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# Fifty-two–Week Treatment With Diet and Exercise Plus Transdermal Testosterone Reverses the Metabolic Syndrome and Improves Glycemic Control in Men With Newly Diagnosed Type 2 Diabetes and Subnormal Plasma Testosterone

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**ABSTRACT:** Men with the metabolic syndrome (MetS) and type 2 diabetes (T2D) often have low testosterone levels. Elevating low testosterone levels may improve features of the MetS and glycemic control. In a single blind, 52-week randomized clinical trial, the effects of supervised diet and exercise (D&E) with or without transdermal testosterone administration on components of the MetS in hypogonadal men with the MetS and newly diagnosed T2D were assessed. A total of 32 hypogonadal men (total testosterone <12.0 nmol/L) with newly diagnosed T2D and with the MetS as defined by the Adult Treatment Panel III and the International Diabetes Federation received supervised D&E, but 16 received it in combination with testosterone gel (50 mg) once daily (n = 16). No glucose-lowering agents were administered prior to or during the study period. Outcome measures were components of the MetS as defined by the Adult Treatment Panel III and the International Diabetes Federation. Serum testosterone, glycosylated hemoglobin ($HbA_{1c}$), fasting plasma glucose, high-density lipoprotein cholesterol, triglyceride concentrations, and the waist circumference improved in both treatment groups after 52 weeks of treatment. Addition of testosterone significantly further improved these measures compared with D&E alone. All D&E plus testosterone patients reached the $HbA_{1c}$ goal of less than 7.0%; 87.5% of them reached an $HbA_{1c}$ of less than 6.5%. Based on Adult Treatment Panel III guidelines, 81.3% of the patients randomized to D&E plus testosterone no longer matched the criteria of the MetS, whereas 31.3% of the D&E alone participants did. Additionally, testosterone treatment improved insulin sensitivity, adiponectin, and high-sensitivity C-reactive protein. Addition of testosterone to supervised D&E results in greater therapeutic improvements of glycemic control and reverses the MetS after 52 weeks of treatment in hypogonadal patients with the MetS and newly diagnosed T2D.

Key words: Male hypogonadism, insulin resistance, HbA1c, lipids, blood pressure.

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Cross-sectional epidemiologic studies have reported a relationship between plasma testosterone, insulin sensitivity, and type 2 diabetes mellitus (T2D). Men with T2D have a lower serum testosterone concentration compared with men without a history of diabetes, and there is an inverse association between testosterone levels and glycosylated hemoglobin ($HbA_{1c}$) concentrations (Svartberg, 2007; Stanworth and Jones, 2009). In men with low plasma testosterone, the risk of T2D is increased (Zitzmann et al, 2006). A recent systematic review and meta-analysis indicated that testosterone level was significantly lower in men with T2D (Ding et al, 2006). Similarly, prospective studies reviewed in the same meta-analysis showed that men with higher testosterone levels had a 42% lower risk of T2D compared with men with a lower serum testosterone concentration (Ding et al, 2006). In hypogonadal men, the effects of exogenous testosterone supplementation on glycemic control are somewhat diverse. Two studies replacing testosterone in hypogonadal men with T2D found no effect on glycemic control (Lee et al, 2005; Basu et al, 2007), whereas another study found that testosterone replacement therapy improved glycemic control (Kapoor et al, 2006).

Individuals with T2D often show disturbances consistent with the metabolic syndrome (MetS; Haffner, 2006). On the other hand, individuals with the MetS have increased risk of developing T2D (Hanley et al, 2005). Several definitions of the MetS have been presented in the literature, of which the definitions from the Adult Treatment Panel III (ATP III; Grundy et al, 2004) and the International Diabetes Federation (IDF; Alberti et al, 2005) are the most commonly used. The syndrome includes atherogenic dyslipedemia, abdominal

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adiposity, and elevated blood pressure in the presence of T2D or an elevated fasting plasma glucose concentration (Kalyani and Dobs, 2007). Most of these symptoms are also often encountered in hypogonadal men (Muller et al, 2005; Traish et al, 2009), and low levels of endogenous sex hormones predict the MetS (Kalyani and Dobs, 2007). Treatment with exogenous testosterone has been shown to improve these metabolic derangements (Kapoor et al, 2006). In another recently published study, testosterone replacement therapy appeared to have beneficial effects on circulating high-sensitive C-reactive protein (hsCRP) levels in individuals with T2D, which some have considered as a key factor in the development of insulin resistance and the MetS (Haffner, 2006).

