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Persistent Poor Metabolic Profile in Postmenopausal Women With Ovarian Hyperandrogenism After Testosterone Level Normalization

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Context: Data on prevalence of metabolic risk factors in hyperandrogenic postmenopausal women are limited. Also, the correlation between metabolic disorders and androgen excess in this scenario is poorly understood.

Objectives: We aimed to assess the prevalence of obesity, hypertension, type 2 diabetes (T2D), and dyslipidemia (DLP) in postmenopausal women with hyperandrogenism of ovarian origin before and after surgical normalization of testosterone (T) levels, as well as the impact of androgen normalization on body mass index (BMI), glucose, and lipid metabolism.

Design: Retrospective study.

Setting: Tertiary health center.

Participants: Twenty-four Brazilian women with postmenopausal hyperandrogenism who underwent bilateral oophorectomy between 2004 and 2014 and had histologically confirmed virilizing ovarian tumor (VOT) or ovarian hyperthecosis (OH) and T-level normalization after surgery were selected.

Main Outcome Measures: FSH, LH, total and calculated free T, BMI, fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) serum levels were accessed before (n = 24) and 24 months after (n = 19) bilateral oophorectomy.

Results: At baseline, the overall prevalence rates of obesity, T2D, DLP, and hypertension were 58.3%, 83.3%, 66.7%, and 87.5%, respectively. No significant difference in prevalence was found between patients with OH and VOTs. At follow-up, FSH, LH, and total and free T levels had returned to menopausal physiologic levels, but mean BMI and mean FPG, HbA1c, LDL-C, HDL-C, and TG levels did not differ from baseline.

Abbreviations: BMI, body mass index; DLP, dyslipidemia; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OH, ovarian hyperthecosis; PCOS, polycystic ovary syndrome; SHBG, sex hormone–binding globulin; T, testosterone; T2D, type 2 diabetes; TG, triglyceride; VOT, virilizing ovarian tumor.

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Conclusions: Postmenopausal hyperandrogenism is associated with adverse metabolic risk. Long-term normalization of testosterone levels did not improve BMI, glucose, or lipid metabolism.

Freeform/Key Words: postmenopausal hyperandrogenism, ovarian hyperthecosis, virilizing ovarian tumor, metabolic risk factors

Hyperandrogenic disorders in postmenopausal women are rare clinical conditions. The most common causes have an ovarian origin and are mainly caused by ovarian hyperthecosis (OH) or virilizing ovarian tumors (VOTs). OH is characterized by histological evidence of luteinized theca cells within the ovarian stroma and the absence of neoplasm [1]. VOTs are predominantly benign sex cord-stromal tumors (Leydig cell tumor, Sertoli cell tumor, ovarian thecomas) [2], which represent only <0.5% of all ovarian tumors [3].

Both conditions usually manifest as hirsutism; androgenetic alopecia; and signs of virilization, such as clitoromegaly, muscle hypertrophy, deepening of the voice, mammary atrophy, male pattern baldness, and elevated serum total and free testosterone (T) levels. Bilateral oophorectomy remains the main diagnostic approach and definitive treatment of postmenopausal hyperandrogenism of ovarian origin.

There is a strong positive correlation between androgen excess and insulin resistance in premenopausal women with polycystic ovary syndrome (PCOS) [4]. Moreover, the association of hyperandrogenism with metabolic syndrome features is well established in premenopausal women [5].

On the other hand, the correlation between androgen excess and insulin resistance in postmenopausal women has been less extensively studied [6–8]. There is a positive correlation of top-quartile T levels with hyperinsulinemia, fasting plasma glucose (FPG) [9, 10], type 2 diabetes (T2D), abdominal adiposity, and a higher risk of cardiovascular disease in postmenopausal women [11–13]. However, the association between metabolic risk factors and T has been poorly examined in postmenopausal women with T levels above the reference range.

Although insulin sensitizer methods, such as weight loss and metformin, have shown improvement in insulin resistance and a T-level decrease in hyperandrogenic diabetic and nondiabetic postmenopausal women [8, 14], the effect of androgen excess in glucose and lipid metabolism in hyperandrogenic postmenopausal women is yet to be elucidated.

