, high blood pressure, and diabetes mellitus type 2 as well as depressive moods in comparison with population-based cohorts (1, 23, 25).

Hormone values were not assessed in the Australian telephone survey, but androgen levels of the MMAS cohort (23) are markedly higher than in our total cohort of patients (with the exception of the men of cluster 3; see above), suggesting that androgen levels play a major role in pathogenesis and aggravation of symptoms, finally leading patients to consult a physician. Overall, the data suggest that the patients described here are representative of the older male in an industrialized Western country in terms of general appearance but are markedly different from the general population concerning prevalence and perception of symptoms. This observation is of paramount value because it underlines the novelty and importance of this investigation as well as its general relevance.

Another important point concerns the usefulness of symptomatological questionnaires. Such tools are probably not sufficiently predictive of prevailing testosterone concentrations in elderly men, as a major review on this topic convincingly demonstrated: the widespread use of such questionnaires as screening tools should be discouraged because of low specificity and sensitivity (2).

The items generally and consistently assessed in this study by the treating physician are fixed in paper and electronic form. The nature of these assessments is complementary to the structured interview form of the MATeS, which describes the prevalence of self-reported reproductive health disorders as well as related concerns and health behavior among middle-aged and older Australian men (1). Such an interview-related approach seems to reflect the essential and actual patient-physician interaction that is encountered on a daily basis better than a questionnaire.

Moreover questionnaires are ill suited to search for low testosterone levels (2). A certain absurdity lies in the application of standardized question-based tools to detect low testosterone levels: these can be measured in a laboratory. Treatment of patients, however, must be first directed by symptoms and should follow accepted recommendations: for older men, short-acting testosterone preparations are preferable (3).

Our study demonstrates that the androgen deficit does not exist *per se* but that symptoms accumulate gradually with decreasing testosterone levels (Fig. 1). In this regard, androgen action may be, as suggested by other studies, modified by a functional polymorphism of the androgen receptor gene, the CAG repeat polymorphism. Relevant findings have been demonstrated concerning symptoms of depression in older men (14, 25) as well as physical traits and social characteristics of Klinefelter patients (19).

In addition, patients receiving testosterone substitution therapy by the long-acting regimen of sc implants corroborate the observation that the symptomatology of a developing androgen deficit occurs gradually. Patients start to feel the need for a renewed implantation by lacking vigor and libido, correspondingly to our cross-sectional cohort of elderly men. Interindividual differences of testosterone concentrations in regard to symptoms were applicable also in these men, putatively pointing to the above-named genetically modified androgen activity (26).

In conclusion, physicians have to be aware that testosterone plays a significant but not omnipresent role in older male patients and that replacement options should be based firstly on symptoms and secondly on hormone concentrations, which should be evaluated on a symptom-specific basis. Consequently, physicians treating older men should take a broad holistic view (see multiple factors of influence on symptoms in Table 3), facing problems related to internal medicine, psychology, and urology. However, we strongly discourage misuse of these concepts to treat men indiscriminately who present with vague symptoms that are not at all testosterone deficient.

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