Testosterone levels increase in association with recovery from acute fracture in men

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Summary:
In this longitudinal case-control study, acute fracture was associated with low serum testosterone, which was transient in 43% of men. While assessment of gonadal status is part of the assessment of bone fragility, measurement of testosterone in the early period after fracture may overestimate the prevalence of androgen deficiency.

Abstract

Purpose
Measurement of circulating testosterone is recommended in the evaluation of bone fragility in men. Since acute illness can transiently decrease circulating testosterone, we quantified the association of acute fracture and serum testosterone levels.

Methods
A case-control study was conducted involving 240 men with a radiologically confirmed minimal trauma fracture presenting to a tertiary referral hospital and 89 age-matched men without a history of minimal trauma fracture serving as controls. Follow-up testosterone levels 6 months after baseline were available for 98 cases and 27 controls. Results were expressed as the median and interquartile (IQR) range.

Results
Compared to controls, cases had lower total testosterone [TT, 7.2 (3.5, 10.8) vs 13.6 (10.9, 17.1) nmol/L, $p<0.001$]. The 143 cases treated as inpatients had lower testosterone levels than the 97 cases treated as outpatients [TT 4.7 (2.3, 8.1) vs 10.3 (7.5, 12.7) nmol/L, $p<0.001$]. Group differences in calculated free testosterone (cFT) were comparable to the group differences in TT.

At follow-up, in 98 cases, median TT increased from 6.5 (3.2, 8.5) nmol/L to 9.6 nmol/L (6.9, 12.0) $p<0.0001$, and SHBG remained unchanged. Of cases with low testosterone, 43% with TT < 10 nmol/L and/or cFT < 230 pmol/L at presentation were reclassified as androgen sufficient at follow-up. TT was unchanged in the controls.

Conclusions
Low testosterone levels in men presenting with an acute fracture may, at least in part, be due to an acute, fracture-associated, stress response. To avoid over diagnosis, evaluation for testosterone deficiency should be deferred until recovery from the acute event.

Introduction

Sex steroid deficiency is a common cause of secondary osteoporosis in men, with an estimated prevalence around 15%[1, 2]. Acute illness has a suppressive effect on the hypothalamic-pituitary-testicular axis resulting in lower sex steroid levels to a level correlated with the severity of the illness[3]. In men with acute illness, such as myocardial infarction, burns, traumatic brain injury, or elective surgery, serum testosterone falls rapidly, by about half within 24 hours. Normalization of testosterone levels occurs 2-8 months after recovery[4-6]. The mechanisms responsible for the fall in testosterone associated with acute illness are unclear. However, this is likely to be mediated centrally, given that gonadotrophin levels are not elevated. A decrease in SHBG is not observed [5].

Measurement of testosterone is recommended for the assessment of bone fragility in men who have had a minimal trauma fracture[7]. No previous studies have examined whether acute fracture, similar to acute illness, is also associated with low testosterone levels.

It is hypothesized that an acute fracture will be associated with a transient decrease in serum testosterone levels in men, and that measurement of serum testosterone around the time of a fracture will overestimate the prevalence of testosterone deficiency. Furthermore, the degree of testosterone suppression is likely to be more marked in those with more severe illness, such as in those requiring admission to hospital or in those with hip fracture. The aims of this study were to quantify the association between circulating testosterone levels in men presenting with an acute fracture, to explore factors affecting severity, and to estimate the proportion of men that are incorrectly diagnosed with androgen deficiency.

Methods

A case control study was performed of 240 men presenting with a minimal trauma fracture to the Emergency Department of a tertiary-referral hospital (Austin Health, Victoria, Australia) from June 2009 to June 2012. Cases were men participating in a 'fracture-capture' program, which provided evaluation and treatment of bone fragility to all patients presenting to the hospital with minimal trauma fracture. Exclusion criteria were pathological fracture, finger, toe or nose fracture, high impact traumatic fractures, patients residing in residential care and those less than 50 years of age. All cases with minimal trauma who had a testosterone level measured were included. Patients were separated according to admission status (inpatients and outpatients based on routine clinical need) and fracture type. All men were offered bone mineral density testing, screening for causes of secondary osteoporosis (total testosterone (TT), calculated free testosterone (cFT), sex hormone binding globulin (SHBG), 25(OH)D (vitamin D) level, serum calcium, renal function, liver function, thyroid function, and serum and urine electrophoresis) as well as an assessment by an Endocrinologist (as an inpatient or outpatient clinic visit). 98 men had a second testosterone level performed at follow-up.

