Blood Testosterone Threshold for Androgen Deficiency Symptoms

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There are few systematic studies of the relationship between blood testosterone concentrations and the symptoms of overt androgen deficiency. Because most testosterone preparations are relatively short-term, the rapid changes in blood testosterone concentrations they cause make it difficult to define any testosterone threshold. By contrast, subdermal testosterone implants provide stable blood testosterone concentrations over days to weeks, while gradually declining to baseline over 5–7 months. Hence, this provides an opportunity to define a blood testosterone threshold for androgen deficiency symptoms by observing androgen-deficient men as their familiar androgen deficiency symptoms return as testosterone pellets slowly dissolve. Among 52 androgen-deficient men who underwent 260 implantations over 5 yr, at the time of return of androgen deficiency symptoms the blood total and free testosterone concentrations were highly reproducible within individuals (F = 0.8, *P* = 0.49 and F = 1.4, 0.24, respectively) but varied markedly between men (F = 167 and F = 138, both *P* < 0.001), indicating that each person had a consistent testosterone threshold for androgen deficiency symptoms that differed markedly between individuals. The most reported symptoms of androgen deficiency were lack of energy, lack of motivation, and reduced libido. The symptomatic threshold was significantly lower in men with secondary hypogonadism compared with men with primary or mixed hypogonadism (total, 9.7 ± 0.5 nmol/liter *vs.* 11.7 ± 0.4 nmol/liter and 10.2 ± 0.3 nmol/liter, *P* = 0.006; free, 146 ± 10 pmol/liter *vs.* 165 ± 6 pmol/liter and 211 ± 18 pmol/liter, *P* = 0.002) but was not affected by the underlying cause of hypogonadism or by specific symptoms of any severity. Despite a wide range in individual thresholds for androgen deficiency symptoms, the mean blood testosterone threshold corresponded to the lower end of the eugonadal reference range for young men. The implications of these observations for the development of more specific quality-of-life measures, as well as for other potential androgen deficiency states such as chronic diseases and aging, remain to be determined. (*J Clin Endocrinol Metab* 89: 3813–3817, 2004)

THE EFFECTS OF androgen deficiency and replacement on objective endpoints, notably bone (1, 2) and muscle (3–7), are well known and increasingly studied. Yet, whereas symptoms of androgen deficiency are discussed in textbooks and form the basis for practical clinical monitoring of androgen replacement therapy (8), there is a paucity of systematic studies of the symptoms of, and symptomatic threshold for, androgen deficiency. The subjective effects of androgen deficiency and replacement have generally been studied as objectively recorded measures of mood, behavior and cognitive responses (9–11), but symptoms themselves are more difficult to study objectively. As a result, subjective effects of androgens have received most attention in the psychology literature, where empirical studies are, however, largely observational and restricted to eugonadal men limiting the salience of any inferences regarding relationships of blood testosterone concentrations to symptoms of overt androgen deficiency.

A major limitation of interventional clinical research on androgen deficiency symptoms is that the available relatively short-term testosterone preparations produce swings in blood testosterone levels over days to weeks, which make it difficult or impossible to distinguish reliably symptom resolution and reappearance from pharmacological effects. The present study overcomes this limitation by using a long-acting depot testosterone preparation, which maintains stable blood testosterone concentrations over days to weeks but, as the biodegradable implants erode, allows them to decline slowly back to baseline over 5–7 months (12–15). Because the treated men return for blood testosterone measurement and reimplantation when their familiar androgen deficiency symptoms return, this allows a prospective evaluation of the relationships between individual androgen deficiency symptoms and the blood testosterone concentrations that accompany them.

Subjects and Methods

Patients

We reviewed prospectively collected data from patients having regular androgen replacement therapy with a standard dose (four 200-mg pellets) of subdermal testosterone implants for androgen deficiency as described previously (12, 13, 15). To standardize the study population and data collection for this study, we reviewed data from three recent randomized clinical trials over the last 5 yr (15–17). Each study was approved by the Central Sydney Area Health Service Human Research Ethics Committee, and all patients provided written informed consent. Although all testosterone products are available at low cost, subdermal testosterone pellet implants are popular because of their convenience, longer intertreatment interval, and stable pharmacokinetics (18, 19). Patients were classified as having primary, secondary, or mixed hypogonadism. The latter were survivors of childhood cancer who have both testicular and pituitary dysfunction as a long-term consequence of previous cancer treatment regimes, including cranial irradiation and combination cytotoxic therapy.

