The Relationships Between Testosterone, Body Composition, and Insulin Resistance

A lesson from a case of extreme hyperandrogenism

ELENA VOLPI, MD, PHD[1]
STEVEN A. LIEBERMAN, MD[1]
DENNIS M. FERRER, MD[1]
CHARLES R. GILKISON, RN[1]
BLAKE B. RASMUSSEN, PHD[1,2]
MANUBAI NAGAMANI, MD[3]
RANDALL J. URBAN, MD[1]

Association between hyperandrogenism and insulin resistance is well recognized in women with polycystic ovary syndrome (PCOS) (1). However, earlier evidence (2) suggesting an insulin-antagonizing effect of androgens has been overshadowed by more recent studies demonstrating that antiandrogen treatment with flutamide (3) or GnRH agonists (4,5) does not alter insulin resistance in PCOS. Conflicting results have been reported in non-PCOS women, with some studies (1,6–9) suggesting that testosterone may be related to insulin resistance and others (10,11) showing no correlation. Recent data suggest that some of these discrepancies may be explained by racial disparities, since only obese African-American women exhibited a positive relationship between insulin resistance and gonadal androgens (6). Inconclusive data have also been reported in men given testosterone in replacement or supraphysiologic doses, with some studies (12) suggesting a sensitizing effect of testosterone on glucose metabolism and others (13–16) showing no effect.

Nonetheless, androgens can influence body composition, which is associated with insulin sensitivity. Thus, it is conceivable that testosterone might indirectly influence insulin sensitivity via its effects on body composition. We report the results of hormonal, metabolic, and body composition studies before and 1 month and 9 months after a Leydig cell tumor removal in a postmenopausal woman.

RESEARCH DESIGN AND METHODS — A 64-year-old gravida 7, para 7, Hispanic woman was referred for evaluation of virilization starting ~10 years earlier and progressing over the past 3 years. Menses were regular before menopause (age 50). Diabetes was diagnosed 2 months before presentation and was well controlled by 1.5 mg glyburide daily (HbA_{1c} 4.8%). She had a 22-year history of hypertension, treated with benazepril and amlodipine. A physical examination revealed male pattern alopecia, masculine habitus, abdominal obesity, clitoromegaly, and breast atrophy but no palpable adnexal masses.

Laboratory studies revealed extreme hyperandrogenism (Table 1). A computed tomography scan and pelvic ultrasound did not detect ovarian masses. Nonetheless, she underwent total hysterectomy with bilateral salpingo-oophorectomy because of the increased risk for endometrial cancer (endometrial thickening, 8.6 mm) and possible virilizing ovarian tumor. Microscopic examination revealed a 0.9-cm Leydig cell tumor, nonhilar type, in the right ovary. Northern blot analysis (17) showed abundant expression of mRNA for $P450_{SCC}$ and $P450_{17a}$ in the tumor but no expression in stromal tissue from the contralateral ovary, indicating absence of hyperthecosis or PCOS.

Glyburide was held pre- and postoperatively, and fasting glucose remained normal (Table 1). Approximately 6 months postoperatively, fasting glucose increased to 204 mg/dl, and glyburide was reinstituted. There were no changes in blood pressure, antihypertensive medications, or self-reported diet or physical activity. Virilization decreased postoperatively.

After institutional review board approval, the patient gave written informed consent and was admitted to the General Clinical Research Center for metabolic studies 1 week before and 1 month and 9 months after surgery. Glyburide was held for at least 72 h before each admission. We measured body composition by dual-energy X-ray absorptiometry and ^{40}K counting, hormones by radioimmuno assay, and insulin sensitivity using a 75-g oral glucose tolerance test (OGTT), an insulin tolerance test (ITT; 0.10 units/kg), and a hyperinsulinemic (prime: 5.4 mU/kg; infusion 0.9 mU · kg^{-1} · min^{-1})-euglycemic glucose clamp with measurement of steady-state glucose kinetics at baseline and during clamp ([6,6-$^2H_2$]-glucose, prime: 17.2 μmol/kg, infusion: 0.2 μmol · kg^{-1} · min^{-1}) (18).

