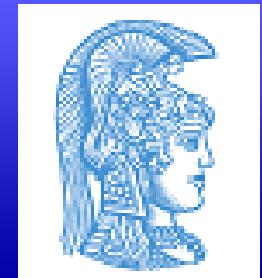


Androgen excess in peri- and postmenopausal women



EMAS

European Menopause and Andropause Society



Irene Lambrinoudaki

Endocrinologist

Associate Professor of Gynecological Endocrinology

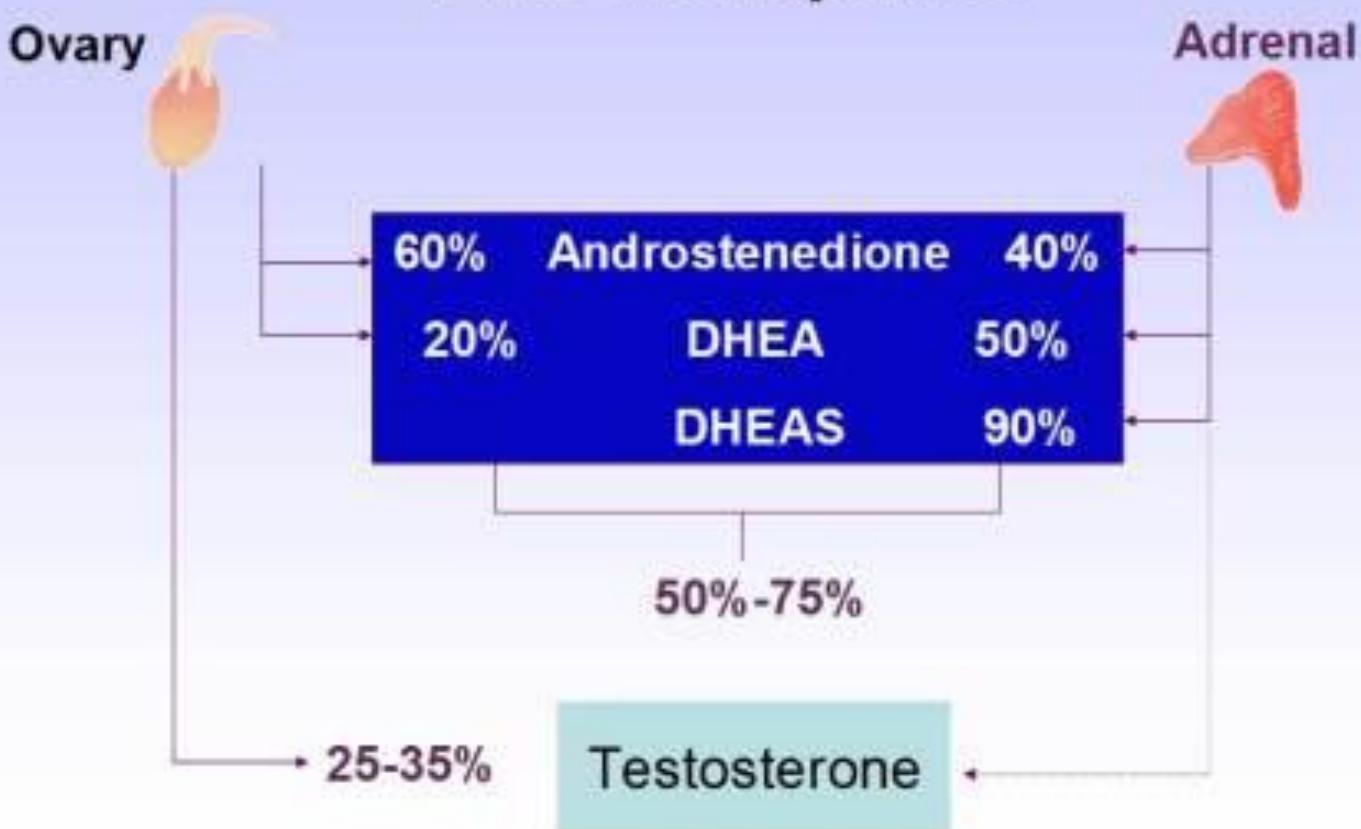
National and Kapodistrian University of Athens, Greece

