

## Does androgen excess contribute to the cardiovascular risk profile in postmenopausal women with type 2 diabetes?

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Received 28 January 2005; accepted 28 June 2005

### Abstract

The purpose of this study was to determine if postmenopausal women with type 2 diabetes have clinical and biochemical evidence of androgen excess as a potential contributor to an increase in risk for coronary heart disease when compared with women without diabetes. Fasting glucose, insulin, lipids, sex hormone-binding globulin (SHBG), and sex steroids (from pooled samples) (total testosterone and free testosterone [non-SHBG-T], androstenedione [A-dione], total estrogens) were measured at baseline in 16 postmenopausal women with type 2 diabetes treated with diet or a sulfonylurea and 17 age-matched controls. Measurements of glucose, insulin, and sex steroids were repeated at hourly intervals for 3 hours after oral glucose administration. Hirsutism scores and insulin sensitivity (homeostasis model assessment [HOMA] insulin sensitivity [SI]) were obtained. Women with type 2 diabetes were more hyperglycemic, hyperinsulinemic, and insulin-resistant (HOMA SI,  $46.7 \pm 7.0$  vs  $12.9 \pm 2.0$ ,  $P < .001$ ), and had higher total to high-density lipoprotein cholesterol (TC/HDL) ratios, lower SHBG ( $20.8 \pm 3.5$  vs  $59.3 \pm 14.4$  nmol/L,  $P < .05$ ), higher non-SHBG-T ( $0.225 \pm 0.025$  vs  $0.135 \pm 0.021$  nmol/L,  $P < .05$ ), and higher hirsutism scores ( $1.1 \pm 0.3$  vs  $0.3 \pm 0.2$ ,  $P = .004$ ) than those without diabetes. No changes in sex steroids occurred after the oral glucose challenge. HOMA SI and area under the curve for glucose correlated significantly with SHBG ( $r = -0.42$ ), non-SHBG-T ( $r = 0.40$ ), and TC/HDL ( $r = 0.41$ ) (all  $P < .05$ ) in the combined groups. Postmenopausal women with type 2 diabetes have both clinical and biochemical evidence of androgen excess that may contribute to more adverse cardiovascular risk profiles.

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### 1. Introduction

Type 2 diabetes has a stronger negative impact on risk for both the occurrence of and the mortality from coronary heart disease (CHD) in women than men [1–3]. This sex-specific acceleration in CHD risk is partially explained by increases in the severity of conventional risk factors, including obesity, hypertension, and dyslipidemia; however, the reasons underlying the greater prevalence of these risk factors remain unexplained [2,4].

This increase in conventional risk factors together with the observation that an accelerated risk for CHD precedes

the onset of clinical hyperglycemia suggests the presence of sex-specific factors that contribute to the overall risk profile [5]. Hyperinsulinemia and insulin resistance precede the onset of clinical diabetes by 10 to 20 years [6–9]. In women with polycystic ovary syndrome (PCOS), hyperinsulinemia contributes to the overproduction of ovarian androgens, which in turn contribute to a greater prevalence of CHD risk factors in this group of women [10]. It is possible that prolonged periods of hyperinsulinemia preceding the onset of type 2 diabetes in women may alter ovarian steroidogenesis toward androgen overproduction with resulting alterations in circulating lipids and an augmentation in CHD risk.

The present study was designed to investigate the hypothesis that women with type 2 diabetes have insulin-mediated androgen excess that contributes to CHD

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Table 1  
Clinical characteristics of subjects

|                                    | Type 2 diabetes<br>(n = 16) | Controls<br>(n = 17) | P    |
|------------------------------------|-----------------------------|----------------------|------|
| Age (y)                            | 59.1 ± 1.3                  | 56.9 ± 1.1 NS        | NS   |
| Race                               | 13 W/3 B                    | 17 W                 |      |
| BMI (kg/m <sup>2</sup> )           | 33.9 ± 2.1                  | 29.4 ± 1.7           | .04  |
| WHR                                | 0.85 ± 0.01                 | 0.81 ± 0.01          | .04  |
| HbA <sub>1c</sub> (%)              | 7.7 ± 0.4                   | 5.7 ± 0.1            | .001 |
| Age at menopause                   | 46.9 ± 3.3                  | 49.9 ± 1.1           | NS   |
| Years postmenopausal               | 8.9 ± 1.7                   | 7.4 ± 0.9            | NS   |
| SBP (mm Hg)                        | 137 ± 7                     | 125 ± 5              | NS   |
| DBP (mm Hg)                        | 83 ± 3                      | 78 ± 2               | NS   |
| MAP (mm Hg)                        | 101 ± 4                     | 94 ± 2               | NS   |
| Pregnancies (n)                    | 3.8 ± 0.7                   | 3.6 ± 0.8            | NS   |
| LH (mIU/mL)                        | 25.5 ± 3.7                  | 30.9 ± 3.8           | NS   |
| FSH (mIU/mL)                       | 57.3 ± 5.4                  | 69.2 ± 5.4           | NS   |
| Hirsutism score                    | 1.1 ± 0.3                   | 0.3 ± 0.2            | .004 |
| Urine albumin<br>(mg/g creatinine) | 54.4 ± 22.1                 | 6.1 ± 1.3            | .004 |
| TC (mmol/L)                        | 5.8 ± 0.3                   | 5.2 ± 0.2            | NS   |
| TGs (mmol/L)                       | 2.2 ± 0.3                   | 1.4 ± 0.2            | NS   |
| Total HDL (mmol/L)                 | 1.01 ± 0.04                 | 1.37 ± 0.07          | NS   |
| LDL (mmol/L)                       | 3.7 ± 0.3                   | 3.2 ± 0.2            | NS   |
| TC/HDL                             | 5.4 ± 0.3                   | 4.0 ± 0.3            | <.05 |
| Lp(a)                              | 19.9 ± 5.0                  | 26.7 ± 6.2           | NS   |