RESULTS — Total and free testosterone levels were markedly elevated preoperatively and declined dramatically

From the [1]Department of Internal Medicine, University of Texas Medical Branch, Galveston, Texas; the [2]Department of Physical Therapy, University of Texas Medical Branch, Galveston, Texas; and the [3]Department of Obstetrics and Gynecology, University of Texas Medical Branch, Galveston, Texas.

Address correspondence and reprint requests to Elena Volpi, MD, PhD, Division of Geriatric Medicine, University of Texas Medical Branch, 301 University Blvd., Galveston, TX 77555-0460. E-mail: evolpi@utmb.

Received for publication 6 May 2004 and accepted in revised form 2 November 2004.

Abbreviations: ITT, insulin tolerance test; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Serum concentrations of androgens and other sexual steroids, body composition, and insulin sensitivity as assessed with OGTT, ITT, and hyperinsulinemic-euglycemic clamp in a 64-year-old Hispanic woman with Leydig cell tumor of the ovary before surgery and 1 month and 9 months after curative surgery*

	Preoperatively	Postoperatively	
		1 month	9 months
Serum hormones			
Androgens			
Total testosterone (ng/dl; NR: 10–57)	1,143	61	41
Free testosterone (pg/ml; NR: 0.2–2.2)	18.7	1.7	1.1
Androstenedione (ng/dl; NR: 64–245)	276	211	159
Dehydroepiandrosterone-S (mg/ml; NR: 650–3,400)	486	829	—
Other hormones			
17-OH progesterone (ng/ml; NR: 0.5–2.0)	0.9	0.7	0.4
Estradiol (pg/ml; NR: 0–47)	62	58	13
Luteinizing hormone (IU/l; NR: 16–64)	2.7	14	15
Follicle-stimulating hormone (IU/l; NR: 18–153)	3.1	12	15
Body composition			
Weight (kg)	72.6	72.0	77.7
Body cell mass (kg)	40.6	41.3	35.1
Fat mass			
Total body fat (kg)	16.7	16.7	23.9
Total body fat (%)	23.1	23.1	30.7
Abdominal fat (kg)	1.7	1.6	3.4
Insulin sensitivity			
75-g OGTT			
Blood glucose (mg/dl)			
Fasting	92	95	106
1 h	180	175	254
2 h	176	170	236
3 h	117	134	148
AUC	461	460	617
Insulin (pmol/l)			
Fasting	126	180	132
1 h	594	492	1,320
2 h	1,104	1,158	1,704
3 h	732	984	374
AUC	2,130	2,232	3,654
ITT			
Blood glucose (mg/dl)			
0 min	90	83	94
5 min	85	79	93
10 min	74	75	83
15 min	65	64	76
20 min	60	65	72
25 min	59	64	69
30 min	58	62	65
40 min	58	67	68
50 min	63	70	72
60 min	68		78
kITT (%/min; NR: 3.84–9.47)	2.299	1.296	1.697
Hyperinsulinemic glucose clamp			
Insulin (pmol/l)			
Basal	149	150	142
Clamp	517	456	514
Free fatty acids (mmol/l)			
Basal	0.420	0.444	0.415
Clamp	<0.100	<0.100	<0.100

Continued on following page

Table 1—*Continued*

	Preoperatively	Postoperatively	
		1 month	9 months
Hepatic glucose production ($\mu mol \cdot kg^{-1} \cdot min^{-1}$)			
Basal	10.9	9.1	8.8
Clamp	5.9	1.6	1.2
Glucose utilization ($\mu mol \cdot kg^{-1} \cdot min^{-1}$)			
Basal	10.9	9.1	8.8
Clamp	18.4	12.4	12.8

