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Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome

A. Aversa, R. Bruzziches, D. Francomano, G. Spera, and A. Lenzi
Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy

ABSTRACT. ***Aim:*** **To investigate efficacy and safety of two different preparations of testosterone undecanoate (TU) in 52 hypogonadal men [mean age 57 yr and mean testosterone (T) < 320 ng/dl] with metabolic syndrome (MS).** ***Subjects and methods:*** **Randomized, double-blind, double-dummy study with three parallel treatment arms [oral TU; transdermal placebo gel (P); im TU] administration for 12 months (mo). Each subject was randomized (1:1:3) to receive either oral TU (2 capsules of 40 mg/twice per day at breakfast and dinner, equalling a total dose of 160 mg/day; no.=10) for 6 mo and continued with im TU for further 6 mo, or P (3-4 g/day; no.=10) and im TU (1000 mg/12 weeks from week 6; no.=32) for 12 mo.** ***Results:*** **After 6 mo, im TU increased T and free-T levels ($p<0.0001$), and improved metabolic parameters [reduction in Homeostasis Model Assessment (HOMA) index, $p<0.0001$; waist circumference and fat mass, $p<0.001$, respectively], in International Index of Erectile Function-5 and Aging Males' Symptoms scores ($p<0.01$, respectively). After 12 months, im TU produced further increases in T and free-T levels ($p<0.0001$) and metabolic parameters (reduction in HOMA-index, $p<0.0001$; waist circumference $p<0.0001$; fat mass, $p<0.001$). No major adverse event due to T treatment occurred.** ***Conclusions:*** **Clinical efficacy of T replacement therapy in hypogonadal men with MS is reached when its plasmatic levels approach into the medium-high range of normality (>5 ng/ml), although subjective threshold values may be different. Administration of im TU was more effective than oral TU to reach the target for T levels and to improve MS parameters. TU was safe over 12 months and discontinuation rates were similar to placebo.**
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INTRODUCTION

Male hypogonadism has a multifactorial etiology that includes genetic conditions, anatomic abnormalities, infection, tumor, and injury. A number of conditions can also be associated with decreased testosterone (T) levels and include metabolic syndrome (MS) (1), Type 2 diabetes mellitus (T2DM) (2), atherosclerosis (3), myocardial infarction (4), chronic heart failure and treatment with a range of medications (5). Low T levels are now being recognized as an independent risk factor for these conditions. The age-related decline in T levels, defined as late onset hypogonadism (LOH), results from defects in both testicular and hypothalamic-pituitary function (6). Because the average decline in serum T levels with aging in men is 1-2% per year after age 40 yr (7), only a subset of aging men has T levels clearly below the lower limit of the normal range for healthy, young men (8). It is estimated to affect between 19-34% of men over the age of 60 (9). Findings from men undergoing short-term androgen suppression as treatment for prostate cancer confirm that the hypogonadal state increases body fat mass and serum insulin and there is a high rate of developing insulin resistance and hyperglycemia, thus suggesting a key-role for T in the development of insulin resistance/MS also (10), and leading to their increased risk of cardiovascular disease (CVD) (11). MS is commonly defined as a group of risk factors that cluster determining central abdominal obesity, elevated triglycerides, reduced HDL, high blood pressure, increased fasting glucose, and hyperinsulinemia, which are all closely associated with insulin resistance (12, 13). The presence of MS indicates a high risk for the development of both T2DM and CVD. Studies have shown that in men low T levels can predict the development of insulin resistance, the basis of MS, and possible progression to overt T2DM (14) and hypotestosteronemia is associated with an increase in many of the known cardiovascular risk factors (15).
Aim of the present study was to investigate the efficacy and safety of long-term T replacement therapy (TRT) with two different preparations of T undecanoate (TU) in a population of hypogonadal men with MS and/or T2DM independently from the presence of erectile dysfunction (ED).

MATERIALS AND METHODS

Study design and patients

This was a randomized, double-blind, double-dummy study with three parallel treatment arms [oral TU; im TU; transdermal placebo gel (P)] administration for twelve months. Each subject was randomized (1:1:3) to receive either oral TU (2 capsules of 40 mg/twice per day with breakfast and dinner, equalling a total dose of 160 mg/day; no.=10) or im TU (1000 mg/12 weeks from week 6; no.=32) for 6 months. Subsequently, the oral TU group was crossed-over to receive im TU while the TU group was maintained for 6 additional months. The P-group (no.=10) was assigned to receive a 3-4 g/day preparation for 12 months. The objective of this study was to determine the efficacy/safety of two different TU formulations, patient's preference regarding

Key-words: Obesity, erectile dysfunction, prostate volume, long-term controlled study, side effects.

