Effects of Two Years of Testosterone Replacement on Insulin Secretion, Insulin Action, Glucose Effectiveness, Hepatic Insulin Clearance and Postprandial Glucose Turnover in Elderly Men

Received for publication 20 February 2007 and accepted in revised form 3 May 2007.

Additional information for this article can be viewed in an online appendix at http://care.diabetesjournals.org.

Running title: Effects of Testosterone

Rita Basu, MD
Chiara Dalla Man, PhD
Marco Campioni, PhD
Ananda Basu, MD
K. Sreekumaran Nair, MD, PhD
Michael D. Jensen, MD
Sundeep Khosla, MD
George Klee, MD, PhD
Gianna Toffolo, PhD
Claudio Cobelli, PhD
Robert A Rizza, MD

Division of Endocrinology, Diabetes, Metabolism & Nutrition, Laboratory Medicine & Pathology, Mayo Clinic College Of Medicine, Rochester, MN; University of Padova, Padova, Italy.

Correspondence:
Robert A. Rizza, MD
Mayo Clinic College of Medicine
200 1st Street SW, Rm 5-194 Joseph
Rochester, MN 55905
E-mail: rizza.robert@mayo.edu
Abstract

**Objective:** To determine if, and if so the mechanism by which, testosterone replacement improves carbohydrate tolerance.

**Research Design and Methods:** Fifty-five elderly men with relative testosterone deficiency ingested a labeled mixed meal and underwent a frequently sampled labeled IVGTT before and after treatment with either placebo or testosterone patch (5 mg/day) for two years.

**Results:** Despite restoring bioavailable testosterone to values observed in young men, the change (24 month minus baseline values) in fasting and postprandial glucose, insulin, C-peptide concentrations, meal appearance, glucose disposal and endogenous glucose production were virtually identical to those observed after two years of placebo. The change over time in insulin and C-peptide concentrations post intravenous glucose injection also did not differ. Furthermore, the change over time in insulin action and glucose effectiveness (measured with the unlabeled and labeled “oral” and “intravenous” minimal models), as well as insulin secretion and hepatic insulin clearance (measured with the C-peptide model) did not differ in the testosterone and placebo groups.

**Conclusion:** We conclude that two years of treatment of elderly men with testosterone does not improve carbohydrate tolerance nor does it alter insulin secretion, insulin action, glucose effectiveness, hepatic insulin clearance or the pattern of postprandial glucose metabolism. Thus testosterone deficiency is unlikely to be the cause of the age associated deterioration in glucose tolerance commonly observed in elderly men.
Testosterone concentrations fall and glucose tolerance deteriorates in men as they age (1-5). It currently is not known if the former contributes to the latter. Data from both animal and human studies suggest this may be the case. In rats, castration decreases insulin stimulated glucose uptake and reduces insulin gene expression in pancreatic beta cells (6,7). On the other hand, testosterone replacement restores insulin action, increases islet insulin content and enhances insulin secretion (6,7). Low testosterone concentrations are associated with insulin resistance and predict the development of diabetes in elderly men (8-12). Furthermore, androgen treatment improves insulin action in abdominally obese middle aged men (13,14). On the other hand, testosterone has been reported to have no effect on insulin action in normal young men (15) or in men with hypogonadism (16). Furthermore, supraphysiologic doses of androgens cause insulin resistance in both humans (17,18) and dogs (19).

We have recently reported that twenty four months of DHEA replacement in physiological doses had no beneficial effects on quality of life, body composition, physical performance in either elderly men or women (20). We also observed that DHEA replacement did not alter net insulin action measure with the unlabeled meal minimal model (21). To our knowledge, the effects of testosterone replacement on insulin secretion, insulin action and postprandial glucose turnover have not been previously evaluated in elderly men. The present studies, conducted as part of a large randomized trial that also evaluated the effects of testosterone replacement on body composition and muscle strength (20), addressed this question by measuring insulin action, insulin secretion and hepatic insulin clearance before and after two years of treatment with testosterone or placebo. Postprandial glucose turnover also was measured to determine if testosterone replacement lowered the rate of meal appearance, enhanced postprandial suppression of endogenous glucose production, and stimulated postprandial glucose uptake. We report that while two years of testosterone replacement resulted in a small but statistically significant increase in muscle mass, it had no effect on insulin action, glucose effectiveness, insulin secretion, hepatic insulin clearance, or postprandial glucose turnover.

