# Deficient testosterone levels in men above 45 years with major depressive disorder – an age-matched case control study

**A M Dikobe,** MB ChB, MMed (Psych)
**C W van Staden,** MB ChB, MMed (Psych), MD, FCPsych, FTCL, UPLM
*Department of Psychiatry, University of Pretoria*

**S Reif,** MB ChB, MMed (Urol), FCS (Urol)
*Department of Urology, University of Pretoria*

**M Bornman,** MB ChB, MD, DSc, PrSciNat
*Department of Physiology, University of Pretoria*

*Background.* Symptoms of partial androgen deficiency in ageing men (PADAM) overlap considerably with those of major depressive disorder. The relationship between these conditions is complicated by the usual age-related decline in serum testosterone concentrations.

*Objectives.* To test the hypothesis that depressed men above 45 years of age have lower serum testosterone concentrations than age-matched controls.

*Method.* Serum testosterone fractions of 20 men above the age of 45 years suffering from a major depressive disorder were compared with those of 20 healthy men. An age-matched controlled design was used to account for the usual age-related decline in serum testosterone concentrations.

*Results.* Testosterone concentrations of men suffering from a major depressive disorder were statistically significantly lower than those of an age-matched control group without depression.

*Conclusion.* The role of testosterone deficiency in depressed men needs to be examined further in order for appropriate treatment options to be developed.

The symptoms of partial androgen deficiency in ageing men (PADAM) overlap considerably with those of major depressive disorder. Symptoms include a reduction in libido, lack of energy, decrease in strength and/or endurance, decreased enjoyment of life, feeling sad and/or grumpy, weak erections, reduced ability to work and play sports, and changes in sleep patterns.[1,2] However the relationship between androgen deficiency and depressive disorders is complicated by the progressive age-related decline in male hypothalamic-pituitary-gonadal (HPG) function, including a decline in serum testosterone concentrations through both central (pituitary) and peripheral (testicular) mechanisms.[3] Previous studies of androgen deficiency in men with depressive disorders have not accounted in a controlled study design for this progressive physiological decline in testosterone concentrations.

## Objective

The study compared serum testosterone concentrations and the bio-available fraction in men older than 45 years suffering from major depressive disorder, and in healthy age-matched controls. Our hypothesis was that the depressed men would have lower serum testosterone concentrations than the age-matched control group.

## Material and methods

### Subjects

Twenty inpatients and outpatients were recruited prospectively from the clinical units of Weskoppies Psychiatric Hospital and 1 Military Hospital in Tshwane (Pretoria). All participants gave written informed consent to participation, and ethical approval was obtained from the Faculty of Health Sciences Research Ethics Committee of the University of Pretoria before commencement of the study.

The depressed group consisted of male patients above 45 years of age, for Gooren[4] demonstrated a gradual decline in HPG functioning after 45 years of age. This group of patients met the diagnostic criteria for 'major depressive disorder with active symptoms' in the *Diagnostic and Statistical Manual of Mental Disorder* as defined (*DSM-IV*). The original diagnosis had been made by study-independent psychiatrists and was confirmed by one of us (AMD) based on medical records and clinical assessments. In addition, patients had to score a minimum of 25 on the Hamilton Depression Rating Scale (HAM-D)[5] for inclusion in the study, which meant that they suffered from at least a moderate degree of a major depressive episode. Only patients capable of giving informed consent to study procedures were included.

Exclusion criteria were: (*i*) night-shift workers; (*ii*) patients suffering from clinically significant co-morbid psychiatric pathology or from abuse of/dependence on alcohol or other substances according

to *DSM-IV* criteria; or (*iii*) patients with a clinically significant co-morbid general medical condition, including past or present prostate cancer, testicular disease, other endocrinological conditions like thyroid disease and diabetes, or those who had had an orchidectomy.

The age-matched control group were recruited from the same geographical area and met the same inclusion and exclusion criteria, except that they had not suffered from a past or present mood or other psychiatric disorder and scored zero on all the items of the measures of depression (see below). No differences between the depressed and control groups were apparent in their socio-economic circumstances and racial profiles. The body mass index of all subjects was less than 25.