The goal of the current study was to assess the effects of 52-week treatment with supervised diet and exercise alone or in combination with transdermal testosterone administration on glycemic control and the various components of the MetS in hypogonadal men with the MetS and newly diagnosed T2D.

## Materials and Methods

### Subjects and Intervention

A total of 32 hypogonadal males with the MetS and newly diagnosed T2D (fasting plasma glucose >7.0 at baseline and/or >11.1 after a 2-hour, 75-g oral glucose tolerance test, and an elevated level of $HbA_{1c}$) were randomized to either supervised diet and exercise (D&E) alone or in combination with testosterone gel (50 mg once daily; Testogel; Bayer Schering Pharma AG, Berlin, Germany). The procedure of randomization followed recommendations as described in Kenjo et al (2000). The gel was provided by the personnel of the Business Unit Primary Care, Men's Healthcare, Scientific Affairs, Bayer Schering Pharma AG, Berlin, Germany; hospital pharmacy not involved in the study. The study design was single blind; that is, study personnel were not aware of the treatment arm to which participants were randomized, and participants were instructed by the prescribing physician not to disclose their treatment to study personnel. Testosterone deficiency was defined as a morning plasma testosterone concentration lower than 12 nmol/L on 2 occasions (normal >14.0 nmol/L). For safety reasons, only participants with a serum prostate-specific antigen (PSA) concentration lower than 4.0 μg/L and with a normal digital rectal examination of the prostate were included. The MetS was defined according to the definition of the IDF (Alberti et al, 2005). Participants had not been treated previously with any oral antihyperglycemic agent or insulin. Participants received supervised D&E recommendations by certified dieticians and physiotherapists. They were frequently (at least twice a week) contacted by telephone, text messaging, and e-mail to encourage adherence to treatment. In short, participants were instructed to have 3 meals per day that were low glycemic load, low in saturated fats, and rich in omega-3 fatty acids, and to attempt to eat approximately 25% fewer calories per meal compared with their pretreatment diet. At each visit, the advised dietary changes were reviewed. Additionally, participants were offered a controlled and supervised physical activity program: participants walked 3 times per week for 30 minutes and were told to do 15 minutes of muscle-building exercises with weights or elastic strings 3 times per week. Probably, as a result of frequent interactions between staff and participants, compliance with diet and exercise was 100%, and none of the participants dropped out of the study. Finally, in both treatment groups, participants were contacted by telephone twice a week for additional follow-up and advice by a research nurse. All participants completed the study without adverse effects and without protocol violations, and no oral or injectable treatment of the diabetes was allowed or used.

### Measures

Participants visited the clinic every 13 weeks for assessment; laboratory tests were done at pretreatment and at 13 and 52 weeks of treatment. Bioavailable and free testosterone levels were calculated using the method available at the International Society for the Study of the Aging Male Web site (www.issam.ch/freetesto.htm). Waist circumference was measured and recorded to the nearest 0.5 cm.

Insulin and C-peptide measurements were conducted under standard fasting conditions (after an overnight fasting for at least 12 hours, and no food or fluid intake prior to sampling). The homeostatic model assessment (HOMA) was calculated using a single sample according to Levy et al (1998). Safety parameters, including digital rectal examination of the prostate and measurement of serum PSA, were performed at all visits. All participants gave their written informed consent. The study was approved by the local ethics review board and conducted according to the principles of the declaration of Helsinki.

### Statistical Analysis

All data were presented as mean ± SE, unless stated otherwise. Between treatment groups, pretreatment parameters were analyzed using an unpaired Student's *t* test. Chi-square tests were used to test dichotomous variables. Between-treatment group comparisons of differences from pretreatment were made with an analysis of covariance model including terms for treatment group, pretreatment value, and pretreatment × treatment group interaction. Thus, the model adjusted for any potential influence of differences in pretreatment value on the response to treatment. Pearson's univariate correlation coefficients were used to describe between-parameter correlations. Statistical analysis was performed with SPSS 16.0 for Mac OS X (SPSS, Chicago, Illinois). *P* values below .05 were considered statistically significant.

