



# Impact of a physician-supervised exercise-nutrition program with testosterone substitution in partial androgen-deficient middle-aged obese men

Ernst R Schwarz, Robert D Willix Jr

Cenegenis Education and Research Foundation, Las Vegas and Heart Institute of Southern California, Beverly Hills, 348 S Oakhurst Dr, Beverly Hills, CA 90212, USA

## Abstract

**Background** Partial androgen deficiency syndrome in the aging male is associated with signs of aging such as a development of abdominal obesity, sexual dysfunction, increase body fat, weight gain and the development of cardiac disease. **Objective** We assessed the outcome of a commercially available physician supervised nutrition and exercise program with concomitant testosterone replacement therapy in middle age obese men with partial androgen deficiency in order to reduce cardiac risks factors. **Methods** Fifty-six self referred men without diabetes mellitus, hypertension, or cardiovascular disease (ages  $52.3 \pm 7.8$  years) were randomly selected from a large cohort. Baseline weight, body fat composition, fasting glucose, hemoglobin A1c and fasting lipid levels, as well as free and total testosterone levels were assessed. All patients were assessed and followed 6–18 months after initiation of the program. The program consisted of a low glycemic load balanced nutrition diet, a recommended structured daily exercise program of 30–60 minutes, as well as once to twice weekly intramuscular testosterone injections ( $113.0 \pm 27.8$  mg). **Results** At follow up, weight was reduced from  $233.9 \pm 30.0$  pounds (lbs) to  $221.3 \pm 25.1$  lbs ( $P < 0.001$ ), BMI was reduced from  $33.2 \pm 3.3$  kg/m<sup>2</sup> to  $31.3 \pm 2.8$  kg/m<sup>2</sup> ( $P < 0.0001$ ). Total body fat was  $27.1\% \pm 5.2\%$  vs.  $34.3\% \pm 5.7\%$  at baseline ( $P < 0.0001$ ). Fasting glucose was reduced from  $95.3 \pm 14.4$  mg/dL to  $87.5 \pm 12.6$  mg/dL ( $P < 0.0001$ ). Total cholesterol was reduced from  $195.4 \pm 33.0$  mg/dL to  $172.7 \pm 35.0$  mg/dL ( $P < 0.005$ ). No clinically significant adverse events were recorded. **Conclusions** Testosterone replacement therapy in middle aged obese men with partial androgen deficiency appeared safe and might have promoted the effects of a weight reduction diet and daily exercise program as long as an adequate physician supervision and follow up was granted. The combination therapy significantly reduced coronary risk factors such as glucose intolerance and hyperlipidemia.

*J Geriatr Cardiol* 2011; 8: 201–206. doi: 10.3724/SP.J.1263.2011.00201

**Keywords:** aging; heart disease; androgen deficiency; testosterone

## 1 Introduction

Middle aged men, even in a good state of health, frequently develop abdominal obesity, impaired glucose tolerance, metabolic syndrome, lack of energy and chronic fatigue, loss of libido, erectile dysfunction, change in body composition as well as coronary artery disease with its sequelae.<sup>[1,2]</sup> These conditions are only in part attributed to ageing itself, and have been referred to a generalized decline of male hormones, including testosterone and dehydroepiandrosterone, which has been referred to the non-scientific term “andropause”.<sup>[3–6]</sup> Of interest, most publications in this

regard are review articles rather than data reports referring to clinical studies, since controversies exist regarding the clinical significance of the male climacterium or late-onset hypogonadism.<sup>[7–9]</sup> The combination of androgen deficiency, sexual dysfunction and metabolic syndrome often presents a re-enforcing triad.<sup>[10]</sup> In addition, low levels of androgens have been associated with cardiovascular disease progression, especially coronary artery disease, and increased mortality.<sup>[11–13]</sup>

The metabolic syndrome itself is considered a risk factor for the development of generalized atherosclerosis, coronary artery disease, myocardial infarction and stroke.<sup>[14,15]</sup> The metabolic syndrome refers to the co-existence of diabetes mellitus or impaired glucose tolerance, hypertension, obesity, dyslipidemia and/or micro-albuminuria, based on definitions that slightly differ with regard to its predictive characteristics for the development of coronary artery disease between the American Heart Association/National Heart/Lung/Blood Institute criteria and others.<sup>[16]</sup> The contributing factor of a diet high in saturated fats and carbohydrates and lack of