Procedures

Implantation procedure. Testosterone pellet implantation procedures are booked throughout the week. At visits, men have a blood sample drawn

to measure blood LH, FSH, SHBG, and total and free testosterone concentrations before subdermal implantation. From their first implantation procedure, men are advised that the duration of action is approximately 6 months but varies from 4–8 months between individuals. They are advised to contact the clinic for an appointment when they become aware of the return of their usual androgen deficiency symptoms. The clinic staff and policies were unchanged throughout the study period.

Symptom survey. A survey of consecutive androgen-deficient men was undertaken over a period of approximately 12 months. Men were asked to list and to describe onset, character, and severity of their symptoms of androgen deficiency. Respondents rated how problematic were their symptoms on a scale of 1 to 4 (1 being worst, and 4 being least obvious symptom). Open-ended comments were encouraged if their symptoms were not sufficiently covered. The questionnaire also determined how long the men waited between first noticing their symptoms and making a booking for pellet implantation, how long they waited for a clinic booking, and how long it took until they felt "100% again" after implantation.

Data analysis

Data were described as mean and SEM unless stated otherwise. Descriptive statistical analysis, including *t* tests, repeated-measures, and one-way ANOVA, and correlation were performed using the Statistical Package for Social Scientists (SPSS, Inc.). Exact *P* values were reported, with a value less than 0.05 being considered significant. Baseline blood hormone concentrations refer to levels measured in the blood sample taken on the day of, but before, testosterone reimplantation. Body mass index (kg/m^2) and surface area [m^2, using the Gehan-George formula (20)] were calculated from height and weight data.

Assays

Hormone assays were performed in a single laboratory as described previously (21–23). Plasma LH and FSH (Axsym, Abbott Laboratories, IL), SHBG, and total testosterone (Immulyte, Los Angeles, Ca) were measured by commercial immunoassays, with all CVs less than 8% except for testosterone (8–13%). Free testosterone was estimated by an in-house centrifugal ultrafiltration assay (24) using Centrifree columns (Millipore, Billerica, MA) and tritiated testosterone to determine the proportion of unbound testosterone, from which the actual free testosterone is calculated, with a CV of 10–12%.

Results

Of 104 men who responded to the survey, 52 identified that they prebooked their implantations to coincide with the time when, from experience, they expected return of symptoms rather than waiting for them to recur. They were therefore considered not eligible for inclusion further into the present study analyzing the relationship of blood testosterone to concomitant symptoms. The remaining 52 men, who wait for their symptoms to recur, form the cohort for the present study. Over 5 yr of data collection, they underwent 260 implantations of standard testosterone dose (four 200-mg pellets) for which necessary data (trough blood hormone levels, dates for a complete reimplantation cycle) were available for analysis.

The underlying cause of hypogonadism was primary in 26 of 52 (50%), secondary in 22 of 52 (42%), and mixed in the remaining 4 of 52 (8%). Although the physical features of men with primary and secondary hypogonadism were well matched (Table 1), the group with mixed hypogonadism were significantly younger, shorter, and lighter and had lower BSA, but did not differ significantly in BMI (*P* = 0.66) from the others. There was no significant difference (*P* = 0.47) among groups in the mean number of days between reimplantation procedures (Table 1). From the actual onset of symptoms, men took 8.1 ± 0.9 d to request an appointment, 7.7 ± 0.5 d to undergo reimplantation, and 5.5 ± 0.5 d to feel 100% again.

Considering the 33 men with at least four consecutive procedures available for analysis, repeated-measures ANOVA showed no significant difference in total testosterone (*P* = 0.49) or free testosterone (*P* = 0.24) within subjects. However, there were highly significant differences for both total (*P* = <0.001) and free testosterone (*P* < 0.001) between men (Table 2). A plot of blood total testosterone for six consecutive implant cycles from a representative sample of 25 men is illustrated in Fig. 1. Analogous findings were observed for the blood LH and FSH among the 14 men with primary (hypergonadotrophic) hypogonadism for whom such analyses were meaningful. There were highly significant between-subject but no within-subject differences in LH or FSH concentrations (Table 2).