## Measures

The HAM-D and the Montgomery-Asberg Depression Rating Scale (MADRS)[6] were used to measure the severity of depressive features. Although these observer-rated instruments measure the same thing in general, we used both in order to increase the validity of our measurements as some of their respective items used to gauge severity are not shared.

Total serum testosterone, bio-available testosterone and the calculated free testosterone concentrations were measured quantitatively according to standardised laboratory tests, using inter-radio-immuno-assay variation coefficients.

Venous blood was collected from all subjects and controls. All blood was collected before 10h00 in the morning in order to avoid the effects of diurnal variation in serum testosterone concentrations.[7] It was centrifuged and frozen within 4 hours of being collected, and analysed within 3 months of being frozen.

## Statistical analysis

After the normality of all the data had been tested, the depressed group was compared with the control group using unpaired Student's *t*-tests, and a linear multiple regression analysis was performed on the data.

## Results

The mean age of all the subjects was 54.9 years (standard deviation (SD) 8.14 years). A cumulative frequency graph showed that the ages in the depressed and control group were well matched (Fig. 1). The mean scores of the depressed group were 29.35 (SD = 4.36) on the HAM-D, and 36.5 (SD = 6.13) on the MADRS. These scores correlated highly statistically significantly ($r = 0.6315$, $p = 0.0028$).
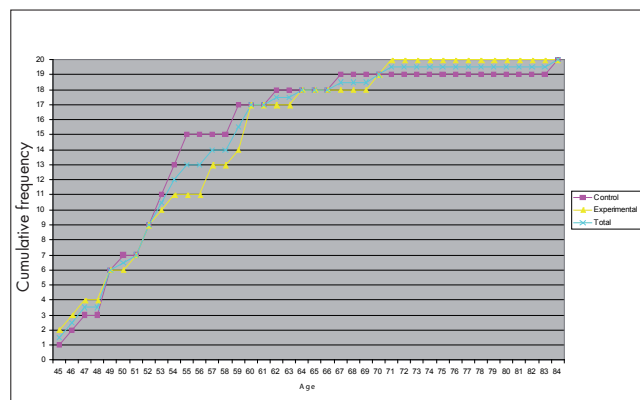


*Fig. 1. Cumulative age distribution.*

Table I shows the mean testosterone concentrations and the statistical comparison between the groups. The depressed and control groups differed highly statistically significantly for bio-available testosterone, and statistically significantly for the other testosterone fractions.

Among the depressed patients, no significant correlations were found between the testosterone fractions and the measures of severity of depression. However, there was a significant negative correlation between bio-available testosterone and free testosterone (but not total testosterone), and the ages of this group. These values were as follows: bio-available testosterone $r = -0.55$, $p = 0.01$; free testosterone $r = -0.52$, $p = 0.02$; and total testosterone $r = -0.12$, $p = 0.61$. In the control group, there was a significant negative correlation between available testosterone and age ($r = -0.46$, $p = 0.04$), but this was not so for total testosterone ($r = -0.28$, $p = 0.24$) and free testosterone ($r = -0.33$, $p = 0.15$).

## Discussion

The main finding of this study was that testosterone concentrations in men above the age of 45 years suffering from a major depressive disorder were statistically significantly lower than levels in an age-matched control group without depression. This finding was observed for total testosterone and for free testosterone concentrations, but more strikingly for bio-available testosterone concentrations.

### Strengths and limitations

The main strength of this study is that it was case controlled for age. As far as we can establish, it is the first study on the subject to do so. Our findings, like those of other studies,[8,9] support the importance of accounting for age. First, there was a significant negative correlation between bio-available testosterone and the ages of men in the depressed group and the control

**Table I. Mean testosterone concentrations compared by group**

|  | Depressed group | Control group | p-value | Difference between means and 95% confidence intervals |
| --- | --- | --- | --- | --- |
| Total testosterone (nmol/l) | 12.96 (± 4.24) | 17.33 (± 7.78) | 0.034* | 4.36 (0.3 - 8.38) |
| Bio-available testosterone (pmol/l) | 2.66 (± 1.70) | 4.17 (± 1.80) | 0.009** | 1.52 (0.4 - 2.63) |
| Free testosterone (pmol/l) | 257.8 (± 123.15) | 343.6 (± 132.86) | 0.041* | 85.80 (3.8 - 167.8) |

*Statistically significant.
**Statistically highly significant.

group respectively. The same applied to the free testosterone concentration and the ages of the depressed group. Second, no statistically significant correlations were found between the testosterone fractions and the measures of depression, meaning that studies that only examined these correlations without accounting for age might have resulted in a type II statistical error.