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

risk profiles, in part, through alterations in circulating lipid profiles.

## 2. Materials and methods

### 2.1. Patients

The study was approved by the Institutional Review Board of the University of Pittsburgh. All patients gave informed written consent before study participation. Participants included 16 postmenopausal women with type 2 diabetes treated with diet alone (n = 8) or a sulfonylurea (n = 8) and 17 postmenopausal women without diabetes by oral glucose tolerance testing or a known family history of type 2 diabetes. Exclusion criteria included a history or bilateral oophorectomy, a hirsutism score of more than 6, a history of oligoamenorrhea, or unexplained infertility in an effort to exclude women with PCOS. The groups were matched for age and years postmenopause (Table 1). All participants described sedentary lifestyles. No subjects were taking metformin, glitazones, acarbose, insulin, lipid-lowering therapy, or medications known to interfere with glucose metabolism or insulin sensitivity (ie, glucocorticoids,  $\beta$ -blockers, or thiazide diuretics). Women on hormone replacement therapy discontinued this for 3 months before the study.

### 2.2. Screening procedures

Physical examination included measurement of seated blood pressure, height, weight, waist-to-hip ratio (WHR), and a modified hirsutism scores [11]. Screening laboratory testing included measurement of a thyroid-stimulating

hormone, hematocrit, serum creatinine, and gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]). Menopausal status was established by the absence of menses for 1 year.

### 2.3. Protocol

Subjects were instructed to follow a 150-g carbohydrate diet for 2 days and a 10-hour overnight fast before admission to the General Clinical Research Center at the University of Pittsburgh Medical Center at 7:30 AM on the study day. Sulfonylurea-treated subjects were asked to withhold their medication for 2 days before the study day. An antecubital intravenous catheter was placed and maintained with a slow infusion of 0.9% saline before the initiation of blood sampling at 8:00 AM for metabolic profiles (glucose, insulin, C-peptide); lipids (total cholesterol [TC], triglycerides [TGs], high-density lipoprotein cholesterol [HDL-C], lipoprotein (a) [Lp(a)]); sex hormones (total testosterone [TT], total estrogens, androstenedione [A-dione], DHEAS); and sex hormone-binding globulin (SHBG). Sampling for metabolic profiles and sex hormones was repeated at 8:30 and 9:00 AM, followed by oral administration of 100 g of dextrose. Repeat sampling for metabolic profiles was performed at 30, 60, 90, 120, and 180 minutes. Repeated sampling for sex hormones was performed at hourly intervals. At the conclusion of the study, all subjects were fed and discharged. Sulfonylurea-treated subjects resumed their medication before the meal.

### 2.4. Analytical methods

Plasma glucose concentrations were determined using the glucose oxidase method with a YSI glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH). Insulin, C-peptide, cholesterol (TC, low-density lipoprotein [LDL-C], HDL-C), and TGs were measured using previously described methods [12,13]. Serum Lp(a) was quantitatively determined using an enzyme-linked immunosorbent assay technique. Measures of insulin resistance were obtained using homeostasis model assessment (HOMA) [14]. Sex hormone-binding globulin was measured by IRMA (Diagnostic Systems Laboratories, Webster, TX). Basal levels of TT, A-dione, DHEAS (Coat-A-Count solid-phase radioimmunoassay, Diagnostic Products, Los Angeles, CA), and total estrogens (ICN Pharmaceuticals, Costa Mesa, CA) were determined from pooled basal samples. The radioimmunoassay for total estrogens has 100% cross-reactivity with both 17 $\beta$ -estradiol and estrone and 9% or less cross-reactivity with estriol, 17 $\alpha$ -estradiol, and equilin.

The determination of non-SHBG-T was based on the separation, by 500 g/L ammonium sulfate precipitation, of serum SHBG-bound testosterone after incubation with <sup>3</sup>H-testosterone at 23°C [15]. The non-SHBG-T concentration was calculated by multiplying the percentage of tracer in the supernatant (not bound to SHBG) by the TT concentration. Postglucose samples were based on a single

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