Considering this, we aimed to retrospectively assess the prevalence of obesity, T2D, dyslipidemia (DLP), and hypertension in postmenopausal women with hyperandrogenism of ovarian origin who underwent bilateral oophorectomy to evaluate the long-term effect of T normalization on BMI, glucose, and lipid profiles.

1. Materials and Methods

A. Patients

The Ethics Committee of Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo approved this study, and all patients provided written informed consent.

Twenty-four postmenopausal women with hyperandrogenism of ovarian origin with histologically confirmed VOTs and OH were identified after a retrospective medical record review. All patients were diagnosed with clinical and hormonal hyperandrogenism and referred to the endocrinology unit of HCFMUSP between 2004 and 2014. The diagnoses of VOT and OH were reviewed and confirmed by an expert in gynecological pathology. The ovarian tumor type diagnosis was confirmed by specific criteria and classified according to the

World Health Organization 2014 criteria [15]. The diagnosis of OH was confirmed by the presence of lutein cells grouped into nests or scattered into the stroma with a typical background of stromal hyperplasia [16]. All women have had clinical features, a hormonal profile, and an ovarian morphological assessment by pelvic radiological images (transvaginal ultrasonography and/or pelvic magnetic resonance) evaluation. Adrenal origin hyperandrogenism was excluded by hormonal evaluation and radiological images. Presurgical and postsurgical management were conducted by an integrated medical team of endocrinologists and gynecologists from our tertiary referral center.

The clinical and anthropometric data included clinical signs of hyperandrogenism (hirsutism, androgenic alopecia, clitoromegaly, deepening of the voice, and muscle hypertrophy) and body mass index (BMI). Hirsutism was defined according to a modified Ferriman-Gallwey score ≥8 [17]. Androgenic alopecia was evaluated by the Ludwig and/or Norwood scale, and the presence or absence of male pattern androgenic alopecia was used as a criterion for virilization [18]. Clitoromegaly was considered as a clitoral body length of ≥2 cm [19]. Deepening of the voice and muscle hypertrophy were considered subjective criteria; they were counted as present once the patient had reported their occurrence and they had been recognized by two different examiners.

Clinical and biochemical evaluations performed at baseline (n = 24) and at 24-month follow-up bilateral oophorectomy (n = 19) were assessed. Five patients were lost to follow-up. Biochemical parameters included FPG, glycated hemoglobin (HbA1c), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) levels. Clinical data before surgery included BMI and presence or absence of an antidiabetic agent, hypolipidemic therapy, and antihypertensive therapy. Presence of T2D was defined as an FPG level ≥126 mg/dL, HbA1c ≥ 6.5%, or antidiabetic agent use. Diagnosis of DLP was defined as LDL-C level ≥ 130 mg/dL, HDL-C level ≤ 50 mg/dL, and/or TG level ≥ 150 mg/dL or hypolipidemic therapy. Hypertension was defined as the use of antihypertensive treatment. Obesity was characterized as a BMI ≥30 kg/m^2.

B. Hormonal Measurements

LH and FSH were measured by immunofluorometric assay (IFMA, AutoDELFIA, Turku, Finland) [20, 21]. Total T levels were measured by immunofluorometric assay (IFMA, AutoDELFIA) [22] until 2011 and by electrochemiluminescence assay (ECLIA, Cobas e601, Roche Diagnostics, Indianapolis, IN) from November 2011 through the present. Age, method-specific, and laboratory-specific reference ranges were used to define biochemical hyperandrogenism. Free T was calculated from total T and sex hormone–binding globulin (SHBG) as determined by immunoassay.

C. Statistical Analysis

Results are presented with means and SD scores (SD) as descriptive data. Differences in baseline characteristics between the groups were analyzed based on the $\chi 2$ test for categorical variables. A standard t test was used to compare normal distributions, and the Mann-Whitney test was used to compare nonnormal distributions. A paired t test was used to compare normal distribution data before *vs* after surgical oophorectomy. The Wilcoxon rank-sum test was performed to compare non–normally distributed data before *vs* after surgical treatment. We used Sigma Stat 4.0 for Windows software, version 4.0 for Windows® (Systat Software Corp., San Jose, CA) for statistical analysis. Statistical significance was set at $P < 0.05$.