The blood testosterone levels at the day of return for reimplantation were lower among men with secondary hypo-

TABLE 2. Reimplantation day hormone data

Hormone	n	Mean	Between-subject effects	Within-subject effects
Total testosterone (nmol/liter)	33	9.2	SD = 4.4 $F_{1,32}$ = 167 P < 0.001	SD = 2.0 $F_{3,96}$ = 0.81 P = 0.49
Free testosterone (pmol/liter)	32	149	SD = 91 $F_{1,28}$ = 138 P < 0.001	SD = 41 $F_{3,84}$ = 1.4 P = 0.24
LH (IU/liter)	14	16.2	SD = 18.1 $F_{1,13}$ = 23 P < 0.001	SD = 6.2 $F_{3,39}$ = 2.0 P = 0.12
FSH (IU/liter)	13	27.0	SD = 28.3 $F_{1,12}$ = 23 P < 0.001	SD = 8.9 $F_{3,36}$ = 1.1 P = 0.35

Data from 33 men with at least four successive testosterone pellet implantation cycles including 14 with primary (hypergonadotropic) hypogonadism for LH and FSH evaluations. SD represents the between- or within-subject SD for the hormone variable. $F_{r,c}$ represent the F test for r and c degree of freedom from the ANOVA with the *P* value from the F distribution indicating the statistical significance of that factor. To convert total testosterone concentration to ng/dl or free testosterone to pg/dl, multiply the values by 28.8.

TABLE 1. Characteristics of study participants based on type of hypogonadism

	Primary (n = 26)	Secondary (n = 22)	Mixed (n = 4)	P
Age (yr)	45.5 ± 2.3	46.2 ± 3.4	26.8 ± 1.1	<0.001
Height (cm)	181.8 ± 0.6	178.2 ± 0.7	168.5 ± 1.7	<0.001
Weight (kg)	98.1 ± 9.3	88.9 ± 1.5	73 ± 3.4	<0.001
Body mass index (kg/m^2)	29 ± 2.5	27 ± 0.4	25 ± 0.7	0.66
Body surface area (m^2)	2.10 ± 0.02	2.08 ± 0.01	1.85 ± 0.02	<0.001
Days since last implant	171 ± 3	175 ± 3	178 ± 6	0.47

Data expressed as mean ± SEM.

gonadism with lower total and free testosterone than among men with primary or mixed hypogonadism (Table 3).

The most reported symptom of androgen deficiency (Table 4) was lack of energy (46 of 52, 88%), with most reporting this symptom as moderate or very problematic (36 of 46, 78%). The second most reported symptom was diminished libido (32 of 52, 62%), followed by loss of motivation (29 of 52; 56%), cantankerous mood (25 of 52; 48%), sleepiness after lunch (23 of 52; 44%), and inability to concentrate (22 of 52; 42%), all relatively common. Hot flushes (16 of 52; 31%), slowed beard growth (15 of 52; 29%), and muscular aches (8 of 52; 15%) were the least reported symptoms. There was no significant difference between reported symptoms in the blood total testosterone concentrations on reimplantation day (data not shown). There was no significant relationship between the type of symptom and either how long it took for the patient to schedule an appointment ($P = 0.34$), or how many days it took them to feel 100% again after treatment ($P = 0.72$).
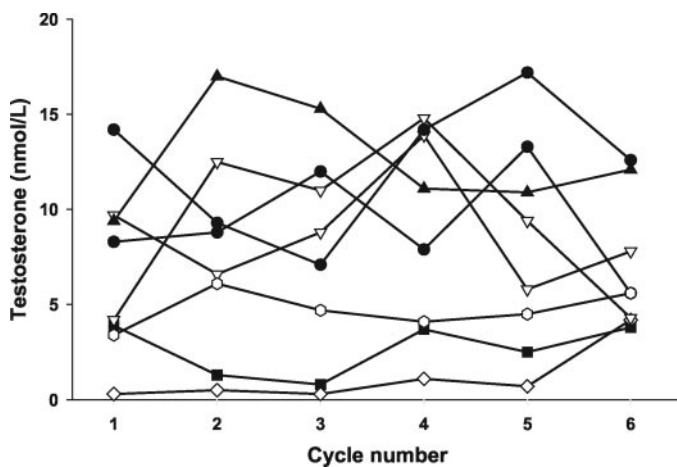

FIG. 1. Plot of blood total testosterone at time of reimplantation for a sample of eight representative androgen-deficient men. Each set of a symbol and connecting line represents one individual over six consecutive implant cycles.