Controls were 89 age-matched, ambulatory men with localized non-metastatic prostate cancer participating in another study and were recruited from an outpatient clinic for men with prostate cancer as part of an ongoing prospective study [8]. These subjects were used as controls as they had assessment of their bone health, including

measurement of serum TT and bone mineral density performed prior to consideration for adjuvant androgen deprivation therapy. They were excluded if they had prior or current androgen deprivation therapy at the time of assessment or any illnesses or other factors predisposing them to androgen deficiency. None had a clinical history of minimal trauma fracture, osteoporosis or neuromuscular disease. Of these 89 controls, 27 not commencing androgen deprivation therapy had a second TT level performed at 6 months follow-up.

The study was approved by the Human Research Ethics Committee, Research Ethics Unit, Austin Health.

Biochemical assays

All participants had morning fasting biochemistry performed. Serum TT was determined using an immunometric testosterone assay (Access, Beckman Coulter, Inc.) with a minimal detection limit of 0.4 nmol/l and an inter-assay variation of 5.7% at 4.7 nmol/L [9]. The reference range for the TT assay was 10.0–27.6 nmol/l, derived from an independent reference panel of 124 healthy young men who had simultaneous testosterone measurements by both immunoassay and gas chromatography/mass spectrometry [10]. Serum SHBG levels were measured with the Immulite 2000 analyzer (Diagnostics Products Corp., Los Angeles, CA, USA) with a minimum detection limit of 0.2 nmol/l and inter-assay variation of 4.6% at 5.0 nmol/l. The reference range for SHBG was 11.2–78.1 nmol/l. cFT was calculated from TT using Vermeulen's formula as described[11]. Measurement of vitamin D was performed using Chemiluminescent assay on the DiaSorin Liaison (DiaSorin Australia, North Ryde, NSW, Australia) prior to 14/01/2008 (CV 20%). This subsequently changed to electro-chemiluminescence immunoassay on Roche E170 (Roche Diagnostics, Castle Hill, NSW, Australia) (CV 8%).

Bone density

Bone mineral density (BMD) at hip and spine (L1–L4) was measured by DEXA (Prodigy version 7.51; GE Lunar, Madison, WI, USA). The coefficient of variation was less than 2% for repeated scans[12]. Weight and height was measured at attendance for bone density scanning.

Statistical analyses

Data is not normally distributed and are presented as median and interquartile range (IQR). Comparisons between groups were made using Wilcoxon rank sum test for continuous variables or chi square test for frequencies. For correlations, Kendall's rank correlation was used. Longitudinal comparisons in the follow-up of the same patients were based on Wilcoxon's signed rank test. P values <0.05 were considered significant. When more than four tests were performed in a sample, p values were corrected for multiple testing using the Benjamini–Hochberg method. Comparison of some variables was adjusted for the influence of covariates using a Generalized Linear Model, as implemented by Deducer 0.7-6 with current dependencies [13]. In case of repeated measurements such as a comparison of baseline vs follow-up levels, the model was extended to a Generalized Linear Mixed Model with baseline values incorporated as a fixed covariate and repeated measure by subject as random effect, which is also robust against regression to the mean. Statistical analyses were performed using R statistical package (version 3.02 for Mac)[14].

Results

Baseline characteristics are presented in Table 1. Cases and controls were age-matched and there was no difference in baseline lumbar spine BMD, vitamin D levels, SHBG and renal function. Cases had lower BMI, and lower BMD at the hip. There was no apparent difference in medical comorbidities in cases and controls.

Baseline TT was measured at median 7 (2, 42) days after fracture. Baseline TT in cases was lowest when measured between day 1 and 10 after acute fracture (Figure 1). At baseline, cases had a lower median TT and cFT than controls before (Table 1), and after adjustment for age, BMI and SHBG [TT 8.8 vs 14.1 nmol/L, p<0.001, cFT adjusted for age and BMI 137 vs 226 pmol/L, p<0.001].