2. Results

Clinical, biochemical, and hormonal data from 24 postmenopausal women with histologically confirmed ovarian-origin hyperandrogenism were reviewed. The diagnosis of OH was

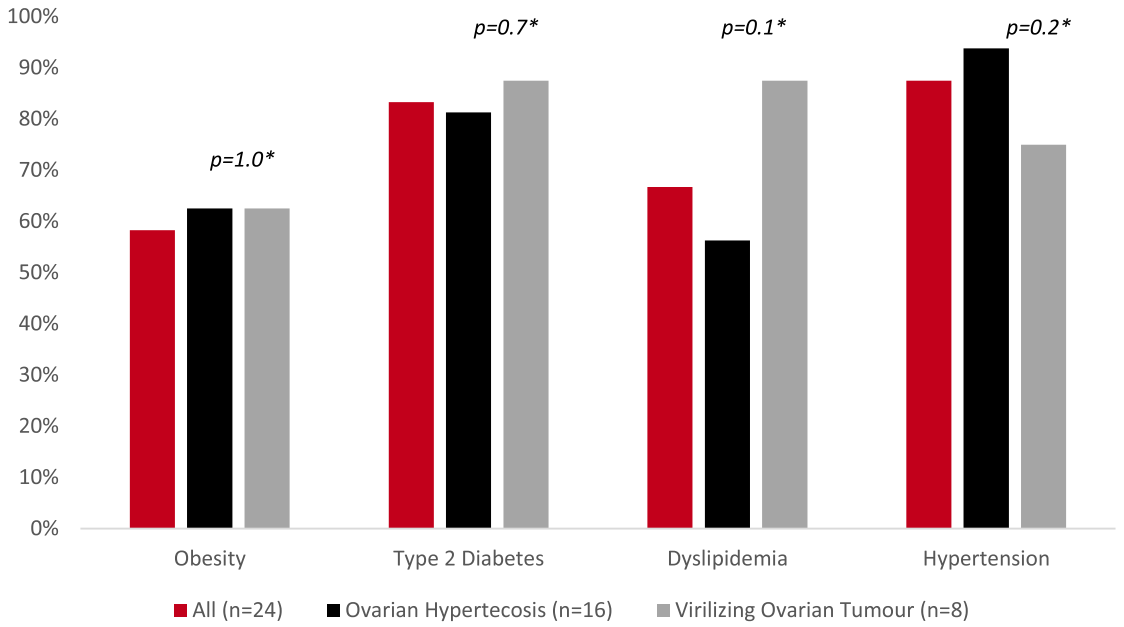
established in 16 patients, and 8 patients had a VOT. All patients had clinical signs of hyperandrogenism at baseline clinical evaluation. Androgen excess clinically manifested as hirsutism, male pattern balding, clitoromegaly, muscle hypertrophy, and/or deepening of the voice (Table 1). The clinical features of hyperandrogenism presented similar prevalence between patients with VOT and OH except for deepening of the voice, which was more common in the VOT group (Table 1). One patient in the OH group had PCOS features during reproductive age. Parity did not differ between women with OH (2.3 ± 1.7 children; range, 0 to 6) and those with VOT (3.0 ± 2.3 children; range, 0 to 6) (Table 1). Biochemical hyperandrogenism was confirmed by serum total T level above the age-, method-, and laboratory-specific reference range. The VOT group presented significantly higher levels of total T (448 *vs* 170 ng/dL; $P = 0.015$) and free T (294 *vs* 106 ng/dL; $P = 0.018$), as well as lower FSH (17.9 *vs* 48.2 IU/L; $P = 0.02$) and LH (10.6 *vs* 28.6 IU/L; $P = 0.01$) levels, compared with the OH group. SHBG levels did not differ between the patients with VOT and those with OH (38 *vs* 35.9 nmol/L; $P = 0.77$).