Methods

The study design and methods have previously been described in detail (20) In brief, men whose bioavailable testosterone (non-sex hormone binding globulin bound) concentration was less than 103 ng/dl and DHEA concentration less than 1.57 µg/ml (15th percentile for young men) were eligible for study and were considered as having relative testosterone deficiency. Volunteer characteristics are given in Table 1. The study was a randomized placebo-controlled double blind trial for two years. Subjects were assigned to wear either testosterone patch (5 mg/ day, D-TRANS), or placebo patch each day. Baseline data and results of DHEA replacement have previously been published (3,4,11).

Subjects were admitted and given a standard 10 Kcal/kg meal. No additional food was eaten until the next morning. On one occasion, a mixed meal (10 kcal/kg) consisting of scrambled eggs, Canadian bacon, [1-13C] glucose Jell-O was consumed within fifteen minutes (3,4). Infusion of [6-3H] glucose was started with the meal and infusion of both [6-3H] glucose and [6,6-2H2] glucose were altered thereby minimizing the change in plasma glucose enrichment (22). On another occasion 0.33 grams/kg of glucose containing [6,63H2] glucose was injected at time 0 and insulin 0.02 units/kg at time 20
minutes (4). Arterialized venous blood was collected at frequent intervals as previously described (3,4).

Plasma glucose concentrations were measured using a glucose oxidase method (YSI, Inc., Yellow Springs, OH). Plasma insulin concentrations were measured by chemiluminescence (Access Assay, Beckman, Chaska, MN). Plasma C-peptide concentrations were measured by radioimmunoassay (Linco Research, St. Louis, MO). Levels of sulfated DHEA, total, bioavailable testosterone and estrogen were measure by a competitive chemiluminescence immunoassay; sex hormone–binding globulin measured by solid phase, chemiluminescence assay (Immulite, Diagnostic Products). In subjects with low testosterone levels, values were obtained with the use of high sensitivity chemiluminescence assay. Body composition was measured using dual energy X-ray absorptiometry (DPX scanner, Lunar Corp, Madison, WI).

Calculations

The “oral” and “intravenous” glucose minimal models (23,24) were used to interpret plasma glucose and insulin concentrations measured following meal ingestion or glucose injection (see appendix).

The systemic rates of meal appearance ($R_{\text{meal}}$), endogenous glucose production (EGP) and glucose disappearance (Rd) were calculated using Radzuik’s two compartment model (25). Values from –30 to 0 minutes were averaged and considered as basal. Area above basal was calculated using the trapezoidal rule. Parameters of all models were estimated by using the SAAMII software (26). Measurement errors have been assumed to be independent and Gaussian, with zero mean and variance for glucose and tracer glucose as described in (27) and for C-peptide as described (28).

Statistical Analysis

Data are presented as mean ± SEM. Area above basal was calculated using the trapezoidal rule. Changes from baseline (i.e. 24 month values minus baseline values) were compared in the testosterone and placebo groups using Student’s t test. Demographic, hormonal and biochemical data are presented as median and interquartile range. Multiple regression analysis were done in which the dependent variable was the change from baseline (with the use of a rank transformation) and the independent variables were study group, sex, age at the time of randomization, length of follow-up and baseline values. A p-value of less than 0.05 was considered to be statistically significant.

Results

Plasma testosterone and estrogen concentrations and body composition (Table 1)

The effects of testosterone replacement on plasma hormone concentrations and body composition have been described in detail elsewhere (20). In brief, plasma testosterone concentration was significantly higher during two years of treatment with testosterone vs. placebo (p<0.005).

On the other hand, plasma testosterone concentrations did not change following two years of treatment with placebo. Estrogen concentrations were no different following treatment with either testosterone or placebo. Two years of treatment with testosterone did not alter visceral fat or percent body fat but resulted in a slight but statistically significant increase (p<0.01) in fat free mass. On the other hand, treatment with testosterone did not alter peak VO$_2$, leg isometric knee extension, double leg press or chest press.
Plasma glucose, insulin and C-peptide concentrations observed prior to and following meal ingestion (figure 1)

The change (i.e. 24 months minus baseline) of fasting glucose, insulin and C-peptide concentrations present on the day of the mixed meal study did not differ following two years of treatment with testosterone or placebo (figure 1). The change in the postprandial increments (i.e. area above basal) of glucose, insulin and C-peptide concentrations also did not differ following treatment with testosterone or placebo.