**Correspondence to:** Ernst R Schwarz, MD, PhD, Professor of Medicine, Cedars Sinai Medical Center and University of California Los Angeles, (UCLA), CA 900478, USA. E-mail: Ernst.Schwarz@cshs.org

**Telephone:** +1-310-4231866 **Fax:** +1-310-423-1498

**Received:** July 13, 2011 **Revised:** September 9, 2011

**Accepted:** September 16, 2011 **Published online:** December 28, 2011

exercise further culminates in endothelial dysfunction as an early marker for an underlying vascular disease process. Several life-style changing programs and diets as well as exercise recommendations have been established to either prevent or reverse early metabolic syndrome with its consequences. Several approaches demonstrated beneficial results, at least transiently. A recently published trial from Germany reported a 50% reduction in the prevalence of the metabolic syndrome following a 12-week low-calorie diet.<sup>[17]</sup> On the other hand, non-adherence to recommended life-style changes that are oftentimes associated with lack of adequate physician supervision, might reverse achievements in reduced body weight, fitness and improved cardiovascular profile over time<sup>[18]</sup> and therefore, lack long-term success rates. Using a more strict physician-supervised strategy, we tested a commercially available nutrition-exercise program with the addition of testosterone substitution in a group of partial androgen deficient obese middle-aged men and evaluated its effect on body weight and composition, glucose and lipid levels and potential side effects.

## 2 Methods

Middle-aged men with overweight or obesity defined as a body mass index (BMI) above 26 kg/m<sup>2</sup> were randomly selected from a commercially available nutritional and exercise program which was part of the Cenegenics™ health evaluation. The program has enrolled more than 20,000 individuals within USA with 2000 new patients per year. Most individuals were self-referrals to the program in order to initiate life-style changes, loose weight, or improve personal fitness. Patients from this pool were included in the study analysis if they fulfilled the following criteria: (1) overweight or obesity, *i.e.*, BMI > 26 kg/m<sup>2</sup>; (2) clinical signs of androgen deficiency such as abdominal obesity, lack of energy, fatigue, loss of libido or erectile dysfunction; (3) total free testosterone serum levels below 100 pg/mL; (4) willingness to undergo a life-style change including preparedness to adhere to a recommended, physician supervised and guided exercise and nutritional program; and (5) consent to undergo testosterone replacement therapy by using weekly self-administered intramuscular injections as long as clinically indicated.

In order to analyze a relative homogeneous group of individuals, only patients without a history of cardiovascular disease or any chronic debilitating diseases that might compromise participation in a scheduled exercise regimen were included. Additional exclusion criteria for the selection

in the analysis was a history of diabetes mellitus, hypertension or hyperlipidemia, with or without treatment, elevated prostate specific antigen (PSA) levels (> 3 ng/mL) and a history of prostate carcinoma. All individuals agreed that their data were analyzed blindly. The study was approved by the review board of the Cenegenics Education and Research Foundation. Data were collected retrospectively. The following parameters were analyzed: (1) age, body weight, body composition with regard to body fat and muscle mass, baseline routine lab parameters (lipid panel, fasting glucose, hemoglobin A1c (HbA1c), prostate specific antigen (PSA), free and total testosterone levels), and maximal exercise capacity (Mixed Venous Oxygen (MVO<sub>2</sub>)) at baseline; (2) Body weight and composition and lab parameters at follow up. Follow-up consisted of data collection, patient evaluation and laboratory tests between 6 months and 18 months after enrollment into the program.

The program consisted of a complete health evaluation which included an 8-hour assessment. The aim of the program, which is physician led and supervised, is risk factor management for aging men with the goal to assess risks and convert these into a proactive self management by use of a customized and individualized guide following a balanced low glycemic nutrition program to manage the effects of high glycemic foods on glucose metabolism without caloric restrictions and a balanced exercise program including aerobic activity and resistance training paired with high intensity exercise. The exercise training program is designed on an individual basis based on personal questionnaires, individual goal, the fitness levels (based on maximal oxygen consumption) and exercise habits. Hormone optimization is based on clinical signs of androgen deficiency or partial androgen deficiency and on baseline free testosterone levels. The entire program is directly guided by a physician with the assistance of trained nutritionists and personal trainers. Most importantly, the physician provides ongoing personal consultation, initially on a weekly base followed by monthly telephone check-ups as well as further follow-up interviews or tests as needed for the entire duration of the program. The consultation was provided directly or over the phone or through electronic mail. The components of the program are depicted in Table 1. All patients were instructed to report any side effects or adverse events immediately to the program physician as well as their primary care physicians, who were informed about the participation of their patients in the program.