## Results

Baseline characteristics are shown in Table 1. Besides a small, statistically significant difference in baseline hsCRP concentration, no significant differences prior

Table 1. *Patient characteristics*[a]

| | D&E Plus Testosterone (n = 16) | D&E Alone (n = 16) | *P* |
|---|---|---|---|
| Age | 57.3 ± 1.4 | 55.9 ± 1.5 | .491 |
| BMI, kg/m$^2$ | 32.1 ± 0.5 | 32.5 ± 0.6 | .514 |
| Waist circumference, cm | 107.9 ± 1.3 | 105.7 ± 1.4 | .260 |
| Testosterone, nmol/L | 10.5 ± 0.2 | 10.4 ± 0.2 | .691 |
| Free testosterone | 0.2 ± 0.0 | 0.2 ± 0.0 | .318 |
| Bioavailable testosterone | 4.5 ± 0.1 | 4.3 ± 0.1 | .316 |
| SHBG, nmol/L | 37.9 ± 2.2 | 39.7 ± 2.0 | .549 |
| PSA, μg/L | 2.3 ± 0.1 | 2.3 ± 0.1 | .914 |
| $HbA_{1c}$, % | 7.5 ± 0.1 | 7.5 ± 0.1 | .708 |
| Fasting plasma glucose, mmol/L | 7.9 ± 0.2 | 8.3 ± 0.2 | .158 |
| Insulin, pmol/L | 113.2 ± 4.4 | 116.9 ± 6.1 | .628 |
| HDL cholesterol, mmol/L | 1.05 ± 0.03 | 1.00 ± 0.05 | .351 |
| LDL cholesterol, mmol/L | 3.8 ± 0.1 | 3.8 ± 0.1 | .831 |
| Triglycerides, mmol/L | 3.2 ± 0.1 | 3.4 ± 0.3 | .364 |
| Blood pressure, mm Hg | | | |
| Systolic | 140.5 ± 2.6 | 143.5 ± 2.1 | .373 |
| Diastolic | 85.6 ± 0.9 | 85.0 ± 1.0 | .681 |
| HOMA-IR | 5.6 ± 0.3 | 6.1 ± 0.4 | .363 |
| Adiponectin, μg/mL | 10.1 ± 0.5 | 9.1 ± 0.4 | .118 |
| hsCRP, mg/dL | 2.5 ± 0.1 | 3.0 ± 0.1 | .032 |

Abbreviations: BMI, body mass index; D&E, diet and exercise; $HbA_{1c}$, glycosylated hemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitive C-reactive protein; HOMA-IR, homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein; PSA, prostate-specific antigen; SHBG, sex hormone–binding globulin.

[a] Data represent mean ± SE.

to treatment were present between the 2 treatment groups.

### Effects on Sex Hormones

In the D&E and D&E plus testosterone treatment groups, mean ± SE serum testosterone concentrations significantly increased from 10.4 ± 0.2 nmol/L to 11.2 ± 0.2 nmol/L and from 10.5 ± 0.2 nmol/L to 15.4 ± 0.2 nmol/L, respectively, after 52 weeks of treatment (between-group difference ± SE, 4.1 ± 0.2 nmol/L; $P < .001$; Figure 1). Bioavailable testosterone increased from 4.3 ± 0.1 nmol/L to 5.5 ± 0.1 nmol/L and from 4.5 ± 0.1 nmol/L to 8.1 ± 0.1 nmol/L in the D&E and D&E plus testosterone groups, respectively (between-group difference ± SE, 2.5 ± 0.1 nmol/L; $P < .001$; Figure 1). Serum sex hormone–binding globulin (SHBG) concentrations decreased from 39.7 ± 2.2 nmol/L to 30.8 ± 1.3 nmol/L in the D&E group and from 37.9 ± 2.0 nmol/L to 28.7 ± 0.7 nmol/L in the D&E plus testosterone group. However, no significant between-group differences in serum SHBG concentration were observed after 52 weeks of treatment ($P = .142$). Compared with D&E alone, D&E plus testosterone administration did not increase circulating PSA levels (between-group difference ± SE, −0.08 ± 0.1 μg/L; $P = .435$).