At baseline, the overall prevalence rates of obesity, T2D, DLP, and hypertension were 58.3%, 83.3%, 66.7%, and 87.5%, respectively (Fig. 1). No significant difference in the prevalence of these cardiovascular risk factors was found between the OH and VOT groups (Fig. 1). Obesity prevalence was 62.5% in the VOT group and 56.3% in the OH group. The overall prevalence of overweight was 37.5%, which corresponded to an overweight prevalence of 25% and 43.7% in the VOT and OH groups, respectively. The prevalence of obesity and overweight did not significantly differ between both groups (Table 1). Before surgery, the overall mean BMI was 31.7 ± 4.5 kg/m^2, the mean FPG was 113.4 ± 31 mg/dL, and the mean HbA1c was 7.0% ± 1.3%. The mean LDL-C level was 108.2 ± 34.0 mg/dL, mean HDL-C level was 44.4 ± 12.4 mg/dL, and mean TG level was 174.2 ± 69.7 mg/dL. The mean BMI (31.4 *vs* 31.7 kg/m^2; $P = 0.97$), FPG (104.6 *vs* 118 mg/dL; $P = 0.98$), HbA1c (6.8% *vs* 7.0%; $P = 0.62$), LDL-col (102.7 *vs* 110.6 mg/dL, $P = 0.59$), and TG (164.1 *vs* 177.3 mg/dL, $P = 0.75$) serum

Table 1. Baseline Clinical, Hormonal, and Metabolic Parameters

Variable	Total (n = 24)	Patients With VOTs (n = 8)	Patients With OH (n = 16)	*P* Value[a]
Age, y	60.2 ± 6.6	59.3 ± 4.9	60.7 ± 7.3	0.65
Ferriman score	16.9 ± 6.3	17.6 ± 4.4	16.6 ± 7.0	0.73
Hirsutism, % (n/n)	95.8 (23/24)	100 (8/8)	93.8 (15/16)	—
Alopecia, % (n/n)	83.3 (20/24)	100 (8/8)	75 (12/16)	—
Clitoromegaly, % (n/n)	62.5 (15/24)	75 (6/8)	43.8 (7/16)	0.14
Muscle hypertrophy, % (n/n)	25 (6/24)	37.5 (3/8)	18.8 (3/16)	0.31
Voice deepening, % (n/n)	33.3 (8/24)	75 (6/8)	12.5 (2/16)	0.002
PCOS features (n/n)	4.2 (1/24)	0	6.3 (0/16)	—
Parity	2.5 + 1.9	3 + 2.3	2.3 + 1.7	0.41
FSH, IU/L	39.0 ± 27.5	17.9 ± 11.8	48.2 ± 27.5	0.02
LH, IU/L	23.1 ± 16.0	10.6 ± 12.5	28.6 ± 14.5	0.01
Total T, ng/dL	247.4 ± 229.0	448 ± 333.1	169.7 ± 74.5	0.015
SHBG, nmol/L	36.6 ± 15.7	38.0 ± 18.5	35.9 ± 14.9	0.77
Free T, ng/dL	162.9 ± 145.5	293.6 ± 200.2	105.7 ± 59.6	0.018
BMI, kg/m^2	31.7 ± 4.5	31.4 ± 6.1	31.7 ± 3.5	0.97
Obesity (BMI ≥ 30 kg/m^2), % (n/n)	58.3 (14/24)	62.5 (5/8)	56.3 (9/16)	0.76
Overweight (BMI ≥ 25 kg/m^2), % (n/n)	37.5 (9/24)	25 (2/8)	43.7 (7/16)	0.53
FPG, mg/dL	113.4 ± 31	104.6 ± 29	118 ± 32	0.98
HbA1c, %	7.0 ± 1.3	6.8 ± 0.7	7.0 ± 1.5	0.62
LDL-C, mg/dL	108.2 ± 34.0	102.7 ± 50.6	110.6 ± 25.4	0.59
HDL-C, mg/dL	44.4 ± 12.4	36.4 ± 13.2	48.0 ± 11.0	0.04
TG, mg/dL	174.2 ± 69.7	167.1 ± 61.5	177.3 ± 74.6	0.75

Values expressed with a plus/minus sign are the mean ± SD.
[a]VOT *vs* OH.