Discussion

The practical aim of androgen replacement therapy is to maintain blood testosterone concentrations within the eugonadal reference range so as to rectify the sequelae of androgen deficiency (8). Many testosterone products are now available with widely varying pharmacological features capable of providing effective androgen replacement therapy within the limitations of their pharmacological characteristics. Virtually all testosterone products so far widely available are short-term, involving daily oral or dermal administration or, at most, 2- to 3-wk intervals between treatments. As a result, these products produce blood testosterone concentrations that vary, often including supraphysiological and/or subphysiological within relatively short periods of time. In fact, by rapidly rectifying the patient's androgen deficiency symptoms, the relationships between blood testosterone levels and more slowly changing symptoms may be overwhelmed and obscured. This has made analytical study of the relationship of symptoms to blood testosterone concentrations particularly difficult. The present study exploits the opportunity provided by a cohort of androgen-deficient men regularly using a depot testosterone product where the relationship between the gradual onset (over weeks to months) of familiar androgen deficiency symptoms and the stable blood testosterone concentrations accompanying them can be discerned.

A key finding of this study is that the threshold for androgen deficiency symptoms occurs at highly reproducible blood testosterone concentrations in hypogonadal men. That is, men reach a distinctively individual trigger level for androgen deficiency symptoms and seek retreatment at similar blood testosterone concentrations each time. Yet, this trigger level differs widely between men. This replicability reinforces the notion of a measurable threshold at which androgen deficiency symptoms occur but recognizes that this threshold differs between individuals. Although this threshold varies from very low to values above the lower limit of

TABLE 3. Reimplantation day hormone values according to type of hypogonadism

Hormone	Reference range	Primary (n = 26)	Secondary (n = 22)	Mixed (n = 4)	P
Total testosterone	11–35 (nmol/liter)	11.7 ± 0.4	9.7 ± 0.5	10.2 ± 0.3	0.006
Free testosterone	170–510 (pmol/liter)	165 ± 6	146 ± 10	211 ± 18	0.002
LH	1.3–12.9 (IU/liter)	13.6 ± 0.9	1.4 ± 0.3	3.3 ± 0.5	<0.001
FSH	0.9–15.0 (IU/liter)	28.1 ± 1.7	2.4 ± 0.7	6.8 ± 1.1	<0.001
SHBG	10.0–80.0 (nmol/liter)	30.8 ± 0.9	27.9 ± 1.5	13.9 ± 1.5	<0.001

Data expressed as mean ± SEM. To convert total testosterone concentration to ng/dl or free testosterone to pg/dl, multiply the values by 28.8.

TABLE 4. Spectrum and severity of androgen deficiency symptoms

Symptom	Not a symptom (%)	Minimally problematic (%)	Mildly problematic (%)	Moderately problematic (%)	Very problematic (%)
Loss of energy	6 (12)	3 (6)	7 (13)	17 (33)	19 (36)
Diminished libido	20 (38)	8 (15)	6 (12)	10 (20)	8 (15)
Lack of motivation	23 (44)	3 (6)	6 (12)	12 (23)	8 (15)
Cantankerous mood	27 (52)	2 (4)	2 (4)	10 (20)	11 (20)
Sleepy after lunch	29 (56)	3 (6)	3 (6)	5 (10)	12 (23)
Inability to concentrate	30 (58)	7 (13)	7 (13)	4 (8)	4 (8)
Hot flushes	36 (70)	6 (12)	4 (8)	2 (4)	4 (8)
Slow beard growth	37 (71)	6 (40)	3 (20)	4 (27)	2 (13)
Muscular aches	44 (84)	0	2 (4)	0	6 (12)

the eugonadal reference range, on average it approximates the lower limit of the eugonadal reference range for young men. The determinants of this symptomatic threshold are unknown but presumably include genetic polymorphisms that influence androgen sensitivity (25), although the magnitude of this genetic determination is uncertain (26). The impact of acquired chronic disease and aging on the threshold for androgen deficiency symptoms remains to be determined. To standardize the study, only men having a single testosterone dose implanted were included. A future study using different doses might provide useful independent confirmation of the specific thresholds identified in this study or whether these depend at all on the ambient blood testosterone concentrations prevailing in the previous few months.