### Effects on Glycemic Control

Glycemic control improved in both treatment groups after 52 weeks of treatment (Figure 1). $HbA_{1c}$ decreased by 0.5% ± 0.1% to 7.1% ± 0.1% in the D&E group and by 1.3% ± 0.1% to 6.3% ± 0.1% in the D&E plus testosterone group (between-group difference ± SE, −0.8% ± 0.1%; $P < .001$). Fasting plasma glucose decreased to 6.6 ± 0.2 mmol/L in the D&E group and to 6.1 ± 0.1 mmol/L in the D&E plus testosterone group; however, this difference did not reach statistical significance ($P = .062$; Table 2). All of the patients treated with combined D&E plus testosterone reached the $HbA_{1c}$ target value of less than 7.0%, and 87.5% reached less than 6.5%, whereas only 40.4% of the D&E alone participants reached less than 7.0%, and none reached less than 6.5% ($P < .001$ for both comparisons). Correlations between the change in testosterone levels and glycemic control are shown in Table 3.

### Effects on Components of the MetS and Insulin Sensitivity

All components of the MetS improved after 52 weeks of treatment with either supervised D&E alone or in combination with testosterone gel (Table 2; Figure 2). Waist circumferences declined in both groups but more so in the D&E plus testosterone group. A total of 62.5% of the patients treated with D&E plus testosterone no longer matched the criteria of the MetS according to the IDF definition, whereas 12.5% of the D&E alone patients did ($P = .003$). When diagnosed with the less-stringent ATP III definition, 81.3% D&E plus testosterone patients and 31.3% D&E alone patients had recovered from the MetS after 52 weeks of treatment ($P = .004$). Changes in serum testosterone concentrations correlated significantly with changes in the individual components of the MetS, and these correlations are shown in Table 3.

In both treatment groups, the pretreatment elevated fasting serum insulin concentrations, often used as a measure of insulin resistance, significantly decreased after 52 weeks of treatment, whereas there was no correlation with homeostatic model assessment for insulin resistance (HOMA-IR). Supervised D&E alone reduced insulin levels from 116.9 ± 6.1 pmol/L to 60.2 ± 2.5 pmol/L ($P < .001$). The addition of testosterone to supervised D&E resulted in an additional decrease to 40.2 ± 2.1 pmol/L (between-group difference ± SE, −19.2 ± 2.8; $P < .001$; Table 2). Insulin sensitivity, assessed by HOMA-IR, improved in both treatment groups compared with pretreatment values, with the