* OH *versus* VOT

Figure 1. Prevalence of cardiovascular risk factors at baseline. At baseline, the overall (red bar) prevalence rates of obesity, T2D, DLP, and hypertension were 58.3%, 83.3%,66.7%, and 87.5%, respectively. The prevalence of these cardiovascular risk factors did not significantly differ between the OH and VOT groups.

levels did not significantly differ between the VOT and OH groups. The HDL-C level was significantly lower in patients with VOTs than in the OH group (36.4 *vs*. 48 mg/dL; $P = 0.04$). Linear regression analysis showed a low but significantly negative association between HDL-C and total T ($R^2 = 0.27$; $P = 0.01$) and between HDL-C and free T levels ($R^2 = 0.3$; $P = 0.006$).

Data from 19 patients were available at 24 months after bilateral oophorectomy. The hormonal profile and metabolic parameters after surgical T-level normalization are shown in Table 2. Serum LH, FSH, and total and free T levels returned to physiological menopause values after bilateral oophorectomy, confirming the ovarian origin of hyperandrogenism. Ovarian histopathology confirmed OH in 73.7% (14 of 19) and VOT in 26.3% (5 of 19) of the

Table 2. Baseline and 24-Month Follow-up Hormonal Profiles and Metabolic Parameters after T-Level Normalization

Variable	Baseline (n = 19)	T-Level Normalization After 24 Months (n = 19)	*P* Value
FSH, IU/L	35.2 ± 23.0	53.8 ± 30.0	<0.05
LH, IU/L	23.1 ± 15.8	28.8 ± 11.7	0.10
Total T, ng/dL	217.2 ± 146.3	13.9 ± 4.0	<0.001
SHBG, nmol/L	31.7 ± 10.8	32.5 ± 14.5	0.69
Free T, ng/dL	163.9 ± 128.2	8.3 ± 3.4	<0.001
BMI, kg/m^2	31.5 ± 4.9	30.1 ± 4.0	0.19
Obesity (BMI ≥ 30 kg/m^2), % (n/n)	47.4 (9/19)	52.6 (10/19)	0.75
Overweight (BMI ≥ 25 kg/m^2), % (n/n)	47.4 (9/19)	31.6 (6/19)	0.31
FPG, mg/dL	114.4 ± 28.2	129.3 ± 50.9	0.44
HbA1c, %	6.9 ± 0.9	7.2 ± 2.4	0.70
LDL-C, mg/dL	105.5 ± 34.0	103.4 ± 40.9	0.81
HDL-C, mg/dL	43.4 ± 12.8	42.3 ± 9.8	0.70
TG, mg/dL	183.0 ± 70.8	193.7 ± 67.5	0.52

Values expressed with a plus/minus sign are the mean ± SD.

patients. At 24 months (n = 19), FSH (40 *vs* 53.2 IU/L; $P \leq 0.05$), total T (223.6 *vs* 13.8 ng/dL; $P < 0.001$), and free T (159.9 *vs* 8.3 ng/dL; $P < 0.001$) levels significantly differed from those before surgical treatment. LH (24.5 vs 27.7 IU/L; $P = 0.27$) and SHBG (33.4 vs 34.6 nmol/L; $P = 0.67$) did not statistically differ. The mean BMI (30.9 vs 30.1 kg/m^2; $P = 0.19$) and the mean FPG (114.4 vs 129.3 mg/dL; $P = 0.44$), HbA1c (6.9% vs 7.2%; $P = 0.7$), LDL-C (105.5 *vs* 103.4 mg/dL; $P = 0.81$), HDL-C (43.4 *vs* 42.3 mg/dL; $P = 0.7$), and TG (183 *vs* 193.7 mg/dL; $P = 0.52$) levels did not significantly change compared with those before treatment. The use of antidiabetic, hypolipidemic, and antihypertensive agents remained the same at follow-up.