Meal rate of appearance, endogenous glucose production and glucose disappearance observed following meal ingestion (figure 2)

The change in fasting rates of endogenous glucose production and glucose disappearance did not differ following two years of treatment with testosterone from those observed following two years of treatment with placebo. The change in the postprandial increment in meal appearance and glucose disappearance or postprandial decrement in endogenous glucose production also did not differ following two years of treatment with testosterone or placebo.

Plasma glucose, insulin and C-peptide concentrations observed prior to and following intravenous injection of glucose (figure 3—online only appendix)

The change in fasting glucose, insulin and C-peptide concentrations present on the day of the IVGTT did not differ in the testosterone or placebo groups. Similarly, the change in glucose, insulin, and C-peptide concentrations observed following intravenous injection of glucose did not differ following two years of treatment with testosterone or placebo.

Insulin action, insulin secretion, glucose effectiveness, and hepatic insulin clearance (table 1)

The change from baseline in net insulin action (Si) measured with either the unlabeled oral or unlabeled “oral” or “intravenous” glucose minimal models did not differ following two years of treatment with either testosterone or placebo. The change in the ability of insulin to stimulate glucose uptake (Si*) measured with either the labeled “oral” or labeled “intravenous” minimal models also did not differ in the testosterone and placebo groups.

The change from baseline in meal indices (Phi<sub>dynamic</sub>, Phi<sub>static</sub>, and Phi<sub>total</sub>) intravenous glucose indices (Phi<sub>1</sub>, Phi<sub>2</sub>, and Phi<sub>total</sub>) of insulin secretion did not differ following two years of treatment with either testosterone or placebo. This resulted in no difference in the change from baseline in either the meal (DI<sub>dynamic</sub>, DI<sub>static</sub>, and DI<sub>total</sub>) or intravenous glucose (DI<sub>1</sub>, DI<sub>2</sub>, and DI<sub>total</sub>) disposition indices.

The change in net glucose effectiveness (GE), the ability of glucose to stimulate its own uptake (GE*), and hepatic insulin clearance measured following intravenous glucose injection also did not differ in the testosterone and placebo groups.

Discussion

The present studies indicate that two years of testosterone replacement has no detectible effect on insulin secretion, insulin action, glucose effectiveness, hepatic insulin clearance or postprandial glucose turnover in elderly men. These data strongly imply that relative or absolute testosterone deficiency does not contribute to insulin resistance or the impairment in insulin secretion that is commonly observed in elderly men. They also argue against the ability of testosterone replacement to delay or reverse the age associated deterioration in glucose tolerance.
We have previously reported that postprandial glucose disposal is lower in elderly compared to young men (3). The present data indicate that this defect is not reversed by testosterone replacement since rates of postprandial glucose disposal were virtually identical prior to and following two years of treatment with testosterone and did not differ from those following treatment with placebo. The increment in glucose concentrations following a mixed meal is also influenced by the rate at which the ingested glucose enters the systemic circulation and by the rate at which endogenous glucose production is suppressed. Neither differed from those observed in young men and neither were influenced by testosterone replacement. Thus, testosterone replacement did not improve glucose tolerance in elderly men and did not restore postprandial rates of glucose disappearance toward rates observed in healthy younger subjects.

Elderly men commonly have low testosterone concentrations and commonly are insulin resistant (5,8-11). Testosterone receptors are present on muscle (29) and some (6,13,14) but not all (15,16,19) studies have suggested that treatment with androgens can improve insulin action in rats (6) or middle aged humans (13,14). We have previously reported that testosterone replacement in elderly men does not improve net insulin action measured with the unlabeled “oral” minimal model (20). The present data extend these observations by showing that testosterone replacement also had no effect on net insulin action measured with the unlabeled “oral” and labeled minimal models respectively. The latter observation is particularly noteworthy since the labeled minimal model specifically measures the ability of insulin to stimulate glucose disposal (Si*). Furthermore, the “oral” and “intravenous” glucose tolerance tests were performed on two separate occasions and insulin action measured with the unlabeled and labeled minimal models provide independent assessments of insulin action. Therefore, while it is possible that an effect of testosterone replacement on insulin action was missed, if so it must have been small and likely of limited biologic significance.