Correspondence: Antonio Aversa, MD, PhD, Dipartimento Fisiopatologia Medica, Università Sapienza di Roma, Viale Policlinico 155, 00161 Rome, Italy.
E-mail: antonio.aversa@uniroma1.it

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the route of administration for TRT and the impact on the social, psychological and sexual life of the treated patients.
The primary outcomes were to assess the changes from baseline of the following parameters: total and free testosterone (TT and FT), SHBG, estradiol; the homeostasis model assessment index of insulin resistance (HOMA-IR); glycemic and lipid control; blood pressure; anthropometric measurements including abdominal obesity measured by waist circumference, body mass index (BMI), and body composition measured by dual energy X-ray absorptiometry (DEXA).
The secondary outcomes were to assess the patient's satisfaction through the modifications from baseline of the scores of the following questionnaires: Aging Males' Symptoms (AMS) rating scale (total score) and rating scales (psychological, somatic and sexual function subdomain), International Index of Erectile Function-5 items form (IIEF-5); the International Prostate Symptoms Score (IPSS) was used as a tool to investigate unwanted effects on micturition.
Inclusion criteria were: age between 50 and 65 yr with MS and/or T2DM defined by International Diabetes Federation (IDF), TT serum level <3.20 ng/ml (11 nmol/l) or calculated FT levels <250 pmol/l (10 pg/ml) on two early morning separate days (between 08:00 and 11:00 h to minimize diurnal variation) at least one week apart, and at least two symptoms of hypogonadism as stated by international guidelines and questionnaires (16-18).
Exclusion criteria were: use of androgen therapy or anabolic steroids within 12 months of entry into the study; suspicion or known history of prostate or breast cancer; history of drug or alcohol abuse; suspicion or known history of tumors; blood coagulation irregularities presenting an increased risk of bleeding after intramuscular injections; diagnosed of symptomatic obstructive sleep apnea syndrome (OSAS); polycythemia with an hematocrit level ≥52% at entry into the study; age-adjusted elevated prostate specific antigen (PSA) level or abnormal digital rectal examination (DRE) of prostate suggestive of cancer and severe symptomatic benign prostatic hyperplasia; patients using 5-α-reductase inhibitors; iperprolactinemia or organic hypothalamic-pituitary pathology; uncontrolled thyroid disorders; uncontrolled diabetes (glycosylated hemoglobin, HbA_{1c} ≥11) and/or in treatment with insulin; severe cardiac (New York Heart Association class III or above), hepatic (alanine aminotransferase/aspartate aminotransferase ≥3 times above the upper limit of normal range) or renal insufficiency (serum creatinine ≥1.5); severe neurological and psychiatric disease; patients requiring or undergoing fertility treatment; any other reason which the investigator feels precludes safe inclusion of the patient. The exclusion criteria have been selected for safety reasons and to ensure efficacy of study treatment.
All concomitant oral hypoglycaemic, anti-hypertensive and lipid-lowering medications were permitted and continued throughout the study without dose adjustments. Subjects were asked to avoid major changes in the pattern of physical exercise and lifestyle for the duration of the study and were enrolled if they were able to attend 3-monthly scheduled visits, willing to voluntarily sign-up a statement of informed consent to participate. Detailed information about the study was provided, and written informed consent was obtained before commencement of the study. This clinical trial was conducted in compliance with this Protocol, the guidelines of the World Medical Association Declaration of Helsinki in its revised edition (Tokyo, Japan, 2004), the guidelines of the International Conference on Harmonization (ICH). In addition, this study was undertaken in accordance with the Protocol and Good Clinical Practice (GCP) on the conducting and monitoring of clinical studies, and approved by the Internal Review Board of 'Sapienza' University of Rome.

Randomization and drug treatment

Fifty-two out of 80 male patients (mean 57±8 yr) who met the study inclusion and exclusion criteria were eligible for the study. Each subject was randomized to receive either oral TU 40 mg (no.=10) or im TU 1000 mg/4 ml (no.=32) for 6 months. Subsequently, the oral TU arm was crossed-over to receive im TU, while the im TU arm kept their treatment for 6 additional months, respectively. A placebo gel preparation was assigned to a control group (P) for 12 months (no.=10). Oral TU was administered at the dosage of 2 capsules of 40 mg/twice per day at breakfast and dinner (equaling a total dose of 160 mg/day of TU). One ampoule of im TU was injected at an interval of 6 weeks (loading dose), followed by an injection every 12 weeks. All im injections were administered into the gluteus medius muscle by the same trained physician. Placebo-gel (3-4 g) was for a daily skin application. The total observation covered a period of 12 months for each treatment modality. The assessment in each treatment phase was 12±1 weeks after the previous visit.