Conversion to SI units: total testosterone: ng/dl × 0.03467 = nmol/l; free testosterone: pg/ml × 34.67 = pmol/l; androstenedione: ng/dl × 0.03492 = pmol/l; dehydroepiandrosterone-S: ng/ml × 0.002714 = μmol/l; 17-OH progesterone: ng/ml × 3.026 = nmol/l; estradiol: pg/ml × 3.671 = pmol/l; glucose: mg/dl × 0.05551 = mmol/l; and insulin: μU/ml × 6 = pmol/l. AUC, area under the curve as calculated with the trapezoidal method; kITT, insulin sensitivity during ITT as calculated by dividing the slope of the blood glucose drop from 5 to 20 min by the average blood glucose in the same period; NR, normal range for age and sex.

following surgery (Table 1). Androstenedione was slightly elevated preoperatively and returned within the normal range postoperatively. Dehydroepiandrosterone-S and 17-OH-progesterone were low before and after surgery, suggesting a normal adrenal androgen production. Luteinizing hormone and follicle-stimulating hormone were low preoperatively and increased postoperatively, reaching values close to the postmenopausal normal range after 9 months, possibly due to a slow recovery of the gonadotrophs from the 10-year suppression by testosterone.

There were no changes in weight or individual compartments 1 month postoperatively. Nine months postoperatively, weight increased by 7%, with marked increases in total and abdominal fat and decreased body cell mass.

Fasting glucose concentrations were normal, and fasting insulin was moderately elevated before surgery and 1 month and 9 months postoperatively. OGTT revealed moderate insulin resistance and glucose intolerance preoperatively that remained unchanged 1 month postoperatively; 9 months postoperatively, OGTT became diagnostic for type 2 diabetes. Conversely, ITT and glucose clamp indicated deterioration of peripheral insulin sensitivity 1 month postoperatively (decreased kITT and glucose utilization), which remained unchanged 9 months postoperatively. Interestingly, the response of hepatic glucose production to insulin was incomplete preoperatively and improved 1 month postoperatively, indicating increased liver insulin sensitivity.

CONCLUSIONS — These data from a postmenopausal woman before and after surgical correction of extreme hypertestosteronemia suggest that testosterone may affect insulin sensitivity. The progressive worsening of insulin sensitivity following tumor removal indicates that in this patient the general effect of testosterone was sensitizing. This was the integrated result of opposite actions of testosterone on liver and peripheral insulin sensitivity, as insulin-stimulated glucose utilization and hepatic glucose production were concomitantly higher with high testosterone concentrations and decreased following testosterone withdrawal. In this patient, increased glucose utilization prevailed during hypertestosteronemia, leading to enhanced insulin sensitivity. However, testosterone concentration in this patient was among the highest reported for women with androgen-producing tumors (19,20). Since the dramatic reduction of these extreme concentrations produced relatively modest changes in glucose tolerance, the overall effect of testosterone on insulin sensitivity appears to be mild. Because of the dual action of testosterone on glucose metabolism, it is also possible that in different conditions the effect of testosterone on insulin sensitivity is neutral, which could explain the variable results of previous studies (12–16,21).

Our data also suggest that testosterone may affect insulin sensitivity both directly and indirectly. One month postoperatively, ITT and glucose clamp revealed deterioration of insulin sensitivity despite unchanged body composition, suggesting a direct effect of testosterone. This effect was subsequently overshadowed by profound changes in body composition that occurred 9 months postoperatively and led to the development of overt diabetes. Loss of lean body mass and gains in fat, particularly abdominal fat, were likely results of testosterone withdrawal, since testosterone increases lean body mass (13–15) and decreases fat mass and abdominal fat (12,13,22,23). The discrepancy between OGTT and ITT and clamp data are likely due to the higher sensitivity of the latter two techniques to detect small changes in insulin sensitivity (24).