Cases admitted to hospital as inpatients (n=143) had lower TT than men treated as outpatients (n=97) [TT 4.7 (2.3, 8.1) nmol/L vs 10.3 (7.5, 12.7) nmol/L, p<0.001 and cFT (80 (40,134) pmol/L vs 151 (113, 203) pmol/L, p<0.001] (Figure 2a and 2b). This difference in TT between inpatients and outpatients remained significant after adjustment for age, BMI and SHBG for TT [6.8 vs 10.5 nmol/L, p<0.001] and adjustment for age and BMI for cFT [106 vs 158 pmol/L, p< 0.001]. In addition, TT [10.3 nmol/L vs 13.6 nmol/L, p<0.001] and cFT [151 vs 224 pmol/L, p<0.001] levels were lower in outpatients compared to controls, and these differences remained significant after adjustment for age and BMI (p<0.001).

There were significant differences in fracture type for cases managed as inpatients and outpatients: inpatients were more like to have sustained a hip fracture, whereas wrist, upper arm and rib fractures were more common in outpatients (Table 2).

Furthermore, cases sustaining a hip fracture (n=77) had lower TT compared with other fracture types (n=163) [TT 4.1 (1.4, 6.9) nmol/L vs 8.5 (5.3, 11.6) nmol/L, p<0.001, and cFT 61 (30, 115) pmol/L vs 136 (78, 179) pmol/L, p<0.001] before and after adjustment for age, BMI and SHBG [TT 6.3 vs 9.5 nmol/L, p=0.006, cFT adjusted for age and BMI 98 vs 144 pmol/L, p=0.01].

Opioid medication use at the time of baseline TT measurement was greater in cases compared with controls (24.2% vs 0.0%, p<0.001), and the majority of cases receiving opioids were inpatients (84.5% inpatients vs 15.5% outpatients, p<0.001). However, baseline TT was not significantly different between those not receiving opioids (7.6 (3.7, 10.9) nmol/L) and those on opioids (5.6 (3.1, 10.2) nmol/L, p=0.12).

Follow-up TT levels were available for 98 cases at a median 5.8 (3.5, 8.8) months after initial fracture and 27 controls at 6.0 (5.8, 6.1) months from baseline (Figure 3a and 3b). There was no difference in age (p=0.41), or fracture type (p=0.49) in those with follow-up TT levels available and those without. Men who had a follow up TT available were more likely to be treated as inpatients: 47% of inpatients had a follow-up testosterone level available vs 31% of controls (p=0.02). Men with a low baseline TT level (<10 nmol/L) were more likely to be followed (p<0.05), and in the men with follow-up available, baseline TT level were representative of the total group (5.2 vs 4.7 nmol/L), p=0.10. Follow-up TT and cFT in cases was higher compared with baseline but still lower than in controls (both p < 0.001) (Table 2). Follow-up TT in cases correlated with baseline testosterone level, r=0.50, p<0.001.

While TT showed a significant increase in cases and no change in controls (Table 3, Figure 3A and 3B), the mean adjusted difference in TT between groups over time in a generalized linear mixed model was 3.3 nmol/L [95%CI: 2.4, 4.2, p<0.001], and after adjustment was 2.1 nmol/L [95% CI: 1.0, 3.3, p<0.001]. At follow-up, TT was no longer different between patients with hip fracture and other fracture types [9.0 (6.3, 11.4) vs 10.2 (7.1, 12.7) nmol/L, p=0.17] but remained lower than controls [15.0 (10.9, 16.9) nmol/L, p<0.001].

At presentation, 98% of the 98 cases had low testosterone levels (TT<10nmol/L and/or cFT <230 pmol/L). Of these, 65 (66%) experienced an improvement in testosterone of more than 30%, while 55% still remained below 10 nmol/L. In 43% of the 98 men, this resulted in a reclassification from testosterone deficiency to sufficiency status.

Discussion

If measured around the time of a fracture, TT levels are lower by an average of 35%, based on follow up TT levels 6 months post fracture. Almost half (43%) of men with initial low TT were reclassified as androgen replete (TT> 10 nmol/L) at follow-up. Those with increasing severity of illness based on need for hospitalization or having sustained a hip fracture, had initially lower TT, but recovered to the same level as outpatients and those with other fracture types. Medical comorbidities, alcohol use and opioid use were not significant confounders. Follow-up testosterone levels 6 months post fracture remained lower than that of the controls, in keeping with the known association of low testosterone levels with increased risk of fractures in men [15-19].