Table 1. Program components.

Exercise
Daily 30-60 minutes exercise, 10 minutes warm up, 2 minutes stretching routine, 15-20 minutes cardiovascular fitness training (treadmill, elliptical, bike) with high intensity interval training for approximately 4 minutes
Five to thirty minutes resistance training (alternate days), using free weights and/or exercise machines
One day of rest/week
Increase exercise as tolerated, exercise plan individualized per patient.
Nutrition
Balanced low glycemic index/low glycemic load
Avoidance of trans fats and hydrogenated oils
Red meat once a week only
Omega-9 fat enriched diet using olive oil, avocados, almonds, cashews and macadamia nuts
Adding daily servings of fruits and vegetables
Two week initiation period, followed by balanced nutrition plan individualized per patient

In contrast to several other commercially available programs, the program described here was not intended to prevent aging and did not claim to increase longevity.

### 3 Results

Data of 56 males were analyzed (age  $52.3 \pm 7.8$  years, median 52.5, range 37 to 69 years, Table 2). Of interest, 12 (21.4%) participants were physicians themselves. As per the patients information, all participated in the recommended nutritional and exercise program that was slightly different among the participants since it was designed per the individual's condition. All men injected once or twice weekly testosterone cypionate between 80 mg and 200 mg per week, with an average dose of  $113.0 \pm 27.7$  mg (200 mg/mL), intramuscularly. Dose and frequency of testosterone injection (once or twice weekly) were chosen by the program physicians based on the individuals' baseline testosterone levels. Baseline total testosterone measured  $437.5 \pm 197.5$  ng/dL, baseline free testosterone was  $76.7 \pm 37.9$  pg/mL ( $1.81 \pm 0.44$  % free testosterone). Baseline free testosterone of less than 100 pg/mL in combination with clinical signs of partial androgen deficiency was considered below acceptable levels. PSA was  $0.91 \pm 0.67$  ng/mL. At follow up, total testosterone was  $890.0 \pm 488.9$  ng/dL, free testosterone was  $217.6 \pm 134.1$  pg/mL ( $2.31 \pm 0.59\%$ ),  $P < 0.005$  compared to baseline for all comparisons.

The average  $\text{MVO}_2$  at baseline was  $28.6 \pm 6.0$  mL/kg per minute, which, within the age group of 50–59 year old males, is considered low, representing a significantly reduced physical capacity for the patients studied (reference

Table 2. Body composition and laboratory changes.

Patients parameters	Baseline	Follow-Up
Age, year	$52.3 \pm 7.8$	$53.6 \pm 8.4^*$
Weight, lbs	$233.9 \pm 30.0$	$221.3 \pm 25.1^*$
Height, cm	$178.8 \pm 6.7$	$178.6 \pm 8.4$
Body fat, %	$34.3 \pm 5.7$	$27.1 \pm 5.2^*$
BMI, kg/m <sup>2</sup>	$33.2 \pm 3.3$	$31.3 \pm 2.8^*$
Glucose, mg/dL	$95.3 \pm 14.4$	$87.5 \pm 12.6^*$
TG, mg/dL	$154.1 \pm 97.6$	$100.2 \pm 38.5^*$
Chol, mg/dL	$195.4 \pm 33.0$	$172.7 \pm 35.0^*$
LDL, mg/dL	$122.4 \pm 29.8$	$108.6 \pm 28.2^*$
HDL, mg/dL	$46.7 \pm 11.5$	$47.3 \pm 13.1$
HbA1c, %	$5.7 \pm 0.6$	$5.5 \pm 0.3$

TG: triglycerides; Chol: total cholesterol; LDL: low density lipoprotein; HDL: high density lipoprotein; HbA1c: hemoglobin A1C; BMI: body mass index; \* $P < 0.005$  compared to baseline (for details see text).

range: very low  $< 26.1$ ; low 26.1–30.9; fair 31.0–35.7, good 35.8–40.9, excellent 41.0–45.3, superior  $> 45.3$ ). Follow up data on  $\text{MVO}_2$  after program enrollment was not available for the current analysis in this patient cohort.