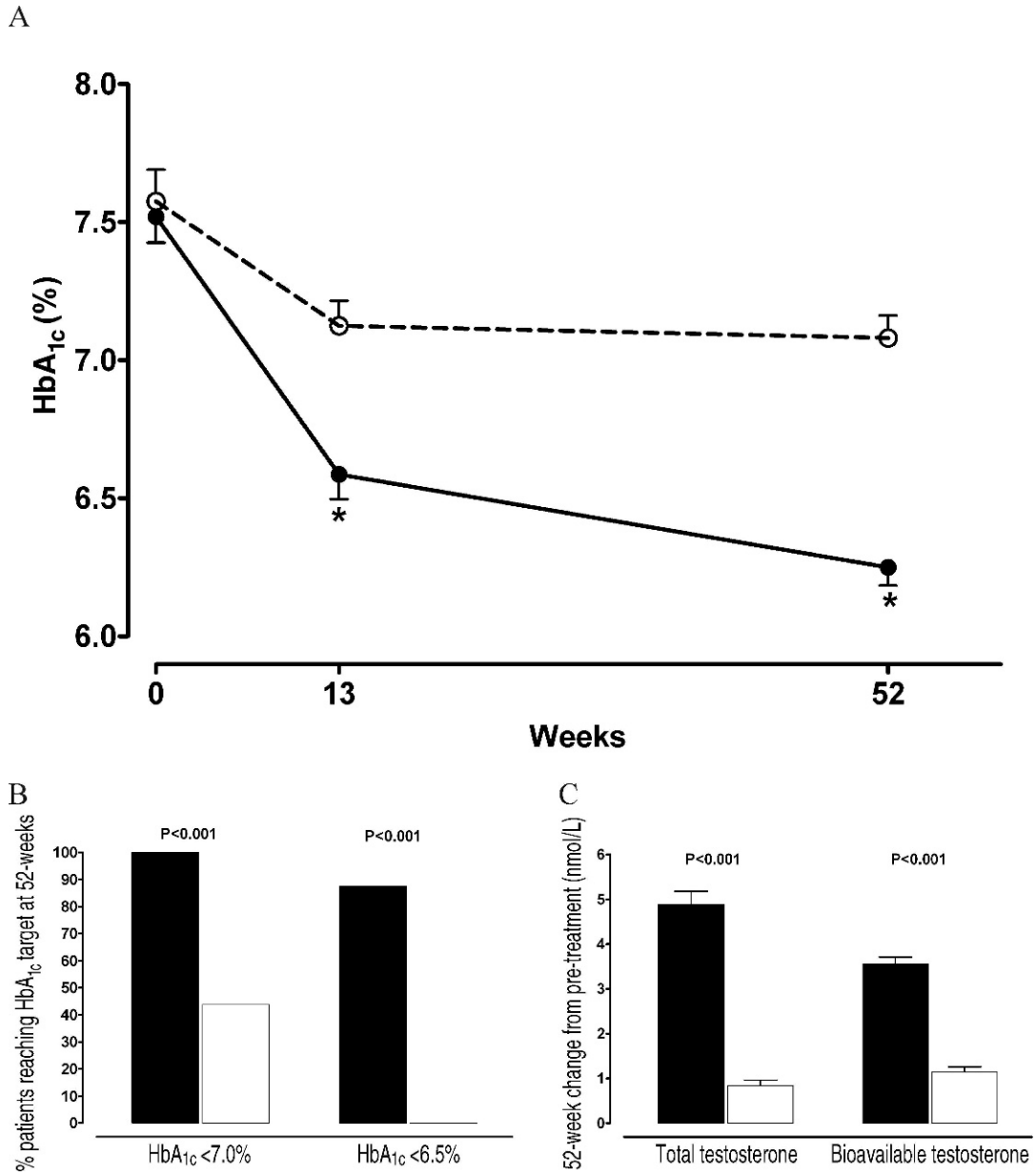


Figure 1. Glycemic control and testosterone profiles. **(A)** Glycosylated hemoglobin ($HbA_{1c}$) values during the course of the study. White circles indicate supervised diet and exercise alone; black circles, supervised diet and exercise in combination with transdermal testosterone administration. **(B)** Percentage of patients achieving $HbA_{1c}$ values less than 7.0% (left) and less than 6.5% (right). White boxes indicate supervised diet and exercise alone; black boxes, supervised diet and exercise in combination with transdermal testosterone administration. **(C)** Change in serum total testosterone and bioavailable testosterone after 52-week treatment with supervised diet and exercise alone (white boxes) or in combination with transdermal testosterone administration (black boxes). Data represent mean and SE. * $P < .001$.

addition of testosterone resulting in a greater decrease in HOMA-IR (between-group difference ± SE, −0.9 ± 0.1; $P < .001$; Table 2). No significant correlation between changes in total testosterone or bioavailable testosterone and HOMA-IR was observed in the current study; however, a significant correlation was present with changes in insulin concentration and changes in total testosterone and bioavailable testosterone ($r = -0.401$; $P = .023$, and $r = -0.480$; $P = .005$, respectively; Table 3). Finally, hsCRP concentrations decreased and adiponectin concentrations increased in both treatment groups (between-group difference ± SE, −0.5 ± 0.1; $P < .001$; and 1.0 ± 0.3; $P = .005$; D&E and D&E plus testosterone groups, respectively; Table 2).