Glucose uptake is regulated by glucose as well as insulin concentrations (30,31). The former is commonly referred to as glucose effectiveness. Net glucose effectiveness and the ability of glucose to stimulate its own uptake can be measured with the unlabeled and labeled minimal models respectively. Experiments in animals suggest that testosterone can regulate islet cell function (7). We have previously reported that insulin secretion is impaired in elderly men (3). The present data indicate that treatment with testosterone does not ameliorate this impairment. Insulin secretion whether evaluated qualitatively by comparing the area above basal of insulin and C-peptide concentrations after meal ingestion or glucose injection or quantitatively by using C-peptide models did not differ following treatment with testosterone or placebo. Since there were virtually no changes over time in insulin or C-peptide concentrations, these data also indicate that hepatic insulin clearance did not change. The “oral” and “intravenous” glucose tolerance tests evaluate different aspects of insulin secretion (32). The former assesses glucose and nutrient induced stimulation of insulin secretion whereas the latter evaluates the response to glucose alone. Similarly, the intravenous Phi\textsubscript{1} is believed to reflect the acute release of insulin from previously docked insulin granules that occurs during the few minutes following glucose injection. In contrast, Phi\textsubscript{dynamic} measures the increment in
insulin secretion that occurs in response to the progressive increase in glucose concentrations observed during the thirty to sixty minutes following meal ingestion. Therefore it presumably is modulated by additional intra-islet events including translocation, priming and docking of insulin granules. On the other hand, the intravenous $\Phi_i^2$ and the meal $\Phi_{\text{static}}$ are believed to be influenced by the still earlier events in the insulin secretory cascade including insulin synthesis and processing. Taken together, the present data indicate that testosterone replacement had no detectible effect on any aspect of beta cell function whether considered as the absolute values of the various insulin secretion indices or when considered in light of the prevailing level insulin action by calculation of disposition indices.

The present study suffers from certain limitations. We recruited men whose bioavailable testosterone concentration (not bound to sex hormone binding globulin) was less than the fifteenth percentile of healthy young men (33). On the other hand, none of the men had undetectable levels. It is therefore possible and even likely that testosterone treatment would improve carbohydrate tolerance in men who were overtly hypogonadal. The body mass index of the subjects averaged ~28 kg/m$^2$. Therefore few of the subjects were overtly obese. Of interest, the effects of testosterone on insulin action ($S_i$ and $S_i^*$) and insulin secretion (disposition indices) did not differ when the subjects whose body mass index or bioavailable testosterone in the upper tertile was compared to those in the lower tertile. Due to concern regarding the potential adverse effects of long term treatment of elderly men with androgens, we sought to raise bioavailable testosterone concentrations to the lower range of normal for healthy young men. While we accomplished this goal, it is possible that larger amounts of testosterone would have altered glucose tolerance. However use of high dose androgens has multiple safety concerns as well may decrease rather than increase insulin action (18,19). It is possible that two years of treatment with androgens was insufficient time to alter carbohydrate metabolism. We doubt this is the case since when such effects have been observed in animals or younger humans, they were detectible within days to weeks (7,13,14).

In summary, the present studies indicate that treatment of elderly men with relative testosterone deficiency for two years with doses sufficient to raise their bioavailable testosterone concentrations to the low normal range for healthy young men, had no detectible effect on fasting or postprandial glucose concentrations. Testosterone replacement also did not alter meal appearance, postprandial suppression of endogenous glucose production or stimulation of glucose uptake. Furthermore, testosterone replacement did not alter insulin secretion, insulin action, glucose effectiveness or hepatic insulin clearance. Thus testosterone deficiency is unlikely to be the cause of the age associated deterioration in glucose tolerance commonly observed in elderly men. These data also argue against the premise that testosterone replacement will delay or prevent the progression of the age associated deterioration in glucose tolerance that is commonly observed in elderly men.