Assessments

Demographics, details of medical, surgical history and concomitant medication history were assessed at baseline.
General physical examination and anthropometric parameters as weigth, height, BMI, waist circumference, systolic and diastolic blood pressure, heart rate, prostate examination with DRE, completion of IIEF-5, AMS, IPSS questionnaires by patient, blood sample for laboratory assessement were assessed at baseline and every 3 months. DRE was performed after blood sampling. The AMS scale used 17-item scoring points; four grades of severity were distinguished: no/little complaints (≤26 points), mild (27-36 points), moderate (37-49 points), and severe complaints (≥50 points) (19). Finally, three dimensions of symptoms/complaints were identified: psychological, somatic, and sexual factor (www.issam.ch/AMS_English_Evaluation.pdf). ED was confirmed by a score of 21 or less, indicating at least mild (17-21), mild-to-moderate (12-16), moderate (8-11) and severe (5-7) ED at IIEF-5 (20). Hormonal assessment included LH, FSH, plasma T and calculated FT, SHBG, 17β-estradiol (E_2), PRL. The following metabolic and safety parameters incluted plasma total cholesterol, HDL and triglycerides, PSA, blood glucose, insulin, HbA_{1c}, hemoglobin and hematocrit, liver and kidney functions serum bilirubin, γ glutamyl transferase (γ-GT), serum glutamate oxalacetate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT), albumin and creatinine.
TT was measured by electrochemiluminescence (Immulite 2000, Siemens, Milan, Italy; within and between-assay coefficients of variation were 5.1 and 7.2%, respectively), E_2 was measured with chemiluminescent enzyme immunoassays (Architect Systems, Abbott Diagnostics, Germany), FSH, LH , PRL using direct chemiluminescent (ADVIA Centaur, Bayer Co, Germany). SHBG, insulin and PSA were analyzed by immunometric assay based on chemioluminescence using an automated clinical chemistry analizer (Immulite 2000, Diagnostic Product Corp., Los Angeles, CA, USA). Plasma glucose, serum total cholesterol, HDL-cholesterol andtriglycerides were mesured by an automated clinical chemistry analizer (Modular P and Modular E for PSA, Roche Diagnostics GmbH, Mannheim, Germany). HbA_{1c} was measured by high performance liquid chromatography (Bio-Rad Laboratories, Hercules, CA, USA). FT was calculated from TT and SHBG and

Table 1 - *Demographic characteristics of the study population at baseline.*

Demografic at baseline	Placebo	Oral TU	Im TU
Patients, no.	10	10	32
Mean age±SD, yr	55±5	57±8	58±10
Caucasian, %	100	100	100
Mean BMI±SD	31±6.2	32.5±5.2	30.2±4.5
Only T2DM, no. (%)	4 (40%)	3 (30%)	10 (31%)
Only MS, no. (%)	6 (60%)	7 (70%)	22 (69%)
T2DM + MS, no. (%)	3 (30%)	3 (30%)	8 (25%)
Erectile dysfunction, no. (%)	6 (60%)	7 (70%)	24 (75%)
Mild (IIEF-5=17-21)	2 (30%)	3 (40%)	10 (41%)
Mild-to-moderate (IIEF-5=12-16)	3 (40%)	2 (30%)	9 (31%)
Moderate (IIEF-5=8-11)	1 (30%)	2 (30%)	5 (28%)
Severe (IIEF-5=5-7)	0	0	0

BMI: body mass index; IIEF-5: International Index of Erectile Function-5; MS: metabolic syndrome; T2DM: Type 2 diabetes mellitus; TU: testosterone undecanoate.

albumin concentration (17). To assess insulin sensitivity, we calculated the HOMA-IR using the formule [fasting insulin in mU/l × fasting glucose in mmol/l]/22.5.

At baseline, at 6 and 12 months the body composition and prostate volume were assessed. Lean body mass, total fat mass and total body mass were calculated using a whole-body DEXA (DEXA-HOLOGIC QDR-1000). Scanning was performed according to the instructions of the manufacturer. Participants were scanned in a horizontal position from dorsal to ventral. Legs and feet were endorotated and fixed to one another. Quality assurance including calibration was performed routinely every morning for DEXA using the standard provided by the manufacturer. This is an accepted method to assess body composition (21, 22). Transrectal ultrasonography (TRUS) of the prostate was always performed by only one operator (X300, SIEMENS, Germany). Patients were scanned in the left lateral decubitus position using a 7-Mhz multiplanar rectal probe. To measure prostate volume, the anterioposterior and transverse diameter were measured in the transverse image and the craniocaudal diameter was measured in the largest area in the sagittal plane. The volume of total prostate was calculated by timing these diameters (height × width × length × π/6) (the ellipsoid method) (23, 24). The transitional zone was measured in the same way except that the craniocaudal diameter was measured in the sagittal plane where the transitional zone is seen at its largest. Furthermore, attention was placed on the presence of hypoechogenic lesions in the prostate. If abnormalities were found, patients were sent to the urology outpatient clinic for further evaluation and the prostate was examined systematically at DRE.

Safety

Patients had to be withdrawn during the course of study if hematocrit level ≥52%, PSA level increase >1.0 ng/ml above the baseline PSA if baseline PSA was <2.0 ng/ml, PSA level increase >50% of the baseline PSA if baseline PSA was >2.0 ng/ml.