Initial TT levels were measured at median 7 days after acute fracture, however the IQR was wide (2, 42). When timing of measurement was taken into account, TT levels fell to a nadir within the first 10 days after acute fracture and thereafter gradually recovered to levels at baseline. A similar dip in TT levels between day 1 and day 10 has been described in critical illness[6].

While this is the first longitudinal case-control study to quantify the effects of an acute fracture on circulating testosterone levels, the magnitude of the deficit of 40-60% is comparable to that of other acute illnesses reported previously [4-6]. The degree of hypothalamic-pituitary-testicular axis suppression is generally proportional to the severity and duration of illness[6,20]. This is consistent with our findings that men requiring admission to hospital or those with hip fracture had lower testosterone levels. Similarly, in small cross-sectional studies, lower testosterone levels were also reported in men with recent minimal trauma fracture. Diamond et al. demonstrated lower free testosterone levels measured 10-14 days after surgical intervention in 41 men with hip fracture compared with outpatient controls. However, free testosterone levels in the hip fracture group were not different to levels measured in inpatient controls admitted for other reasons[21]. In a study of 27 men with hip fracture, 30% had TT two standard deviations below the mean of age-matched healthy men when measured 1- 3.5 months after fracture[22]. Wong et al. reported that 6 out of 16 men had low testosterone levels when evaluated at a mean of 12.7 months following their fracture [23]. None of these studies provided longitudinal data to assess changes in testosterone levels over time.

The underlying mechanism responsible for the low TT around the time of acute fracture is not known. A rise in gonadotrophins has been reported in some studies, however suppressed levels, without any change in gonadotrophin bioactivity, is the predominant finding in acute illness [5, 24]. Furthermore, SHBG remains unchanged in critical illness in this and other studies [4, 5, 25, 26]. While suppression of the gonadal axis by acute illness is thought to be reversible, few studies have included a control group. This is important because testosterone levels fluctuate markedly, even in healthy men. Previous studies have shown that low TT levels in older men with or without diabetes may normalize on repeat measurement in up to 30% of men [9, 27]. The magnitude of improvement and the fact that the serial testosterone levels in the controls remained stable, support our inference that the rise in testosterone at follow-up is due to gonadal axis recovery, rather than attributable to regression to the mean.

There are a number of limitations to this study. Due to the observational nature of the study we cannot infer causation between fracture and the low TT. The controls are not normal healthy controls but men with prostate cancer. These were ambulatory age- and comorbidity-matched men without metastatic disease undergoing treatment with curative intent and without any major systemic disease, which would be thought to influence testosterone levels. All had normal performance status (Eastern Cooperative Oncology Group 0). Furthermore, there is no documented association between serum testosterone and development of prostate cancer[28].

Moreover, follow-up testosterone levels were available for less than half of the cases, and limited to a single measurement. It remains possible therefore that these men had not attained their stable, post-acute testosterone level. However, if true, our study, if anything, could therefore have underestimated the impact of a fracture on testosterone levels. In addition, the time to normalisation of testosterone may depend on the type of fracture and other patient-specific factors not captured in this study.

Although we did not measure estradiol, the intent was to assess the effects of acute fracture on circulating testosterone. Recent evidence has suggested circulating estradiol, which is derived from testosterone by aromatisation, is a better predictor of fractures in men than serum testosterone, however, routine measurement of estradiol in the assessment of osteoporosis is impractical due to the limited availability of assays that accurately quantify the low estradiol levels in men[29]. Therefore, recent Endocrine Society guidelines recommend the measurement of serum testosterone, but not estradiol, in men being evaluated for osteoporosis[7]. While testosterone levels were measured by immunoassay rather than mass spectrometry, relationships of testosterone measured by the immunoassay, used here, with BMD at various skeletal sites are similar to that of mass spectroscopic measures[30,31].

In conclusion, acute fracture is associated with low serum testosterone, which is transient in 43% of men, hence measurement in the early period after fracture may overestimate the prevalence of androgen deficiency. Consistent with Endocrine Society guidelines, evaluation of gonadal status should be part of the assessment of bone fragility, but caution is needed in the interpretation of the data under circumstances of acute fracture and coexisting morbidities. Serial measurements are recommended before making a final diagnosis of androgen deficiency.