3. Discussion

Our study showed a high prevalence of metabolic disorders among postmenopausal women with hyperandrogenemia of ovarian origin. About 60% to 80% of the patients presented obesity, T2D, DLP, and hypertension before surgical T-level normalization (Fig. 1). Our findings exceeded the prevalence of these cardiovascular risk factors in older Brazilian women pointed out by the telephone-based Surveillance of Risk and Protective Factors for Chronic Diseases (VIGITEL) survey conducted in Brazil in 2016 [23]. According to VIGITEL 2016, the prevalence rates of obesity, T2D, dyslipidemia and hypertension were 25%, 19.1%, 46.4%, and 49.8%, respectively, in women age 55 to 64 years and 23.4%, 28%, 47.5%, and 67.8% in those age ≥65 years. According to the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), which included >15,000 civil servants, the presence of T2D among women age 65 to 74 years was 20.3% (similar to that in VIGITEL). Its prevalence increased to 33.5% at a BMI >30 kg/m^2, whereas T2D was present in 92.9% of the obese patients in our cohort of postmenopausal women with ovarian hyperandrogenism. Data on the prevalence of hypertension and DLP in Brazilian postmenopausal women according to age and BMI are not yet available [24].

The positive association of metabolic syndrome, insulin resistance, and coronary heart disease with T levels in the top quartile of the normal range has been previously documented in healthy postmenopausal women [10, 11, 25]. However, few reports associate OH with metabolic syndrome features and implicate hyperinsulinemia in its pathogenesis [7, 26]. This association has not yet been established for VOTs. In our cohort, the prevalence of obesity, T2D, and DLP did not significantly differ between the VOT and OH groups (Table 1), suggesting an association of ovarian androgen excess with insulin resistance in both conditions.

The correlation of androgen excess to insulin resistance in women has been known since the 1970s. The first descriptions include rare cases of severe insulin resistance associated with androgen excess [27]. Subsequently, studies have described its mechanism in premenopausal women. It is known that insulin amplifies the response of theca cells to LH, increasing the expression of P450c17 and 3βHSD2 by acting on ovarian insulin receptors, and leads to secondary increased androgen production in premenopausal women with PCOS [28, 29] (Fig. 2). In addition, hyperinsulinemia contributes to androgen excess by suppressing SHBG hepatic production and consequently increasing serum free T levels [30]. Furthermore, O'Reilly *et al.* [31] recently postulated that a vicious cycle in adipose tissue drives metabolic risk in premenopausal women with PCOS. Increased androgen generation in adipose tissue by hyperactivity of the enzyme AKR1C3 promotes *de novo* lipogenesis, reduces lipolysis and β-oxidation, and therefore induces lipotoxicity in patients with PCOS. Subsequent lipid accumulation and increased fat mass result in systemic insulin resistance, with androgen generation further exacerbated by hyperinsulinemia [31] (Fig. 2). Despite improvements in comprehension of the mechanisms by which androgens regulate adipose tissue function, lipid metabolism, and fat mass in women with PCOS, the direction of causality between androgen excess and insulin resistance remains to be elucidated.

Mirroring this and considering that 58.3% of our cohort was obese and 37.5% was overweight, the hyperinsulinemia secondary to fat mass accumulation and insulin resistance, along with physiologically elevated postmenopausal LH levels, might have contributed to