It is important to underscore that our patient's disease, involving autonomous production of testosterone by a Leydig cell tumor that resolved with surgical removal of the tumor, was fundamentally distinct from PCOS, in which insulin resistance is the primary abnormality stimulating ovarian androgen production (25), and treatment of hyperandrogenism does not affect insulin resistance (3–5). Finally, it is unlikely that other androgens played any role in the worsening of the patient's insulin sensitivity following surgery, since androstenedione, whose potential effects on insulin sensitivity parallel those of testosterone, mildly decreased after surgery, and dehydroepiandrosterone-S, which has been linked to increased insulin sensitivity (9), slightly increased postoperatively to the low-normal range.

In summary, the hormonal, metabolic, and body composition changes following correction of extreme hyperandrogenism in this patient indicate that testosterone may improve insulin sensitivity both directly and through changes in body composition. Our data suggesting that testosterone is not unequivocally sensitizing, and that sex or other characteristics may influence the response of glucose metabolism to testosterone, underscore the need for further investigations in this area.

Acknowledgments— This work was supported in part by the National Institutes of Health/National Institute of Child Health and Human Development Grant no. R01 HD36092 (to R.J.U.), the National Institutes of Health/National Cancer Institute Grant no. R01 CA45181 (to M.N.), the National Institutes of Health/National Institute on Aging Grant no. R01 AG18311 (to E.V.), the National Institutes of Health/National Center for Research Resources General Clinical Research Center Program no. M01 RR00073, and the Brookdale Foundation (to E.V.).

The authors thank Drs. Andrew Coggan and Cathy Weickart for their advice and assistance with the clamp procedures, Dr. Fernando Cesani for the dual-energy X-ray absorptiometry analyses, Dr. Oliver Esch for the ^{40}K analyses, and the staff of the General Clinical Research Center at the University of Texas Medical Branch for their assistance and dedication.