The strength of our findings, furthermore, resides in the selection of subjects, even though the sample size was relatively small. The study group all suffered from depression to at least a moderate degree of severity, whereas the control group did not have any current depressive features, nor did they have a present or past psychiatric disorder. Night-shift workers who may have altered diurnal variation in their testosterone circadian rhythm and patients suffering from endocrinological conditions, which may have confounded the results, were excluded from both groups. The control group, moreover, consisted of healthy volunteers rather than being from an ill population.

In addition to the progressive age-related decline in testosterone concentrations, the diurnal rhythm of testosterone secretion also wanes with age. Testosterone secretion is usually at its highest in the early morning and lowest (about 20% less than the peak value) in the late afternoon.[3] Our study attempted to reduce the influence of the usual diurnal variation of testosterone concentrations as a potential confounding variable, by obtaining blood samples from both groups before 10h00 in the morning. A difference in diurnal variation in testosterone concentrations between the depressed and control groups could nonetheless be the reason for the observed differences in testosterone concentrations between the groups. All the same, this would suggest that the difference in diurnal variation is related to the depressive illness.

This cross-sectional study does not provide insight as to whether lower testosterone concentration is a cause or consequence of depressive illness among men above 45 years of age. Longitudinal cohort and/or experimental studies would better serve such purposes.

## Ageing and serum testosterone concentrations

The decrease in testosterone concentrations in healthy ageing men is the result of combined testicular changes, altered neuroendocrine regulation of Leydig cell function and the independent increase of serum sex hormone binding globulin (SHBG) concentrations.[10] Mean serum total testosterone concentrations in the male population decrease by about 30% and bio-available testosterone decreases by about 50% from the age of 25 to 75 years.[11] Yet only about 7% of men in the 40 - 60-year age group have serum testosterone concentrations below the limit for young adults but the figure rises to 20% in the 60 - 80-year age group.[1]

This means that testosterone concentrations can fall significantly in an individual's lifetime while remaining within the normal reference range.[4] There is, moreover, a striking variability in serum testosterone concentrations in both young and elderly men. The clinical implication of this is that while below-normal testosterone concentrations may be indicative of androgen deficiency, concentrations within the normal range would not necessarily exclude it.

The steeper decline of the biologically active fractions of testosterone compared with total testosterone concentrations in the ageing male is the result of the age-related increase in SHBG-binding capacity.[12] Since only about 1 - 2% of the total testosterone concentration is not plasma-bound and thus biologically active, the biologically active fractions may be low even if the total testosterone concentrations are within normal ranges. The bio-available and free testosterone concentrations are therefore the important indicators of androgen deficiency. Previous studies that measured only the total testosterone concentration may therefore have missed critical findings on androgen deficiency in ageing depressed men. This point is supported by our results, which showed significance most strikingly for the bio-available fraction in the comparison between depressed men and the control group.

## Previous clinical studies

Clinical studies[13] have demonstrated HPG dysfunction among some men suffering from depressive disorders. A study[14] showed that elderly men between ages 60 and 82 years with dysthymic disorder had significantly lower total testosterone concentrations (mean total testosterone 11 nmol/l) than their counterparts with major depressive disorder (mean total testosterone 14.9 nmol/l) and those without depression (mean total testosterone 15.1 nmol/l). The majority of elderly men with dysthymic disorder had total testosterone concentrations in the hypogonadal range (i.e.: < 10.4 nmol/l).[14]

Preliminary data suggested that major depressive disorder in men with hypogonadism remits with testosterone replacement or augmentation in those cases where treatment with selective serotonin reuptake inhibitors is partially effective.[15] In HIV-infected men with hypogonadism, testosterone replacement was associated with improvement in mood, libido and energy level.[16] In a study of men between the ages of 20 and 60 years, testosterone replacement reversed the hypogonadic manifestations of an increase in body weight and adipose deposition, decreased haemopoiesis, facial hair growth and libido, and a low mood and decline in memory function.[17]

However, a double-blind, randomised clinical trial[3] of testosterone replacement versus placebo in 30 men with major depressive disorder and hypogonadism found that testosterone replacement was indistinguishable from placebo with regard to antidepressive efficacy. But in a number of randomised placebo-controlled studies[16,18,19] augmentation of antidepressants with testosterone seemed promising in patients with a partial response to antidepressants.