Table 2. *Between-group comparison of metabolic parameters after 52 weeks of supervised diet and exercise (D&E) alone (n = 16) or in combination with transdermal testosterone (n = 16)*[a]

| | Pretreatment | Endpoint (Week 52) | Adjusted Mean Change ± SE | Between-Group Difference | *P* |
|---|---|---|---|---|---|
| Fasting plasma glucose, mmol/L | | | | | .062 |
| D&E alone | 8.3 ± 0.2 | 6.6 ± 0.2 | −1.6 ± 0.1 | −0.3 ± 0.2 | ... |
| D&E plus testosterone | 7.9 ± 0.2 | 6.1 ± 0.1 | −1.9 ± 0.1 | | ... |
| HOMA-IR | | | | | <.001 |
| D&E alone | 6.1 ± 0.4 | 2.5 ± 0.1 | −3.4 ± 0.1 | −0.9 ± 0.1 | ... |
| D&E plus testosterone | 5.6 ± 0.3 | 1.5 ± 0.1 | −4.2 ± 0.1 | | ... |
| Adiponectin, μg/mL | | | | | .005 |
| D&E alone | 9.1 ± 0.4 | 11.2 ± 0.4 | 2.1 ± 0.2 | 1.0 ± 0.3 | ... |
| D&E plus testosterone | 10.1 ± 0.5 | 13.1 ± 0.4 | 3.0 ± 0.2 | | ... |
| hsCRP, mg/dL | | | | | <.001 |
| D&E alone | 3.0 ± 0.1 | 2.2 ± 0.1 | −0.6 ± 0.1 | −0.5 ± 0.1 | ... |
| D&E plus testosterone | 2.5 ± 0.1 | 1.5 ± 0.1 | −1.1 ± 0.1 | | ... |

Abbreviations: hsCRP, high-sensitive C-reactive protein; HOMA-IR, homeostatic model assessment for insulin resistance.
[a] Data represent mean ± SE and adjusted mean change from pretreatment ± SE.

## Discussion

In the present study, we investigated the effects of 52-week transdermal testosterone administration in addition to supervised D&E in hypogonadal men with the MetS and newly diagnosed T2D. A low serum testosterone concentration predicts or is associated with the MetS (Svartberg et al, 2004; Traish et al, 2009) and T2D (Chubb et al, 2008). In addition to the evidence from epidemiologic studies, there appears to be a positive correlation between serum testosterone levels and insulin sensitivity in men across the full spectrum of glucose tolerance (Pitteloud et al, 2005), and this relationship is at least partially direct and not fully dependent on (changes in) elements of the MetS (Yialamas et al, 2007). However, intervention studies are needed to test whether normalization of testosterone levels in hypogonadal men improves insulin resistance and other features of the MetS.

Table 3. *Univariate correlation coefficients between 52-week change in total and bioavailable testosterone and measures of glycemic control, insulin resistance, and the metabolic syndrome*

| | Total Testosterone | | Bioavailable Testosterone | |
|---|---|---|---|---|
| | *R* | *P* | *R* | *P* |
| $HbA_{1c}$ | −0.759[a] | <.001[a] | −0.764[a] | <.001[a] |
| FPG | −0.042 | .821 | −0.123 | .502 |
| Insulin | −0.401[a] | .023[a] | −0.480[a] | .005[a] |
| Waist circumference | −0.736[a] | <.001[a] | −0.764[a] | <.001[a] |
| HDL cholesterol | 0.692[a] | <.001[a] | 0.671[a] | <.001[a] |
| Triglycerides | −0.395[a] | .025[a] | −0.314 | .080 |
| Systolic blood pressure | −0.231 | .203 | −0.170 | .353 |
| Diastolic blood pressure | −0.435[a] | .013[a] | −0.447[a] | .010[a] |
| hsCRP | −0.614[a] | .029[a] | −0.653[a] | .004[a] |
| Adiponectin | 0.298 | .098 | 0.431[a] | .014[a] |
| HOMA-IR | −0.133 | .467 | −0.247 | .173 |

Abbreviations: FPG, fasting plasma glucose; $HbA_{1c}$, glycosylated hemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitive C-reactive protein; HOMA-IR, homeostatic model assessment for insulin resistance.
[a] Statistically significant values.