References

1. Burghen GA, Givens JR, Kitabchi AE: Correlation of hyperandrogenism with hyperinsulinism in polycystic ovarian disease. *J Clin Endocrinol Metab* 50:113–116, 1980
2. Woodard TL, Burghen GA, Kitabchi AE, Wilimas JA: Glucose intolerance and insulin resistance in aplastic anemia treated with oxymetholone. *J Clin Endocrinol Metab* 53:905–908, 1981
3. Diamanti-Kandarakis E, Mitrakou A, Hennes MM, Platanissiotis D, Kaklas N, Spina J, Georgiadou E, Hoffmann RG, Kissebah AH, Raptis S: Insulin sensitivity and antiandrogenic therapy in women with polycystic ovary syndrome. *Metabolism* 44:525–531, 1995
4. Dunaif A, Green G, Futterweit W, Dobrjansky A: Suppression of hyperandrogenism does not improve peripheral or hepatic insulin resistance in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 70:699–704, 1990
5. Lasco A, Cucinotta D, Gigante A, Denuzzo G, Pedulla M, Trifiletti A, Frisina N: No changes of peripheral insulin resistance in polycystic ovary syndrome after long-term reduction of endogenous androgens with leuprolide. *Eur J Endocrinol* 133:718–722, 1995
6. Kitabchi AE, Imseis RE, Bush AJ, Williams-Cleaves B, Pourmotabbed G: Racial differences in the correlation between gonadal androgens and serum insulin levels. *Diabetes Care* 22:1524–1529, 1999
7. Evans DJ, Hoffmann RG, Kalkhoff RK, Kissebah AH: Relationship of androgenic activity to body fat topography, fat cell morphology, and metabolic aberrations in premenopausal women. *J Clin Endocrinol Metab* 57:304–310, 1983
8. Peiris AN, Mueller RA, Struve MF, Smith GA, Kissebah AH: Relationship of androgenic activity to splanchnic insulin metabolism and peripheral glucose utilization in premenopausal women. *J Clin Endocrinol Metab* 64:162–169, 1987
9. Schriock ED, Buffington CK, Hubert GD, Kurtz BR, Kitabchi AE, Buster JE, Givens JR: Divergent correlations of circulating dehydroepiandrosterone sulfate and testosterone with insulin levels and insulin receptor binding. *J Clin Endocrinol Metab* 66:1329–1331, 1988
10. Hauner H, Ditschuneit HH, Pal SB, Moncayo R, Pfeiffer EF: Fat distribution, endocrine and metabolic profile in obese women with and without hirsutism. *Metabolism* 37:281–286, 1988
11. Toscano V, Bianchi P, Balducci R, Guglielmi R, Mangiantini A, Lubrano C, Sciarra F: Lack of linear relationship between hyperinsulinaemia and hyperandrogenism. *Clin Endocrinol* 36:197–202, 1992
12. Marin P, Holmang S, Jonsson L, Sjostrom L, Kvist H, Holm G, Lindstedt G, Bjorntorp P: The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. *Int J Obes Relat Metab Disord* 16:991–997, 1992
13. Tenover JS: Effects of testosterone supplementation in the aging male. *J Clin Endocrinol Metab* 75:1092–1098, 1992
14. Urban RJ, Bodenburg YH, Gilkison C, Foxworth J, Coggan AR, Wolfe RR, Ferrando A: Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis. *Am J Physiol* 269:E820–E826, 1995
15. Bhasin S, Storer TW, Berman N, Callegari C, Clevenger B, Phillips J, Bunnell TJ, Tricker R, Shirazi A, Casaburi R: The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *N Engl J Med* 335:1–7, 1996
16. Singh AB, Hsia S, Alaupovic P, Sinha-Hikim I, Woodhouse L, Buchanan TA, Shen R, Bross R, Berman N, Bhasin S: The effects of varying doses of T on insulin sensitivity, plasma lipids, apolipoproteins, and C-reactive protein in healthy young men. *J Clin Endocrinol Metab* 87: 136–143, 2002
17. Nagamani M, Urban RJ: Increased expression of messenger ribonucleic acid encoding cytochrome P450 cholesterol side-chain cleavage and P450 17alpha-hydroxylase enzymes in ovarian hyperthecosis. *Fertil Steril* 71:328–333, 1999
18. Wolfe RR: Calculation of substrate kinetics: single pool model. In *Radioactive and Stable Isotope Tracers in Biomedicine. Principles and Practice of Kinetic Analysis.* 1st ed. Wolfe RR, Ed. New York, Wiley-Liss, 1992, p. 119–144
19. Young RH, Scully RE: Ovarian Sertoli-Leydig cell tumors: a clinicopathological analysis of 207 cases. *Am J Surg Pathol* 9:543–569, 1985
20. Friedman CI, Schmidt GE, Kim MH, Powell J: Serum testosterone concentrations in the evaluation of androgen-producing tumors. *Am J Obstet Gynecol* 153: 44–49, 1985
21. Seidell JC, Bjorntorp P, Sjostrom L, Kvist H, Sannerstedt R: Visceral fat accumulation in men is positively associated with insulin, glucose, and C-peptide levels, but negatively with testosterone levels. *Metabolism* 39:897–901, 1990
22. Lovejoy JC, Bray GA, Greeson CS, Klemperer M, Morris J, Partington C, Tulley R: Oral anabolic steroid treatment, but not parenteral androgen treatment, decreases abdominal fat in obese, older men. *Int J Obes Relat Metab Disord* 19:614–624, 1995
23. Marin P, Oden B, Bjorntorp P: Assimilation and mobilization of triglycerides in subcutaneous abdominal and femoral adipose tissue in vivo in men: effects of androgens.*J Clin Endocrinol Metab* 80:239–243, 1995
24. Perriello G, Misericordia P, Volpi E, Pampanelli S, Santeusanio F, Brunetti P, Bolli GB: Contribution of obesity to insulin resistance in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 80: 2464–2469, 1995
25. Nagamani M: Polycystic ovary syndrome variants: hyperthecosis. In *Reproductive Endocrinology, Surgery, and Technology.* Adashi EY, Rock JA, Rosenwaks Z, Eds. Philadelphia, Lippincott-Raven, 1996, p. 1258–1269