Statistical analyses

Clinical and biochemical data were compared before and after treatment and with placebo arm. Data are expressed as means ± standard deviation (SD) only when normally distributed, and as median (quartiles) when non parametric. Kolmogorov-Smirnov test has been used to test the parameter distribution. Paired t-test and Wilcoxon test (for parametric and non-parametric distributed parameters, respectively) have been used to test the parameter changes during the study. A p value <0.05 was taken as statistically significant.

RESULTS

Baseline characteristics of the study population are shown in Table 1. No significant differences prior to treatment were present between the treatment groups. There were no serious adverse drug reactions recorded during the study. Both oral TU and im TU were well tolerated by the patients.

After 6 months oral TU produced no increases from baseline in TT and FT levels. Patients in the oral TU arm that crossed-over to receive im TU for 6 additional months showed increased levels of TT and FT. After 6 months im TU produced increases from baseline both in TT and FT levels, and after 12 months further increases in mean circulating T and FT levels (Fig. 1A and B). No

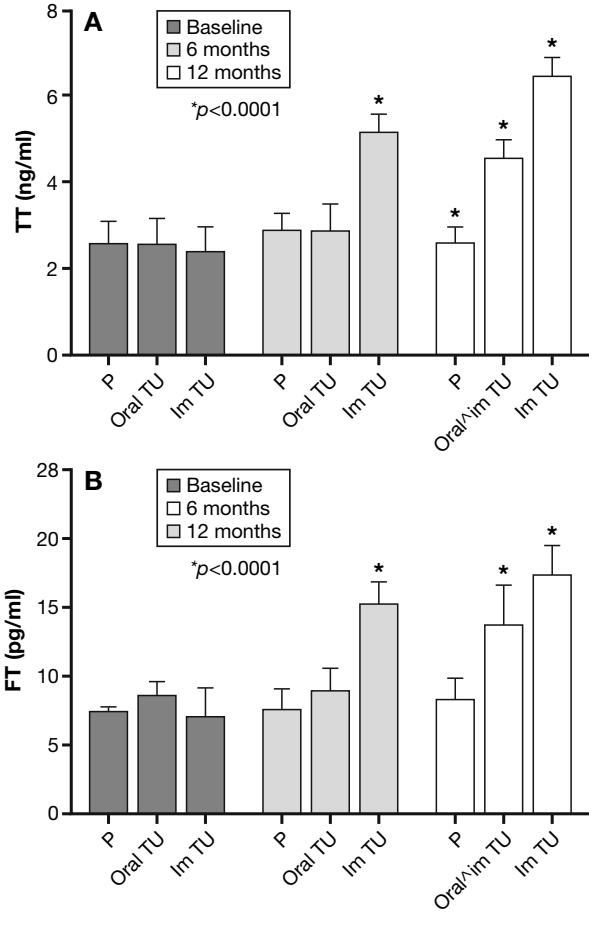

Fig. 1 - *Changes in plasma total testosterone (TT) (panel A) and free testosterone (FT) levels (panel B) after 6 and 12 months of placebo (P), oral testosterone undecanoate (TU) and im TU treatments. Oral^im TU means that patients in the oral TU arm were shifted to the im TU arm treatment after 6 months.*

Table 2 - *Changes from baseline in all parameters studied: total serum cholesterol (Tot chol), triglycerides (Trygl), glycosylated hemoglobin (HbA_{1c}), systolic and diastolic blood pressure (BP), SHBG, 17-β estradiol (17β-E_2), prostatic volume (Prost Vol).*

	Placebo				Oral TU			Oral^im TU		Im TU			
	Baseline	6 months	12 months		Baseline	6 months		12 months		Baseline	6 months	12 months	
BMI	31±6.2	29.5±6	30±5.5	ns	32±5	32±5	ns	31±5	ns	30.2±3.4	29.5±4	29±3	ns
Tot chol, mg/dl	217±51	222±8	197±35	ns	206±30	207±36	ns	205±31	ns	210±33	204±32	200±27	ns
HDL, mg/dl	42±6	41±6	45±7	ns	42±9	39±7	ns	44±10	ns	44±11	48±12	50±10	ns
Trygl, mg/dl	146±32	158±43	154±52	ns	150±34	168±34	ns	146±68	ns	158±36	150±45	158±46	ns
HbA_{1c}, %	6.3±1.2	6.6±1.5	6.7±1.6	ns	5.8±0.5	6.1±0.6	ns	6±0.4	ns	5.7±0.5	5.5±0.4	5.5±0.4	ns
Systolic BP, mmHg	138±16	138±12	136±16	ns	140±10	138±12	ns	142±14	ns	136±8	140±12	140±10	ns
Diastolic BP, mmHg	84±12	82±10	84±10	ns	82±14	84±14	ns	86±12	ns	84±12	84±10	86±6	ns
SHBG	30.8±7	28.1±3.6	24.3±5.6	ns	34.7±18.5	32±14	ns	31.2±10	ns	27.8±9	20.5±8	30.7±9	ns
17β-E_2, pg/ml	30±10	31±11	28±4	ns	30±12	31±11	ns	38±14	ns	25±11	23±9	28±8	ns
Prost Vol ml	26.5±2	-	26±2.5	ns	27±2	-	-	27±2.5	ns	26±3	-	26±3.5	ns

BMI: body mass index; TU: testosterone undecanoate. Oral^im TU means that patients in the oral TU arm were shifted to the im TU arm treatment after 6 months.

modification in SHBG, FSH, LH, E_2 or PRL levels were found after 12 months of any treatment (Table 2). No changes were statistically significantly different at any time-point in the P-arm.