In our study, supervised D&E alone led to significant improvements in testosterone concentrations, glycemic control, and components of the MetS. The addition of a relatively low-dose testosterone preparation (ie, 50 mg of transdermal testosterone gel per day), raising serum testosterone concentrations to the lower range of normal, led to a significant, additional, improvement of glycemic control, insulin sensitivity, and reversal of the MetS in most participants. Results of this study indicate that diet control, exercise, and testosterone supplementation may be beneficial in the management of men with T2D.

The main weakness of our study is the absence of an actively treated placebo group; however, this was not possible because of the design of the study and medication used. Despite this shortcoming in study design, our study was randomized, and the investigators were blinded; only the patients were aware of the treatment group to which they were randomized. Also, supervised D&E by certified staff was offered to both treatment groups.

Clinical studies that evaluate the effect of normalization of serum testosterone concentrations on glucose homeostasis are few (Lee et al, 2005; Basu et al, 2007). These studies employed different experimental designs, and their results showed limited beneficial effects of testosterone administration (Kapoor et al, 2006). In

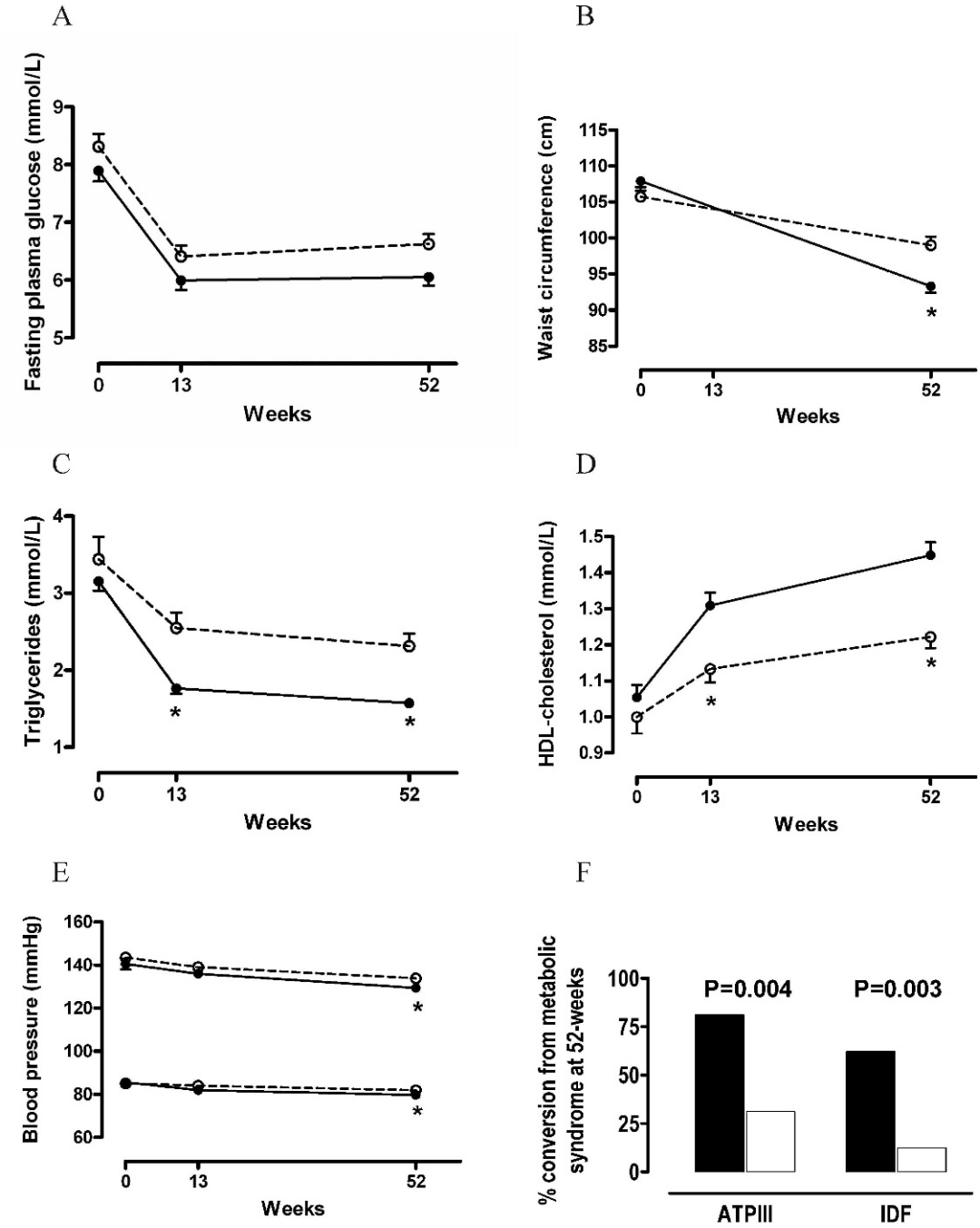


Figure 2. Components of the metabolic syndrome and metabolic syndrome conversion rate during the course of the study. **(A)** Fasting plasma glucose, **(B)** waist circumference, **(C)** triglycerides, **(D)** high-density lipoprotein (HDL) cholesterol, **(E)** systolic and diastolic blood pressure, and **(F)** metabolic syndrome conversion rate after 52-week treatment with supervised diet and exercise alone (white circles and white boxes) or in combination with transdermal testosterone administration (black circles and black boxes). Data represent mean and SE. ATP III indicates Adult Treatment Panel III; IDF, International Diabetes Federation; * $P < .005$.

addition, androgen-deprivation therapy in males with prostatic cancer may be associated with an increased risk for T2D, which may be caused by negative effects on insulin sensitivity (Smith et al, 2006).

In our study, insulin sensitivity, measured by HOMA, improved in both groups and with a significantly greater degree when testosterone was added to supervised D&E. Fasting insulin concentrations, a good representative of insulin sensitivity, did show a significant correlation with changes in circulating androgen levels, an observation in support of Pitteloud et al (2005), who showed a direct relationship between insulin sensitivity and