## Implications and future research

Particularly useful would be follow-up studies that develop a risk index; the risk of developing a depressive disorder may then be calculated based on age and testosterone concentrations. For those patients who already suffer from a major depressive disorder, more double-blind placebo-controlled studies are needed to investigate augmentation of antidepressant treatment with testosterone replacement among older men who do not respond or only partially respond to antidepressant treatment. Our study suggests that double-blind placebo-controlled studies would be even more helpful if they account for the age-related decline in testosterone concentrations, including the bio-available fraction. Such studies could, for example, develop and test an age-based index of testosterone concentrations that would predict a response, whether this be a response to testosterone replacement without the use of an antidepressant or a response to the augmentation of antidepressants with testosterone replacement.

Treatment of major depressive disorder has progressed considerably owing to increased understanding of the action of receptors on cell membranes of neurons, whereas the action of intracellular receptors in the treatment of major depressive disorder has been relatively unexplored even though it has been well established that intracellular receptors with an affinity for steroidal agents influence mood – consider for example the mood effects of hypercortisolaemia. Studies like ours pave the way for the exploration of treatments targeting intracellular mechanisms, as the development of such treatments requires a better understanding of the relationship between steroidal hormones, including testosterone, and major depressive disorder.

## Significant outcomes

Significant outcomes of the study include the following: (*i*) men above the age of 45 years who suffer from a major depressive disorder may have reduced serum testosterone concentrations, especially the bio-available fraction; (*ii*) follow-up studies are needed to develop a risk index – the risk of developing a depressive disorder may then be calculated based on age and testosterone concentrations; and (*iii*) double-blind placebo-controlled studies need to account for the age-related decline in testosterone concentrations when investigating testosterone replacement as primary agent or as augmenting agent in the treatment of major depressive disorder in ageing men.
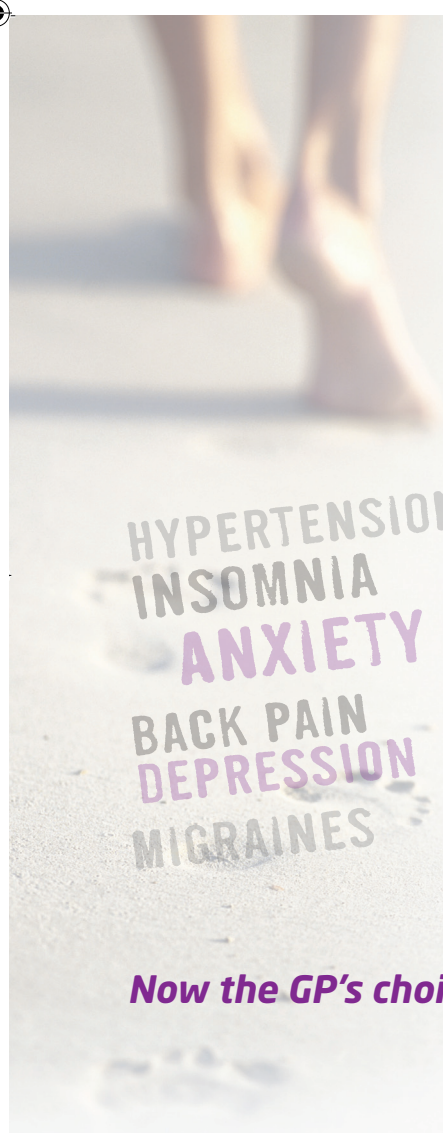
## Limitations

Limitations of the study include the following: (*i*) the study does not provide insight as to whether lower testosterone concentrations are a cause or consequence of depressive illness among men above 45 years of age; (*ii*) a difference in diurnal variation in testosterone concentrations between the depressed and control groups could have been the reason for the observed differences in testosterone concentrations between the groups; and (*iii*) the sample size was relatively small.

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