Metabolic parameters

After 6 months oral TU produced no improvement in insulin sensitivity (HOMA-IR=4.61±1.03 *vs* 4.37±1.81, ns) from baseline; after cross-over to im TU, this group showed an improvement in insulin sensitivity (HOMA-IR=3.01±1.16; $p<0.001$) that was determined by a reduction in both fasting glucose and fasting insulin, though only the effect on fasting glucose was statistically significant (106±11 *vs* 98±8 mg/dl; $p<0.05$). After 6 months oral TU produced a marked improvement in insulin sensitivity (HOMA-IR=4.27±1.11 *vs* 2.78±0.53; $p<0.001$) from baseline, while after 12 months of treatment a further significant decrease in HOMA-IR occurred (2.17±0.4; $p<0.001$) (Fig. 2). This effect was explained by a reduction from baseline in both fasting glucose (105±8 *vs* 97±7 *vs* 96±5 mg/dl, after 6 and 12 months, respectively; $p<0.05$) and fasting insulin (18±4 *vs* 11±3 *vs* 12±2 mIU/l, after 6 and 12 months, respectively; $p<0.05$). No significant changes from baseline were seen in HbA_{1c}, total cholesterol, HDL-cholesterol, triglycerides, SGOT, SGPT, γGT in all groups after 6 and 12 months of treatment (Table 2). P did not determine any significant changes in metabolic parameters.

Body composition and blood pressure

After 6 months, only im TU produced a decrease in waist circumference from baseline (105±10 *vs* 101±10 cm; mean –4 cm; $p<0.0001$) and in fat mass (33±5 *vs* 29±6%; mean –4%; $p<0.001$), and an increase in fat-free mass (57±5 *vs* 61±4 kg; mean +4 kg; $p<0.001$). Also, after 12 months patients who were shifted from oral to im TU reported a significant increase in in fat-free mass (56±6 *vs* 60±5 kg; mean +3.8 kg; $p<0.001$). After 12 months im TU produced a further decrease in waist circumference from baseline (97±7 cm; mean –8 cm; $p<0.001$) (Fig. 3) and in

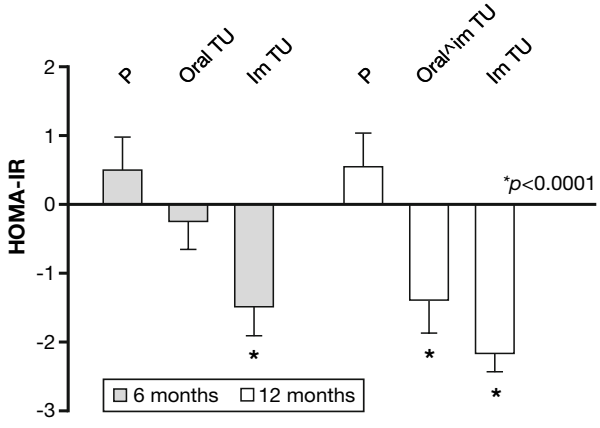

Fig. 2 - *Changes from baseline in the homeostasis model assessment index of insulin resistance (HOMA-IR) after 6 and 12 months of placebo (P), oral testosterone undecanoate (TU) and im TU treatments. Oral^im TU means that patients in the oral TU arm were shifted to the im TU arm treatment after 6 months.*

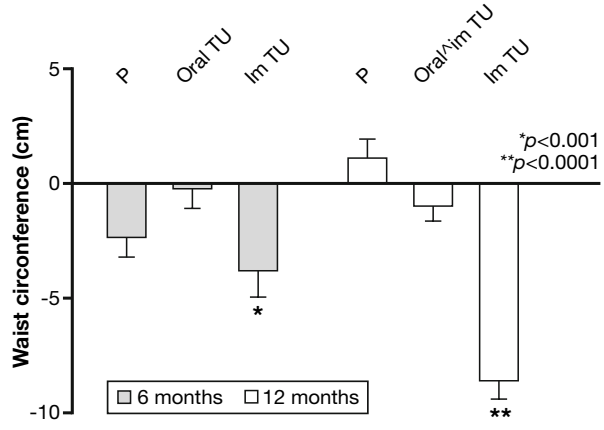

Fig. 3 - *Changes from baseline in waist circumference (cm) after 6 and 12 months of placebo (P), oral testosterone undecanoate (TU) and im TU treatments. Oral^im TU means that patients in the oral TU arm were shifted to the im TU arm treatment after 6 months.*