Acknowledgments
Supported by grants from the National of Health (P01 AG-14283, RR00585, DK29953) and by the Mayo Clinic. Dr Rizza also is supported by the Earl and Annette McDonough Professorship. We wish to thank R. Rood, B. Dicke, L.Heins, J. Feehan, B. Norby, P.Hellwig, T. Hammer, and L.
Wahlstrom for technical assistance and assistance in recruiting the subjects, R.Rood for assistance with graphics, M. Davis for assistance in the preparation of the manuscript and the staff of the Mayo General Clinical Research Center for assistance in performing the studies. We also wish to thank our co-investigators on the program project, including Drs. Peter O’Brien, and Donald Tindall for thoughtful comments and suggestions.
References


<table>
<thead>
<tr>
<th></th>
<th>Placebo group (n=29)</th>
<th>Testosterone group (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Treatment</td>
<td>Post Treatment</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>67 (64, 73)</td>
<td>---</td>
</tr>
<tr>
<td>BMI</td>
<td>27 (26, 30)</td>
<td>28 (25, 29)</td>
</tr>
<tr>
<td>Body Fat (%)</td>
<td>28 (24, 32)</td>
<td>28 (22, 32)</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>61 (57, 64)</td>
<td>61 (57, 63)</td>
</tr>
<tr>
<td>Peak VO$_2$ (ml/kgFFM)</td>
<td>40 (36, 42)</td>
<td>38 (34, 46)</td>
</tr>
<tr>
<td>Sulfated DHEA (ug/mL)</td>
<td>0.7 (0.5, 1.0)</td>
<td>0.6 (0.4, 0.8)</td>
</tr>
<tr>
<td>Total Testosterone (ng/dL)</td>
<td>398 (296, 465)</td>
<td>395 (342, 528)</td>
</tr>
<tr>
<td>Bioavailable Testosterone (ng/dL)</td>
<td>53 (46, 62)</td>
<td>53 (40, 64)</td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>24 (20, 28)</td>
<td>22 (19, 28)</td>
</tr>
<tr>
<td>Bioavailable Estradiol (pg/mL)</td>
<td>9 (8, 12)</td>
<td>9 (6, 10)</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>42 (36, 50)</td>
<td>40 (36, 51)</td>
</tr>
</tbody>
</table>

Median and Inter-quartile range of hormones and biochemical markers before and after treatment with placebo and testosterone.
* indicates p<0.01 vs. pre-treatment
Table 2: Meal and IVGTT indexes of Insulin Action and Secretion

<table>
<thead>
<tr>
<th></th>
<th>Si (10^{-4} dl/kg/min per uU/ml)</th>
<th>PhiD (10^{-9})</th>
<th>PhiS (10^{-9} min^{-1})</th>
<th>PhiTot (10^{-9} min^{-1})</th>
<th>DI (10^{-14} dl/kg per min^2 per pmol/L)</th>
<th>GE (dl/kg per min)</th>
<th>Si* (10^{-4} dl/kg/min per uU/ml)</th>
<th>GE* (dl/kg per min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>Pre</td>
<td>11.7 ± 1.8</td>
<td>419.2 ± 28.6</td>
<td>34.1 ± 1.9</td>
<td>37.7 ± 2.1</td>
<td>685.0 ± 87.1</td>
<td>0.04 ± 0.0</td>
<td>9.6 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>11.9 ± 1.4</td>
<td>411.9 ± 44.5</td>
<td>33.0 ± 2.2</td>
<td>36.6 ± 2.5</td>
<td>673.8 ± 67.1</td>
<td>0.04 ± 0.0</td>
<td>9.0 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>Delta</td>
<td>0.2 ± 1.5</td>
<td>-7.3 ± 34.5</td>
<td>-1.1 ± 1.7</td>
<td>-1.1 ± 1.5</td>
<td>-11.2 ± 78.5</td>
<td>0.00 ± 0.0</td>
<td>-0.6 ± 1.0</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Pre</td>
<td>12.6 ± 1.6</td>
<td>410.5 ± 40.5</td>
<td>33.8 ± 1.9</td>
<td>37.2 ± 2.0</td>
<td>731.0 ± 76.0</td>
<td>0.00 ± 0.0</td>
<td>7.8 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>14.1 ± 1.7</td>
<td>386.4 ± 41.3</td>
<td>32.8 ± 2.7</td>
<td>35.0 ± 3.0</td>
<td>759.0 ± 84.0</td>
<td>0.00 ± 0.0</td>
<td>9.4 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>Delta</td>
<td>1.5 ± 1.6</td>
<td>-24.1 ± 41.5</td>
<td>-1.0 ± 1.8</td>
<td>-2.2 ± 2.2</td>
<td>28.0 ± 83.2</td>
<td>0.00 ± 0.0</td>
<td>1.6 ± 0.5</td>
</tr>
<tr>
<td>IVGTT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>Pre</td>
<td>5.8 ± 0.8</td>
<td>130.3 ± 15.1</td>
<td>10.3 ± 0.8</td>
<td>16.6 ± 1.3</td>
<td>153.3 ± 19.8</td>
<td>0.03 ± 0.0</td>
<td>6.7 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>5.5 ± 0.8</td>
<td>135.5 ± 11.7</td>
<td>10.3 ± 0.7</td>
<td>17.2 ± 1.2</td>
<td>150.1 ± 20.2</td>
<td>0.03 ± 0.0</td>
<td>7.6 ± 1.2</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Pre</td>
<td>5.4 ± 0.7</td>
<td>119.9 ± 11.0</td>
<td>10.5 ± 0.8</td>
<td>16.8 ± 1.3</td>
<td>148.3 ± 22.0</td>
<td>0.03 ± 0.00</td>
<td>6.4 ± 0.7</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------</td>
<td>-----------</td>
<td>--------------</td>
<td>------------</td>
<td>------------</td>
<td>--------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>5.7 ± 0.6</td>
<td>119.3 ± 11.0</td>
<td>10.3 ± 0.8</td>
<td>16.4 ± 1.2</td>
<td>144.1 ± 16.0</td>
<td>0.03 ± 0.00</td>
<td>7.9 ± 0.9</td>
</tr>
<tr>
<td>Delta</td>
<td>0.3 ± 0.5</td>
<td>-0.5 ± 7.0</td>
<td>-0.2 ± 0.6</td>
<td>0.4 ± 0.8</td>
<td>-4.2 ± 10.6</td>
<td>0.00 ± 0.00</td>
<td>1.5 ± 0.5</td>
<td>0.00 ± 0.00</td>
</tr>
</tbody>
</table>