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Tables and Figures

Table 1. Baseline Characteristics of Cases and Controls

	Cases (n=240)	Controls (n=89)	P-Value
Age (years)	72 (63, 82)	69 (65, 73)	0.055
Body Mass Index (kg/m^2)	23.3 (20.7, 25.9)	27.9 (24.8, 31.7)	<0.001
Renal function (eGFR ml/min)	78 (58, 90)	81 (71, 90)	0.061
Vitamin D (nmol/L)	58 (42, 81)	66 (47, 88)	0.20
Total testosterone (TT) (nmol/L)	7.2 (3.5, 10.8)	13.6 (10.9, 17.1)	<0.001
Calculated free testosterone (cFT) (pmol/L)	113 (55, 171)	224 (190, 275)	0.004
Sex hormone binding globulin (SHBG) (nmol/L)	50.5 (38.0, 68.8)	45.0 (35.0, 55.5)	0.09
Lumbar Spine Bone Mineral Density g/m^2	1.156 (1.053, 1.279)	1.218 (1.096, 1.334)	0.06
Lumbar Spine T score	-0.6 (-1.4, 0.4)	0.0 (-1.0, 1.0)	0.06
Total Hip BMD g/m^2	0.921 (0.802, 1.043)	1.008 (0.901, 1.088)	<0.001
Total Hip T score	-1.3 (-2.1, -0.4)	-0.6 (-1.2, 0.0)	<0.001
Medical comorbidities			
Myocardial infarction	56 (23.4%)	16 (18.0%)	0.36
Congestive cardiac failure	22 (9.2%)	3 (3.4%)	0.16
Cerebrovascular Disease	27 (11.2%)	9 (10.1%)	0.92
Chronic Obstructive Pulmonary Disease	25 (10.4%)	6 (6.7%)	0.42
Connective tissue disease	5 (2.1%)	1 (1.1%)	1.00
Liver disease	11 (4.6%)	4 (4.5%)	0.49
Diabetes (treated with medication)	44 (18.3%)	14 (15.7%)	0.80
Hypertension	127 (52.9%)	54 (60.7%)	0.46
Hypercholesterolemia	97 (40.4%)	40 (44.9%)	0.75
Alcohol abuse	16 (6.7%)	6 (6.7%)	1.00

Data presented are median (interquartile ranges) or proportion affected by comorbidity N (%). P values for continuous variables were adjusted for multiple testing by the Benjamini-Hochberg method, while comorbidities were considered as explanatory only.

Table 2. Type of minimal trauma fracture sustained by admission status in cases

Fracture Type	Total n=240 N (%)	Inpatients n=143 N (%)	Outpatients n=97 N (%)	P value (outpatients vs inpatients)
Hip	77 (32.1)	74 (51.8)	3 (3.1)	<0.001
Lower leg	47 (19.6)	24 (16.8)	23 (23.7)	0.19
Wrist	33 (13.8)	7 (4.9)	26 (26.8)	<0.001
Upper arm	34 (14.2)	14 (9.8)	20 (20.6)	0.02
Vertebral	16 (6.7)	10 (7.0)	6 (6.2)	0.52
Ribs	26 (10.8)	8 (5.6)	18 (18.6)	0.002
Pelvis	2 (0.8)	2 (1.4)	0 (0)	0.52
Other site	5 (2.1)	4 (2.8)	1 (1.0)	0.42