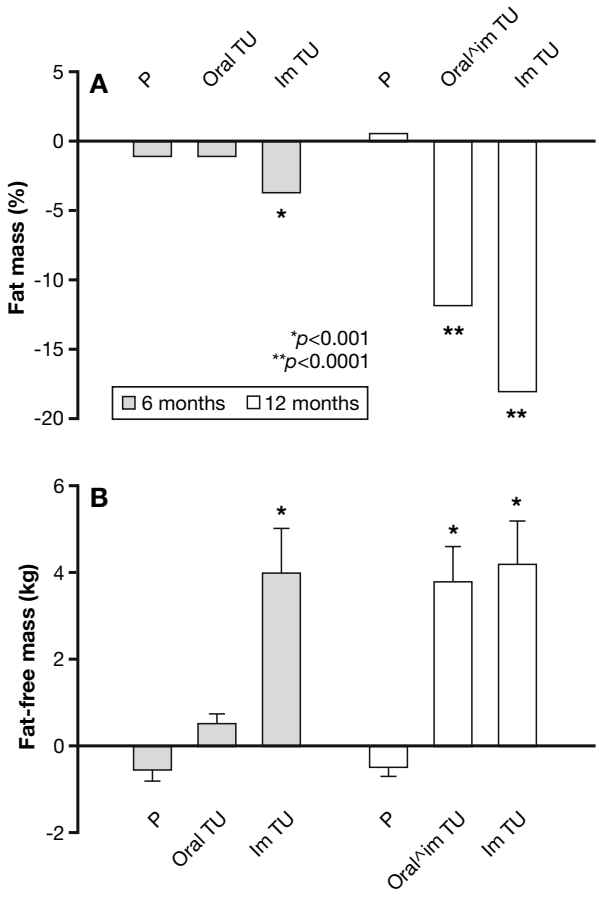

Fig. 4 - *Changes from baseline in fat mass (%) (panel A) and fat-free mass (kg) (panel B), measured by dual energy X-ray absorptiometry (DEXA) system, after 6 and 12 months of placebo (P), oral testosterone undecanoate (TU) and im TU treatments. Oral^im TU means that patients in the oral TU arm were shifted to the im TU arm treatment after 6 months.*

fat mass (26±4%; mean –17.2%; $p<0.001$), without any modification of fat-free mass parameters (Fig. 4A and B). The BMI remained constant during the 12 months of initial observation and no further changes were observed over the study period. No significant changes were observed in either systolic or diastolic blood pressure following T treatment (Table 2). P did not determine any significant changes in body compositon and blood pressure.

AMS and IIEF-5 questionnaires

After 6 months of treatment oral TU produced neither improvements in IIEF-5 nor in AMS scores from baseline; after cross-over to im TU arm, an improvement in IIEF-5 and in AMS total scores was found, with a major improvement in the somatic domain of the AMS score (Table 3).

After 6 months of treatment im TU produced an increase in IIEF-5 and a reduction in AMS total scores from baseline. Therefore, the changes were bigger over 12 months with further significant improvement in the IIEF-5 and AMS score. Men switching from oral to im TU and those in the im TU arm had significantly better results in the total and somatic domain scores of the AMS at 12 months (Table 3). Also, men in the im TU arm reported improvements in AMS sexual domain scores at 12 months.

Safety aspects

Active treatments did not determine significant variations from baseline in PSA levels (Fig. 5), prostate volume (Table 2) and IPSS scores (Table 3).

A significant increase from baseline was found for hemoglobin and hematocrit value ($p<0.05$) within the first 6 months of treatment with im TU in both groups, but remained stable within the normal range during long-term period of observation (Fig. 6A and B). At last observation carried forward, there were two discontinuations due to prostate adverse events. One patients withdrew in the im TU arm (mild and transient heritrocytosis) and one in the P arm (acute myocardial infarction).

DISCUSSION

The results of the present study are novel in that they show for the first time a comparison between two different TU preparations for the treatment of hypogonadism, the oral one being reimbursed by the social assistance service of our country, the im one being charged to the patients. Furthermore, it is clearly shown that after 6 months of therapy the oral formulation determined a modest increase in circulating androgen levels that was not sufficient to produce a beneficial effect from a clini-

Table 3 - *Modifications from baseline of the International Index of Erectile Function-5 (IIEF-5), Aging Males' Symptom (AMS) rating scale (expressed as total score, psycological, somatic and sexual function sub-domains), International Prostate Symptoms Score (IPSS).*