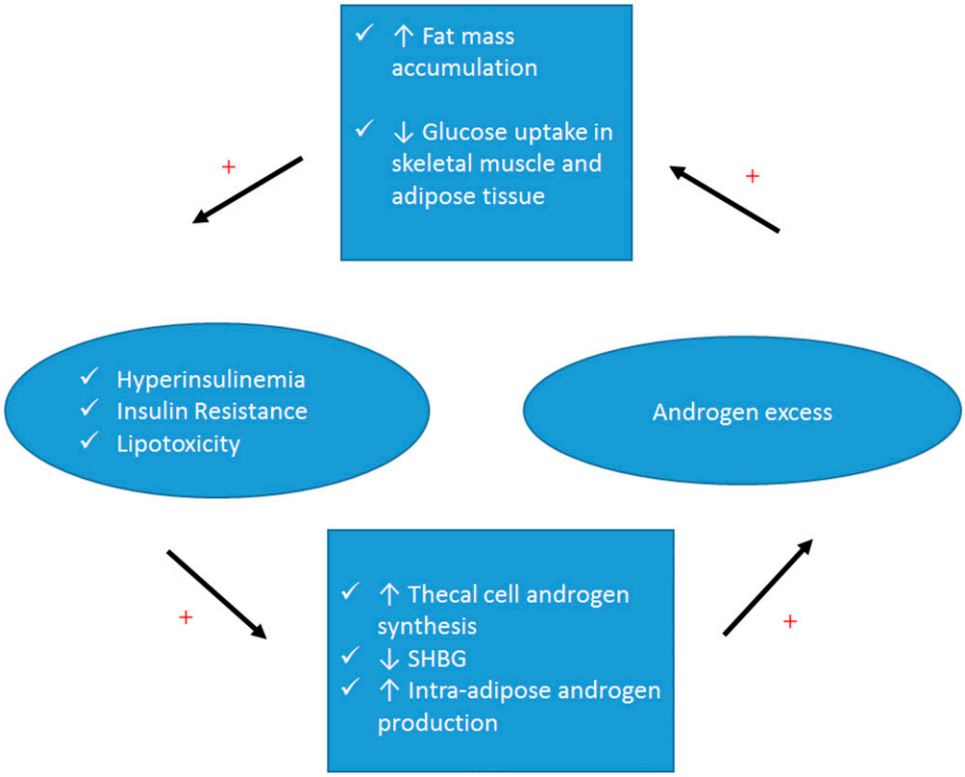


Figure 2. Link between insulin resistance and androgen excess in postmenopausal women with ovarian hyperandrogenism. Insulin amplifies the response of theca cells to LH by acting on ovarian insulin receptors and leads to secondary increased androgen production [28, 29]. In addition, hyperinsulinemia contributes to androgen excess by suppressing SHBG hepatic production and consequently increasing serum free T levels [30]. An increased androgen generation in adipose tissue induces lipotoxicity in patients with PCOS. Subsequent lipid accumulation and increased fat mass result in systemic insulin resistance, with androgen generation further exacerbated by hyperinsulinemia [31].

androgen excess in this population. We have found no significant differences in SHBG levels between the VOT and OH cohorts despite significant differences in T levels, supporting the hypothesis that hyperinsulinemia mainly suppressed SHBG in both groups. No differences were found in the analysis of SHBG levels before *vs* after T-level normalization, indicating that hyperinsulinemia persisted and did not significantly improve after androgen level normalization.

The hypothesis of hyperandrogenism adversely impairing insulin action in postmenopausal women has been investigated. Clinical and experimental data suggest that high T levels can impair insulin signaling in muscle and adipocytes, resulting in increased insulin resistance (Fig. 2): Androgen administration to healthy women has been shown to reduce insulin sensitivity and impair peripheral glucose uptake, as assessed by the hyperinsulinemic-euglycemic clamp [32, 33]. In addition, antiandrogen treatment partially improved the peripheral insulin resistance in hyperandrogenic premenopausal women [34]. In animals, the administration of T to female oophorectomized rats induced decreased insulin-mediated glucose uptake by reduced glycogen synthase expression in skeletal muscle [35]. However, long-term prospective studies to evaluate whether androgen excess treatment improves metabolic risk factors are scarce.

Based on the hypothesis that hyperinsulinemia secondary to insulin resistance enhances ovarian androgen production, Vaikkakara *et al.* [7] used the insulin sensitizer metformin combined with weight loss measures in premenopausal and postmenopausal women with ovarian hyperandrogenism and observed a significant normalization of serum T levels. However, this was a small study that could not determine the cause of ovarian hyperandrogenism

[7]. A randomized controlled trial by Patel *et al.* [14] demonstrated that the treatment of insulin resistance with metformin decreased T levels, but the pharmacological lowering of T levels with leuprolide acetate did not affect insulin resistance in a population of postmenopausal women with insulin resistance and higher T levels after 12 weeks of follow-up . This study investigated the direction of causality in the association between insulin resistance and androgen excess in postmenopausal women. Aligned with Patel and colleagues' findings, we've also found that long-term T-level normalization did not improve metabolic disorders in our cohort of postmenopausal women with ovarian hyperandrogenism.

On balance, our data indicate that hyperinsulinemia was the driver event in our cohort of ovarian-origin hyperandrogenic postmenopausal women with adverse metabolic risk further exacerbated by lipotoxic organ damage induced by androgen excess. The long-term androgen excess exposure might have led to irreversible fat mass accumulation, lipotoxicity, and hyperinsulinemia. Further investigation is needed to evaluate the impact of these high-risk metabolic factors on long-term cardiovascular outcomes.

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