An important consideration for interpreting the present findings is whether the blood testosterone concentrations on the day of reimplantation accurately reflect those when these men first experience return of their symptoms. To refine our analysis, we excluded the 50% of androgen-deficient men who no longer rely on return of symptoms that are so predictable that they book reimplantation ahead. The hormonal replacement regimen provided requires men to contact the clinic, without reminders, when they notice the return of their typical androgen deficiency symptoms. The delay in the men making contact (~8 d) and in making a booking for implantation (~8 d) are minimal compared with the overall time course (~6 months). Hence, whereas these minor delays add time (~16 d) to the apparent duration of an implant cycle, the actual thresholds must be slightly higher, although the relatively short delay relative to the slow rate of decline in blood testosterone over months (12, 14, 15) means the magnitude of this bias is likely to be small (<1 nmol/liter). However, this is unlikely to influence the effects of variables such as type of hypogonadism or underlying disease on an implant treatment cycle. This study is a reasonably representative sample of men with genuine androgen deficiency due to hypothalamo-pituitary testicular disease but excludes men with so-called late-onset hypogonadism (also known as andropause or male menopause), where androgen deficiency is contentious (27, 28). The small subgroup of men with mixed hypogonadism were younger, shorter, and leaner than those with primary or secondary hypogonadism, presumably reflecting earlier diagnosis of androgen deficiency during ongoing surveillance following childhood cancer, with their shorter stature and lower weight being long-term side-effects of their cancer treatments.

The present findings provide support for the common clinical practice of monitoring the adequacy of androgen replacement therapy by how well the presenting symptoms of androgen deficiency are rectified by the treatment. They also support the notion that each person has a subset of key androgen deficiency symptoms, although these differ between men. Similar insights have long been discussed anecdotally among experienced clinicians, but the present study is the first to provide objective verification for this concept. The present findings imply that, whereas certain symptoms occur commonly among androgen-deficient men, none are specific or sufficiently common to make it likely that any set of symptoms would be diagnostically valid when screening men without well-defined

androgen deficiency (29–32). This skeptical prediction is supported by independent evaluation (33).

The present study also provides some additional insight into the possible significance of androgen deficiency as a component of the effects of chronic illness and male aging (34, 35). Although lowering of testosterone is a frequent nonspecific consequence of chronic disease and aging, it remains unproven and contentious whether such mild reductions in testosterone have any therapeutic or clinical significance (27, 28). Our findings suggest that, if androgen deficiency symptoms do contribute to the pathogenesis of chronic disease and/or aging, they may occur in only some men with only modest reductions of testosterone, assuming the effects of chronic disease or illness do not also correspondingly lower the symptomatic threshold for androgens.

The concept of a threshold for androgen deficiency symptoms still lacks much empirical support. A variety of studies have suggested the threshold for androgen effects on male sexual function, primarily libido, are evident at very low blood testosterone concentrations (36–40). These studies were, however, not able to define explicitly such a threshold. Conversely, muscle appears to exhibit linear dose-response relationship to testosterone from below to above the eugonadal reference range for blood testosterone concentrations (41). Whether linear dose-response or threshold models apply to other androgen-sensitive tissues, such as bone and prostate, psychosexual and the cardiovascular effects remain to be determined.

The blood testosterone concentrations on the day of reimplantation differed between type of hypogonadism but not between different underlying diseases or according to specific symptoms or their severity. In particular, men with gonadotrophin deficiency had lower blood testosterone concentrations than men with primary or mixed hypogonadism. As the number of days, because the last implantation did not differ, this is unlikely to be simply explained by men with secondary hypogonadism better tolerating lower blood testosterone concentrations. Rather, the gonadotrophin-deficient men must absorb subdermal testosterone less completely or metabolize circulating testosterone faster. Because blood SHBG concentrations did not differ, whereas SHBG concentration is the major known determinant of whole-body testosterone clearance rate (42), lower absorption of subdermal testosterone seems more likely. Similar findings of differences between primary and secondary hypogonadism in psychosexual responses to testosterone replacement have been reported previously (43). Whether habitually lower testosterone concentrations have wider implications for men with secondary hypogonadism is not clear, but it is notable that men with pituitary insufficiency are reported to be more likely to suffer long-term deficits in bone (44).

The present study therefore identifies blood testosterone thresholds for androgen deficiency symptoms that are highly consistent within a person but differ between people and between men with primary and secondary hypogonadism but not according to specific symptoms or their severity. These findings may assist further studies in creating improved disease-specific quality of life measures and analysis of whether androgen deficiency contributes to the pathogenesis of chronic nongonadal disease and male aging.

Acknowledgments

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