Score	Placebo				Oral TU			Oral^im TU		Im TU			
	Baseline	6 months	12 months		Baseline	6 months		12 months		Baseline	6 months	12 months	
IIEF-5	16±2	19±4	17±2	ns	17±3	18±3	ns	21±2*	*$p<0.01$	17±2	20±3	25±2*	*$p<0.01$
AMS tot. score	37±5	36±4	37±4	ns	38±5	36±3	ns	33±3*	*$p<0.01$	38±3	29±2	27±1*	*$p<0.01$
AMS Somatic	19±5	18±3	17±4	ns	20±5	19±3	ns	17±1*	*$p<0.05$	21±4	16±2*	12±2**	*$p<0.05$ **$p<0.01$
AMS Sexual	11±4	10±4	11±4	ns	12±3	10±2	ns	9±2	ns	11±3	8±2	7±2*	$p<0.05$
AMS Psychol.	7±2	8±3	9±2	ns	6±3	7±3	ns	7±2	ns	6±3	7±2	8±3	ns
IPSS	2±1	1.5±1	1.5±0.5	ns	1.5±1	1.5±1	ns	1.5±0.5	ns	2±1	2±0.5	1.5±1	ns

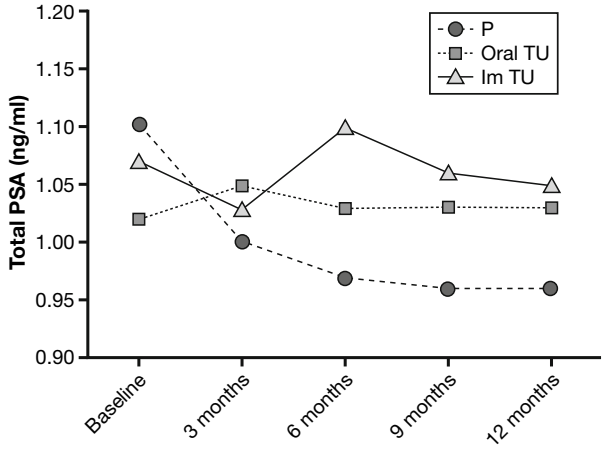

Fig. 5 - *Changes from baseline in prostate specific antigen (PSA) serum levels after 6 and 12 months of placebo (P), oral testosterone undecanoate (TU) and im TU treatments.*

cal standpoint on most symptoms complained by the patients at study entry. In the oral TU arm, plasma TT and FT levels achieved were in the low-normal range of normality, and did not determine either improvements in metabolic parameters, or in anthropometric measurements or in sexual questionnaire scores from baseline. By contrast, Boyanov et al. reported a greater reduction in HbA_{1c} after 3 months using oral TU treatment in poorly controlled diabetic patients (25). However, their study was not a blinded placebo-controlled study, and the changes observed in HbA_{1c} were much bigger than would be expected within 3 months using conventional anti-diabetic medications. In a 12-month placebo-controlled study, Haren et al. reported no changes in plasma TT levels, concluding that 80 mg twice per day oral TU does not improve overall LOH questionnaire scores (26). In the im TU arm, plasma TT and FT levels rose within the middle of normal range after 6 months of treatment and further increased after 12 months of treatment, resulting into the medium-high range of normality. This was paralleled by significant increases in IIEF-5 and AMS scores and all features of MS improved significantly within 6 months, reaching a significant change after 12 months. Thus, it is concluded that clinical efficacy of TRT in this population of hypogonadal men with MS is reached when its plasmatic levels approach into the medium to medium-high range of normality (>5 ng/ml), although subjective threshold values may be different. From the results of the primary efficacy analysis, only im TU determined a decrease in mean HOMA-IR either at 6 and 12 months. This effect was explained by a significant reduction in both fasting glucose and insulin levels from baseline. Surprisingly, this trend occurred also in the P arm within the first 6 months and this was mainly explained by a 'placebo' effect of the new treatment introduced for their MS and ED and by the fact that they were under continuous medical control; in fact, this effect was lost at 12-month follow-up where both waist circumference and fat mass were again comparable with those reported at baseline. We are aware of the small sample size that represents a study limitation, but previous studies have shown a statistically significant effect on insulin sensitivity with a lower number of patients (27). Also, in our population, a significant reduction of waist circumference that resulted in better body composition favoring fat-free mass instead of visceral fat mass occurred in all im TU treatment groups (without changes in BMI), and might account for by the modifications of insulin sensitivity. However, the mechanisms by which T may reduce insulin resistance are still uncertain. In addition a positive correlation between serum T levels and insulin sensitivity in men seems to exist across the full spectrum of glucose tolerance (28) and this relationship is, at least partially, direct and not fully dependent on the elements of the MS (29) or obesity (30). Other studies have found a dose-dependent effect of T on fat mass, showing that T treatment appears to induce a region-specific decrease in intra-abdominal (visceral) fat mass (31). There is considerable evidence linking abdominal obesity to insulin resistance and the excess of