**MEAL: Si* T pre vs.post p=0.06**

Appendix:
Si = Net insulin action is the overall effect of insulin to stimulate glucose disposal and inhibit glucose production
GE = Glucose effectiveness is the ability of glucose per se to promote glucose disposal and inhibit glucose production
Si* = Effect of insulin to stimulate glucose disposal
GE* = Effect of glucose to stimulate glucose disposal
\( \Phi_{\text{total}} \) = Overall beta cell response to glucose following a meal or IV glucose
\( \Phi_{\text{dynamic}} \) = Beta cell response to a given increment in glucose concentration following a meal
\( \Phi_{\text{static}} \) = Beta cell response to an increment in glucose above basal following a meal.
\( \Phi_1 \) = First phase insulin secretion that presumably represents release of previously docked insulin granules following IV glucose
\( \Phi_2 \) = Slow/second phase of insulin secretion that represents the response to a given increment in glucose following IV glucose
Disposition index = the appropriateness of insulin secretion for the prevailing level of insulin resistance
\( D_{\text{dynamic}} \) = \( \Phi_{\text{dynamic}} \) multiplied by Si
\( D_{\text{static}} \) = \( \Phi_{\text{static}} \) multiplied by Si
\( D_{\text{total}} \) = \( \Phi_{\text{total}} \) multiplied by Si
HEb = Hepatic insulin extraction in the basal state
HE = Hepatic insulin extraction following meal ingestion
Figure Legends

Figure 1
Plasma glucose, insulin, and C-peptide concentrations observed in elderly men after meal ingestion before (baseline) and following two years of treatment with either placebo (left panels) or testosterone (right panels).

Figure 2
Meal appearance, endogenous glucose production and glucose disappearance observed in elderly men after meal ingestion before (baseline) and following two years of treatment with either placebo (left panels) or testosterone (right panels).

Figure 3 (online only appendix)
Plasma glucose, insulin, and C-peptide concentrations in observed elderly men after intravenous glucose injection at time 0 and insulin injection at time 20 minutes before (baseline) and following two years of treatment with either placebo (left panels) or testosterone (right panels).
Men

Placebo

Glucose

mmol/L

Baseline

24 mos.

Testosterone

Glucose

Baseline

24 mos.

Insulin

pmol/L

C-peptide

nmol/L

Figure 1

Minutes

-60 0 60 120 180 240 300 360 420