#### 3.1 Body weights and body fat

Upon self-referral, the weight was  $233.9 \pm 30.0$  lbs, average height was  $178.6 \pm 6.7$  cm, BMI was  $33.2 \pm 3.3$  kg/m<sup>2</sup>, median 32.2 kg/m<sup>2</sup>, range 27.5 to 45.0 kg/m<sup>2</sup>. Accurate follow-up weights were available on 51 patients. Forty seven patients lost weight, ranging from 1 lbs to 42.9 lbs, only 4 patients gained weight ranging from 4.8 lbs to 17.2 lbs. At follow up, weight was  $221.3 \pm 25.1$  lbs ( $P < 0.001$  vs. baseline, BMI was  $31.3 \pm 2.8$  kg/m<sup>2</sup>,  $P < 0.0001$  vs. baseline). Total body fat was  $27.1\% \pm 5.2\%$  at follow-up compared to  $34.3 \pm 5.7\%$  at baseline,  $P < 0.0001$ . Total body fat was reduced in 50 patients, only two patients each had a slight increase in total body fat of 2.2%. One of these patients also had an increase in total body weight, and one patient had no change. Upon examination of the patients' medical records, it appeared that these two patients did not strictly adhere to the program recommendations for exercise and nutrition for more than one month after initiation of the program, supposedly because of lack of time and opportunity, as assessed in a personal interview at the end of the observation period. For the entire group, no changes were found in total body bone density between baseline and follow up measurements.

#### 3.2 Laboratory changes

Considering the normal range for fasting blood glucose between 70 mg/dL and 100 mg/dL, at baseline, 16 patients (of 53 patients in whom data was available, 30.2%) were considered above normal values even though no history of

diabetes was known in any of the patients. At follow up, only seven patients still had fasting glucose levels above 100 mg/dL (13%).

Fasting glucose was reduced from  $95.30 \pm 14.40$  mg/dL at baseline to  $87.51 \pm 12.58$  mg/dL at follow up,  $P < 0.0001$ . HbA1c measured  $5.7\% \pm 0.6\%$  at baseline vs.  $5.5\% \pm 0.3\%$  at follow up,  $P < 0.05$ . Total fasting cholesterol was  $195.4 \pm 33.0$  mg/dL and reduced to  $172.7 \pm 35.0$  mg/dL at follow up,  $P < 0.005$ . Triglyceride levels were reduced from  $154.1 \pm 97.6$  mg/dL to  $100.2 \pm 38.5$  mg/dL, and LDL was reduced from  $122.4 \pm 29.8$  mg/dL to  $108.6 \pm 28.2$  mg/dL at follow up ( $P < 0.005$  for both comparisons), whereas HDL was unchanged ( $46.7 \pm 11.5$  mg/dL at baseline,  $47.3 \pm 13.1$  mg/dL at follow up,  $P = 0.33$ ). No significant adverse events were reported from intramuscular testosterone injections except slight pain at the injection site in five cases, in one case development of a hematoma (size not quantified), in another case the development of a hard nodule at the injection site that did not require any further intervention. PSA levels at follow up were slightly elevated  $1.31 \pm 1.27$  ng/mL vs.  $0.91 \pm 0.67$  at baseline, but within the normal range. No follow up lab results resulted in cessation of testosterone supplementation, *i.e.*, there was no reported polycythemia, significant elevation of PSA levels above normal, or significant side effects that prompted either the primary care physicians or the program physicians to stop testosterone injections or any portion of the program within the reported follow up period of 6–18 months after enrollment.

#### 4 Discussion

In the present analysis, we present data on 56 middle-aged obese men undergoing a physician-directed and supervised dietary and exercise program in order to improve general health, which is combined with an attempt to achieve hormonal balance with testosterone substitution in case of documented laboratory or clinical signs of androgen deficiency. The motivation for participation was a desire to improve overall health, reduce weight, improve fitness and reduce cardiac (coronary) risk factors. Our data demonstrate that by conducting the recommended dietary and daily exercise changes in combination with testosterone substitution, obese males achieved significant weight loss and a significant reduction in common risk factors for the development of coronary artery disease.

Of importance, there is a high prevalence of the metabolic syndrome among men who willingly undergo a life-style modification, as reported earlier.<sup>[19]</sup> Moreover, the implementation of the prescribed program including the application of testosterone in men without contraindications

did not result in any serious side effects and thus, is considered safe if adequately supervised and controlled by a physician appropriately trained in hormone therapy.