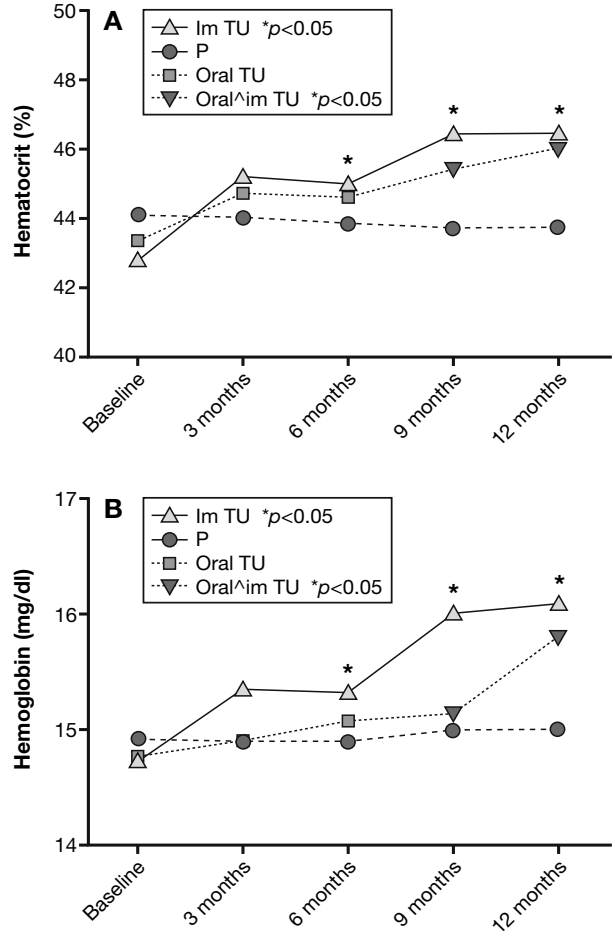

Fig. 6 - *Changes from baseline in plasma levels of hematocrit (%) (panel A) and hemoglobin (mg/dl) (panel B) after 6 and 12 months of placebo (P), oral testosterone undecanoate (TU) and im TU treatments. Oral^im TU means that patients in the oral TU arm were shifted to the im TU arm treatment after 6 months.*

visceral fat results in the liver being exposed to higher amounts of free fatty acids leading to hepatic and eventually systemic insulin resistance (32). In another study, TRT appeared to have beneficial effects on circulating high senstitive C-reactive protein (hsCRP) levels in T2DM patients, which some have considered as a key factor in the development of insulin resistance and the MS (33). The biomarkers of abdominal obesity and inflammation have not been investigated in the present study. Other authors have demonstrated that waist circumference is a practical indicator of visceral fat (34), and that improvement in abdominal obesity is particularly important, since an excess of intra-abdominal adiposity increases cardiometabolic risk directly *via* altered secretion of adipokines (35), and indirectly via promotion of insulin resistance and MS (36). The effects of weight loss on reproductive hormones in moderately obese men are known from old studies where it was reported that a robust diet-induced weight loss was able to restore the steroid abnormalities, i.e. increased estrogens and reduced T at baseline (37). Rapid weight loss with successful weight maintenance in abdominally obese men with the MS leads to a sustained increase in T with a dramatic increase in SHBG levels (38). Plasma SHBG has been proposed to be an indicator of the degree of hyperinsulinemia of the MS (39, 40). We found a little but not significant difference in patterns of SHBG levels after im TU that could have been the result of an higher increase in plasma T levels; a reduction in hyperinsulinemia would probably have occurred (41) leading to concomitant rise in plasma SHBG levels. These effects translated also to morbidly obese men with the MS suggest that T levels may be raised by beneficial 'lifestyle' correction programs and this may be important with regard to prevention of progressive metabolic decompensation and CVD. Since hypogonadism associated with ED is very frequent in men with obesity/MS (42) and is associated with an increased lethality (43), we believe that T administration in such men might have acted two-fold: firstly, to improve insulin resistance mainly through reduction in visceral adiposity as previously suggested by elegant meta-analyses (44), thus reducing the burden of major adverse cardiovascular events; secondly, to improve ED complaints of the patients. Almost all patients in our study abandoned the use of phosphodiesterase type-5 inhibitors for enhancing their erectile function within 6 months of im TU treatment as confirmed by IIEF-5 and AMS sexual score questionnaires, in contrast to those in the oral TU and P arms, respectively.

Both oral and im TU were safe over the entire period of study and did not produce any significant increase in PSA, prostate volume and symptom score. A significant modification in hematocrit and hemoglobin was found in the im TU arm within 6 months from commencing treatment, although these changes were always within the normal range and did not require any warning to the patient. Noteworthy, one patient was discontinued in the im TU arm because of a rise in the hematocrit level above the normal range within 6 months, however the patient had a baseline level of 51% that was almost critical at the study entry. By contrast, in the P arm one patient was discontinued because of the occurrence of acute myocardial infarction.

CONCLUSIONS

This study shows for the first time that oral formulation of TU is clinically ineffective compared with im route in improving insulin sensitivity, body composition and ED in men with hypogonadism and MS. Im TU administration was more effective than oral to reach the target for T levels and to improve MS parameters and produced no major unwanted effects after long-term administration, with no increase in prostate volume or obstructive symptoms. The encouraging results of this study and the observation that T plasma levels in the medium-high range of reference values (> 5 ng/ml) are more effective than levels in low-middle normal range indicate that there may be a dose-effect relationship that must be interpreted with caution until more appropriate long-term intervention studies are performed.

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