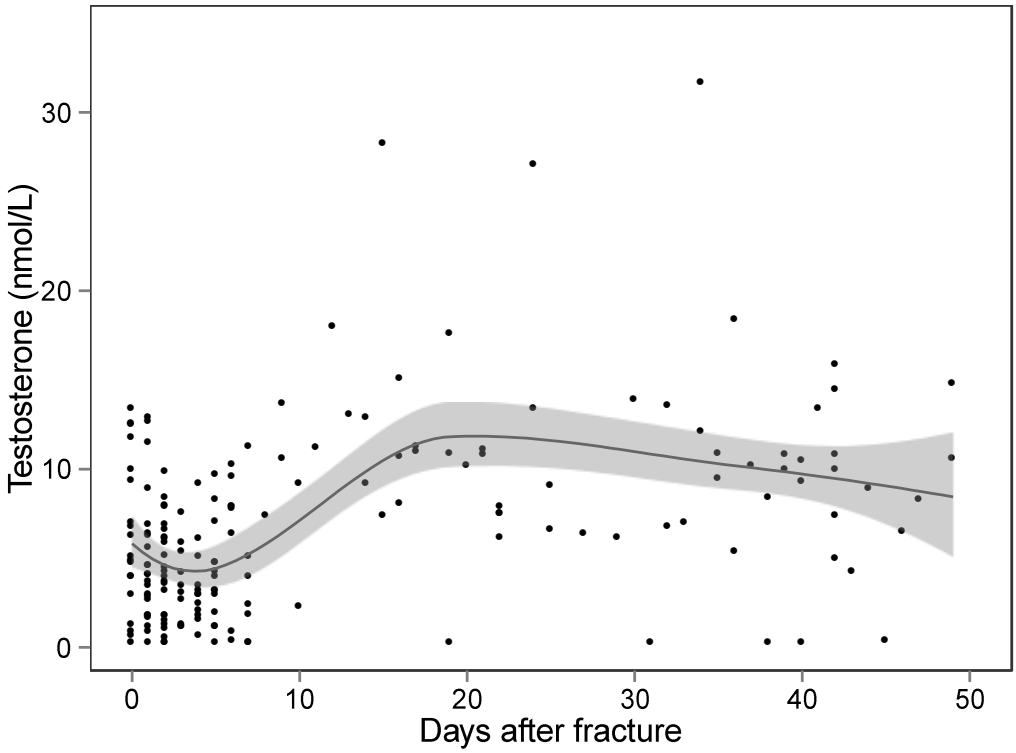
P values calculated by Fisher's exact test. Other site (elbow, distal femur or femoral shaft)

Table 3. Testosterone levels in cases and controls who had follow-up levels measured

	Cases (n=98)			Controls (n=27)		
	Baseline	Follow-up	P value	Baseline	Follow-up	P value
Total testosterone level nmol/L	6.5 (3.2, 8.5)	9.6* (6.9, 12.0)	<0.0001	15.0 (10.9, 16.9)	14.3 (9.9, 17.3)	ns
Free testosterone level pmol/L	90 (49, 145)	152* (108, 225)	<0.0001	228 (197, 304)	253 (201, 296)	ns
SHBG nmol/L	45 (34, 69)	50 (33, 69)	0.64	44 (34, 49)	40 (35, 50)	ns

Data presented are median (interquartile ranges). * indicates significant difference (p< 0.001) to follow-up TT in controls.

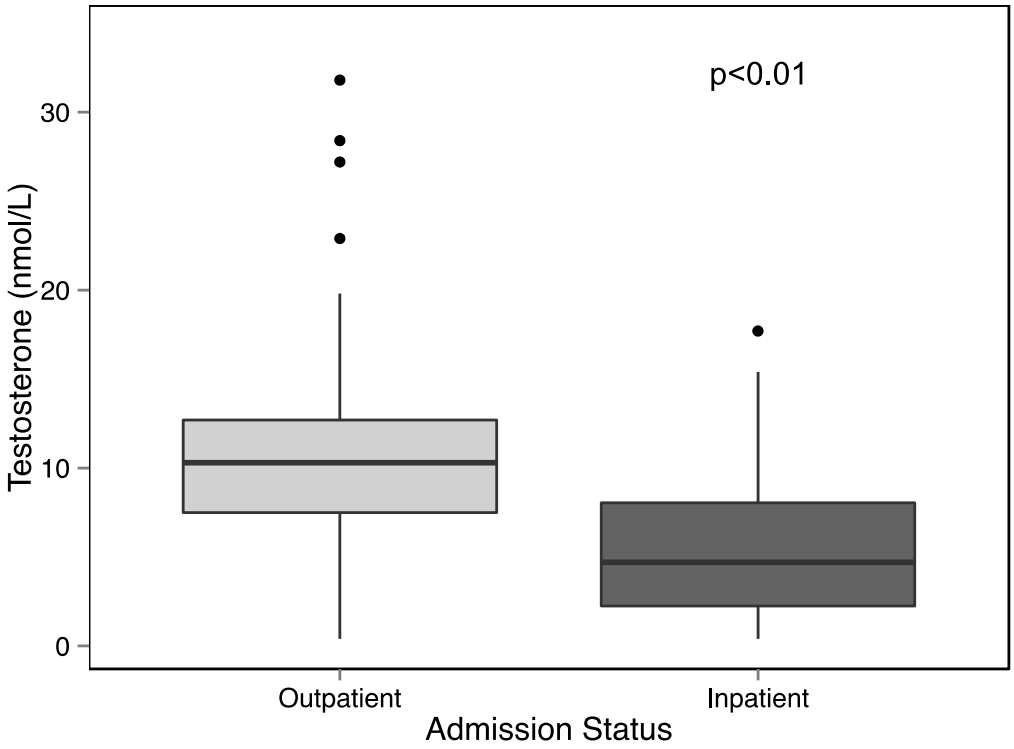
Figure 1. Baseline total testosterone level according to days after fracture.