circulating testosterone concentrations using the hyperinsulinemic euglycemic clamp technique, the gold standard for the assessment of whole-body insulin sensitivity.

Other than insulin sensitivity, 52 weeks of testosterone treatment also significantly improved circulation levels of adiponectin and hsCRP, key serum markers of insulin sensitivity and hepatic steatosis, respectively. Reports from the 1960s and 1970s already reported the beneficial effects of testosterone administration on hepatic fat content in patients with hepatosteatosis (Resnick and Iber, 1972). The changes in both adiponectin and hsCRP were significantly correlated with the therapy-induced changes in bioavailable testosterone. Our findings are not in line with a previous placebo-controlled, randomized study in hypogonadal T2D patients. In these studies, adiponectin levels decreased after 3 to 6 months of treatment with mixed testosterone esters (Lanfranco et al, 2004). As in our study, a negative correlation was found between hsCRP levels and bioavailable testosterone. The opposing findings in the circulating adiopnectin concentrations could be a result of the different routes of testosterone administration used. After intramuscular testosterone injections, circulating testosterone levels are known to peak above the physiologic range, whereas transdermal testosterone gel produces testosterone levels within the reference range for young adults (Gooren and Bunck, 2004). We found a decline in serum levels of hsCRP upon D&E plus testosterone, a finding not reported by Kapoor et al (2007) but replicated in a recent study (Haider et al, 2009).

In summary, our study shows the beneficial effects of supervised D&E treatment on glycemic control, components of the MetS, and insulin sensitivity in hypogonadal patients with the MetS and newly diagnosed T2D. These effects were even greater when transdermal testosterone gel was added to the supervised D&E, which resulted in more than 80% of the patients showing conversion from the MetS, reaching all of the currently set targets for glycemic control. However, more intervention studies investigating the effects of testosterone replacement therapy on pancreatic beta-cell function in hypogonadal men with T2D are needed to fully understand the relationship between circulating sex hormones and carbohydrate metabolism. Finally, serum PSA concentrations did not differ between the 2 treatment groups, indicating that short-term testosterone administration appears to be acceptably safe.

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