The fact that an exercise program can improve overall health and reduce risk factors is not innovative. However, only few studies investigated a comprehensive nutritional and exercise program combined with hormone balancing in middle aged men. A recent study among sedentary women with metabolic syndrome showed that an incremental approach to 10,000 steps per day resulted in improvements of waist circumference and fasting glucose, BMI and resting heart rate.<sup>[20]</sup> Similar to our data, a study from Japan demonstrated that heart rate recovery also has been shown to be beneficially altered by exercise training among obese men with metabolic syndrome.<sup>[21]</sup> Exercise by itself has been shown in several studies to promote weight loss, especially in women.<sup>[22]</sup> The combination of certain diets exercise (resistance) training appears to be more efficient in changing body composition.<sup>[23]</sup> Outside the frame of clinical trials, however, there is a lack of data on long-term success rates after cessation of the programs. Therefore, predictors have been stratified to identify individuals who can successfully undergo life-style modification programs including weight loss.<sup>[24]</sup> There is no head to head comparison between the exercise-dietary program described here with different strategies or programs. The scientific analysis of additional androgen substitution, however, in this context is a novel approach that has not been described before in a similar manner. In fact, a PubMed analysis with the search terms “exercise training”, “weight loss”, “diet” and “testosterone” does not reveal any studies performed in men. In contrast, a vast number of publications on hormonal therapy in combination with life style changes in women were published.

The role of testosterone replacement has been controversially discussed. In particular its effects on ageing, the metabolic syndrome, diabetes mellitus, and atherosclerosis require further controlled studies. Of interest, agents targeting the androgen receptor, called selective androgen receptor modulators, are under clinical trials to test for its anabolic and tissue preservation effects, as it has been reviewed recently.<sup>[25]</sup> Controlled studies have revealed a positive effect of testosterone substitution on body composition, muscle strength, bone metabolism and erythropoiesis. Moreover, a protective effect on the development of coronary artery disease can be expected by an improvement of the lipid profile, decrease of obesity and insulin resistance, *i.e.*, a reduction of risk factors for the development of progression of atherosclerosis. Contraindications for testosterone-supplementation such as carcinoma of the prostate and elevated PSA-values as well as possible side

effects of the treatment such as polyglobuly and sleep-apnea-syndrome require close attention before and observance during the replacement therapy.<sup>[26]</sup>

Whether testosterone substitution is clinically indicated in cases as described here with clinical features of the partial androgen deficiency remains a matter of debate. Testosterone therapy in our cases was initiated based on clinical findings of (partial) androgen deficiency in combination with a reduction in total free testosterone serum levels below 100 pg/mL. This cut-off level might be debatable, however, in combination with the clinical findings and our past experience, raising free testosterone to levels above 120-150 pg/mL had been associated with improved well-being and reduction in coronary risk factors.

Despite our significant results with regard to weight loss and reduction in total body fat and coronary risk factors, our study has several limitations: (1) No control group has been studied. However, the data represent the analysis of 56 patients following a systematic and physician supervised program that has not been reported in a similar way before. (2) Since all patients were self-referred to a commercial life-style changing program, a selection bias might be considered since the participants were highly motivated to undergo and follow through the program. On the other hand, this motivation may support compliance and usually provides a more strict adherence to the nutritional and exercise portions, which ensured analysis of a relative homogeneous group of patients. Also, HDL was unchanged but was considered normal even before starting the program, which most likely is caused by the fact that most of the individuals already did some degree of exercise training before but without appropriate guidance and supervision that was not adequate enough to loose weight. (3) Data were collected retrospectively. A prospective study is in progress.

The program described here did not consist of testosterone substitution alone but also of an exercise and nutritional program with the goal of weight loss and enhancing physical fitness. No patients were studied without testosterone replacement therapy, but in our experience, the combination of weight loss nutrition, exercise and hormonal balancing had been more successful in achieving the targeted endpoints.

#### 4.1 Conclusions

We present the first report of a combined commercially available exercise-nutrition program with testosterone replacement therapy in middle aged men with a partial androgen deficiency syndrome that resulted in a highly significant weight loss, reduction of total body fat and improvement in lipid and glucose levels among the participants. Testosterone substitution in this group appeared safe and might have supported the effects of weight

reduction diet and exercising, as long as adequate physician supervision and follow-up was provided. Further studies on the long term effects of hormone replacement in partial androgen deficient men for the purposes of changes in body composition and reduction of risk factors for the development of chronic diseases such as atherosclerosis and coronary artery disease are required.

#### Acknowledgement

The study was supported by the Cenegenics Education and Research Foundation, a non-profit entity.

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