Circles represent individual cases. Solid line represents mean and shaded area is 95% confidence interval fitted by least square approximation.

Figure 2. Total Testosterone (A) and calculated Free Testosterone (B) levels in men treated as inpatients vs outpatients. (p<0.01)

A.



B.

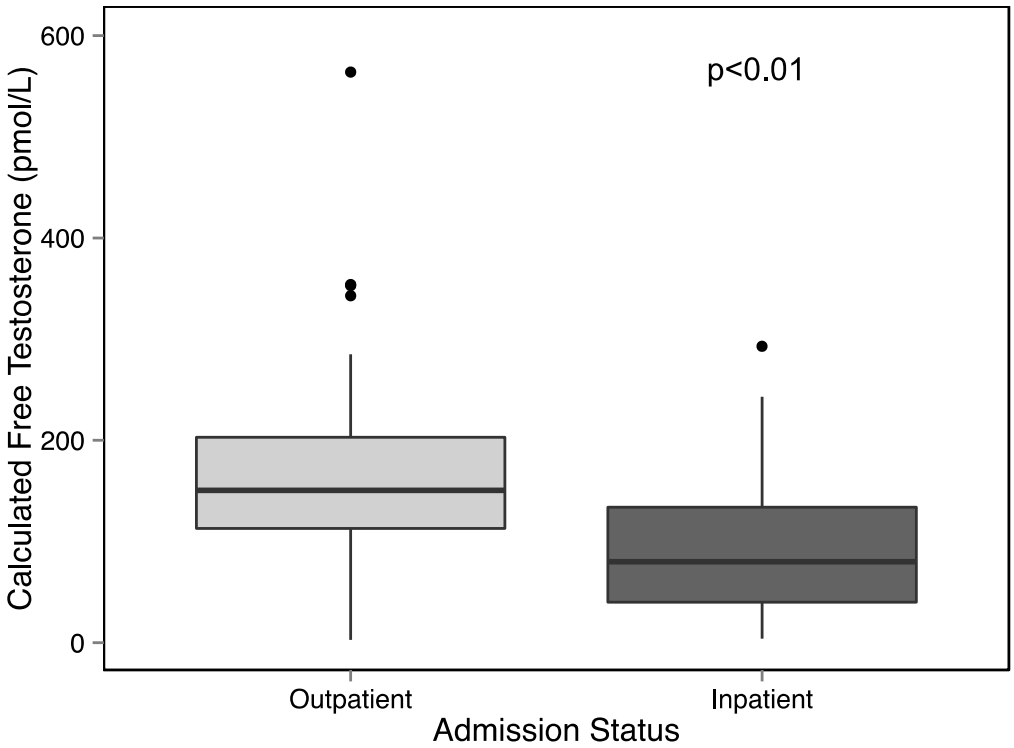
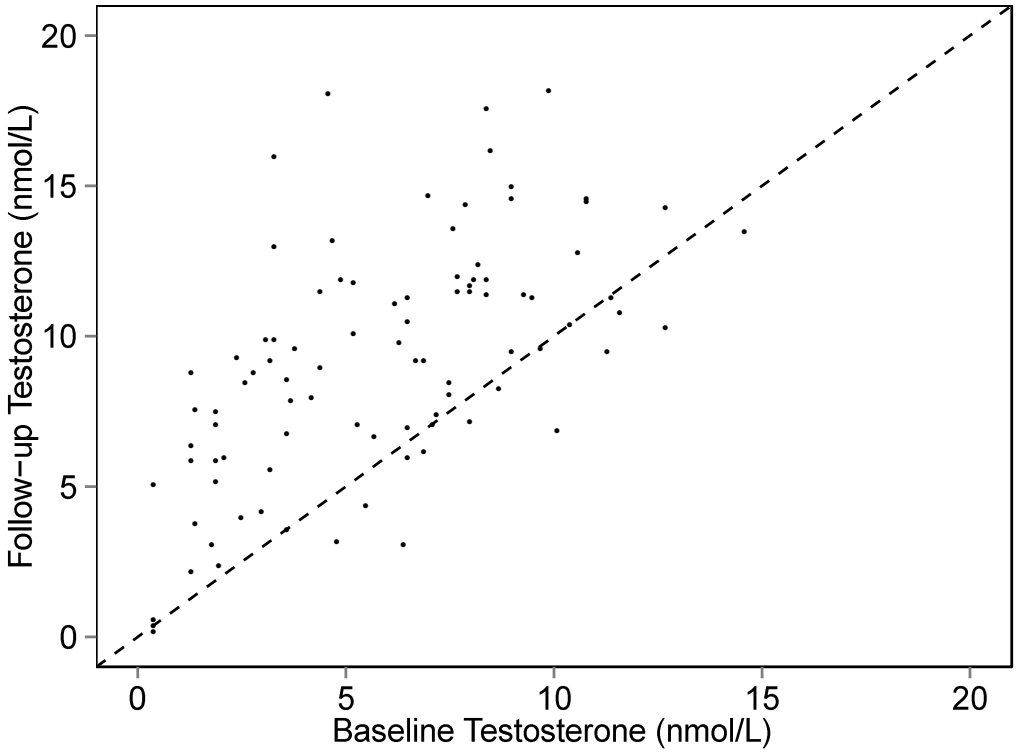
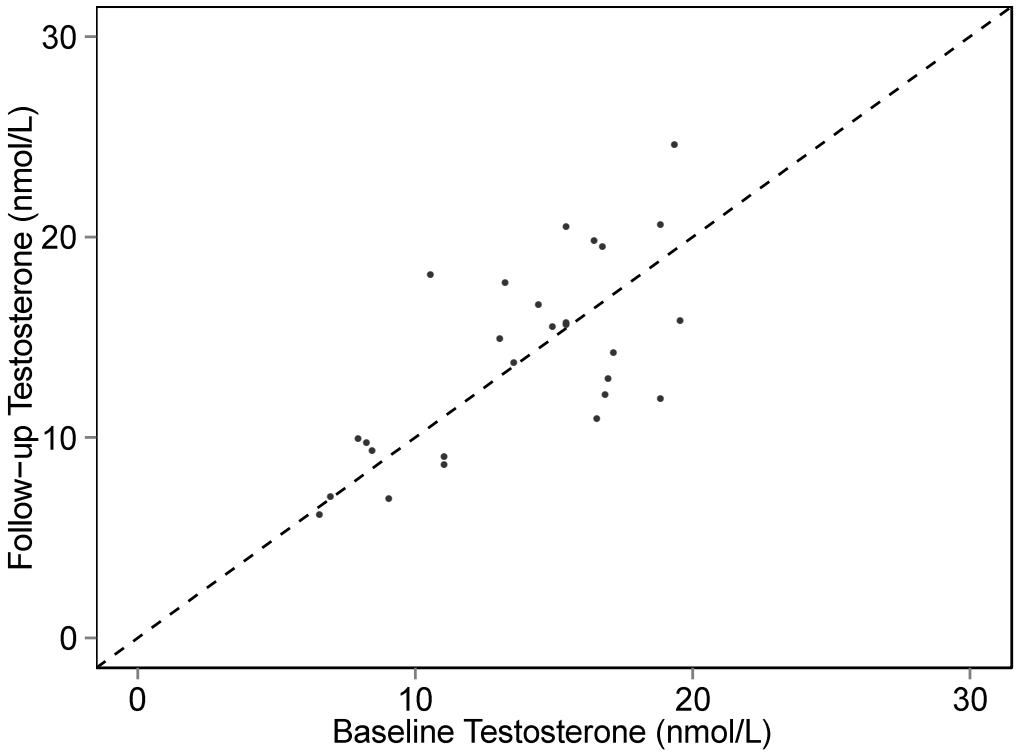


Figure 3. Follow-up testosterone levels compared with baseline testosterone levels in cases (n=98, A) and controls (n=27, B).
A. Cases



B. Controls



Closed round circles represent individual cases. The dotted line represents no change at follow-up compared with baseline. Cases above the dotted line had a rise in TT levels at follow-up. For statistical comparison, see Text and Table 2.