EMAS, Scientific Director

Presentation outline

- **Androgen levels in menopause**
- **Causes of androgen excess in menopause**
- **Cardiovascular implications of androgen excess in menopause**
- **Differential diagnosis**
- **Management**

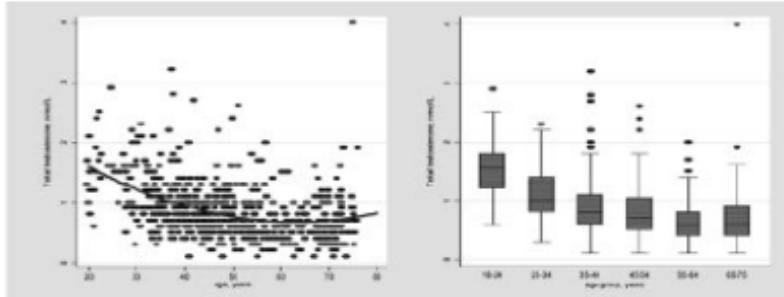
Androgen Production PRE menopause



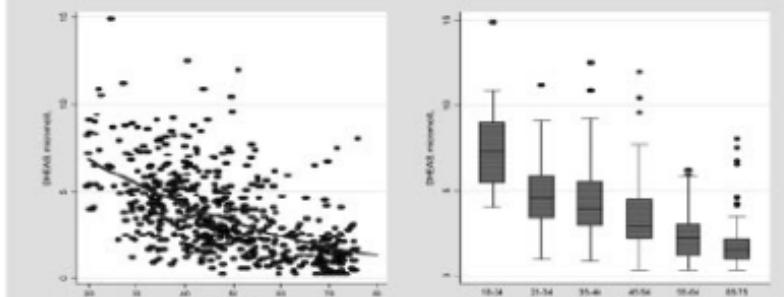
Davis 2005

Androgen levels: effect of aging and menopause

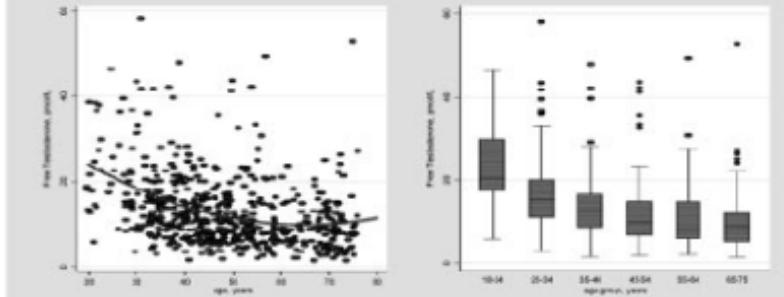
Total Testosterone



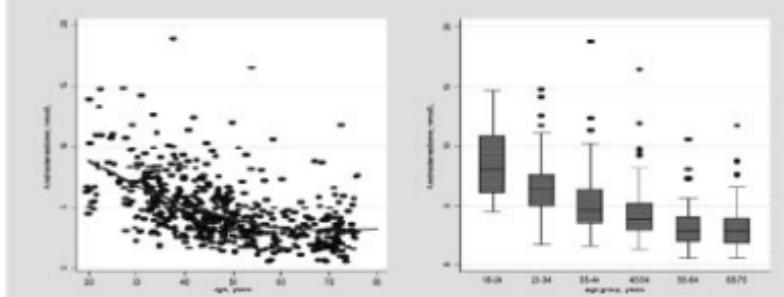
DHEAS



Free Testosterone



Androstenedione



- Androgen production declines during the reproductive years
- Menopause has no effect on androgen levels
- Aging is associated with a gradual decline in androgen production

Menopause: a state of relative androgen excess

- Abrupt decline of estrogen production



A / E ratio
increase

- No change in androgen production

- SHBG decline (aging, central obesity associated with menopause)



Bioavailable
A increase

- SHBG binding: Testosterone > estradiol

Table 1 Causes of hyperandrogenism in women after menopause.

Non tumorous (functional) hyperandrogenism

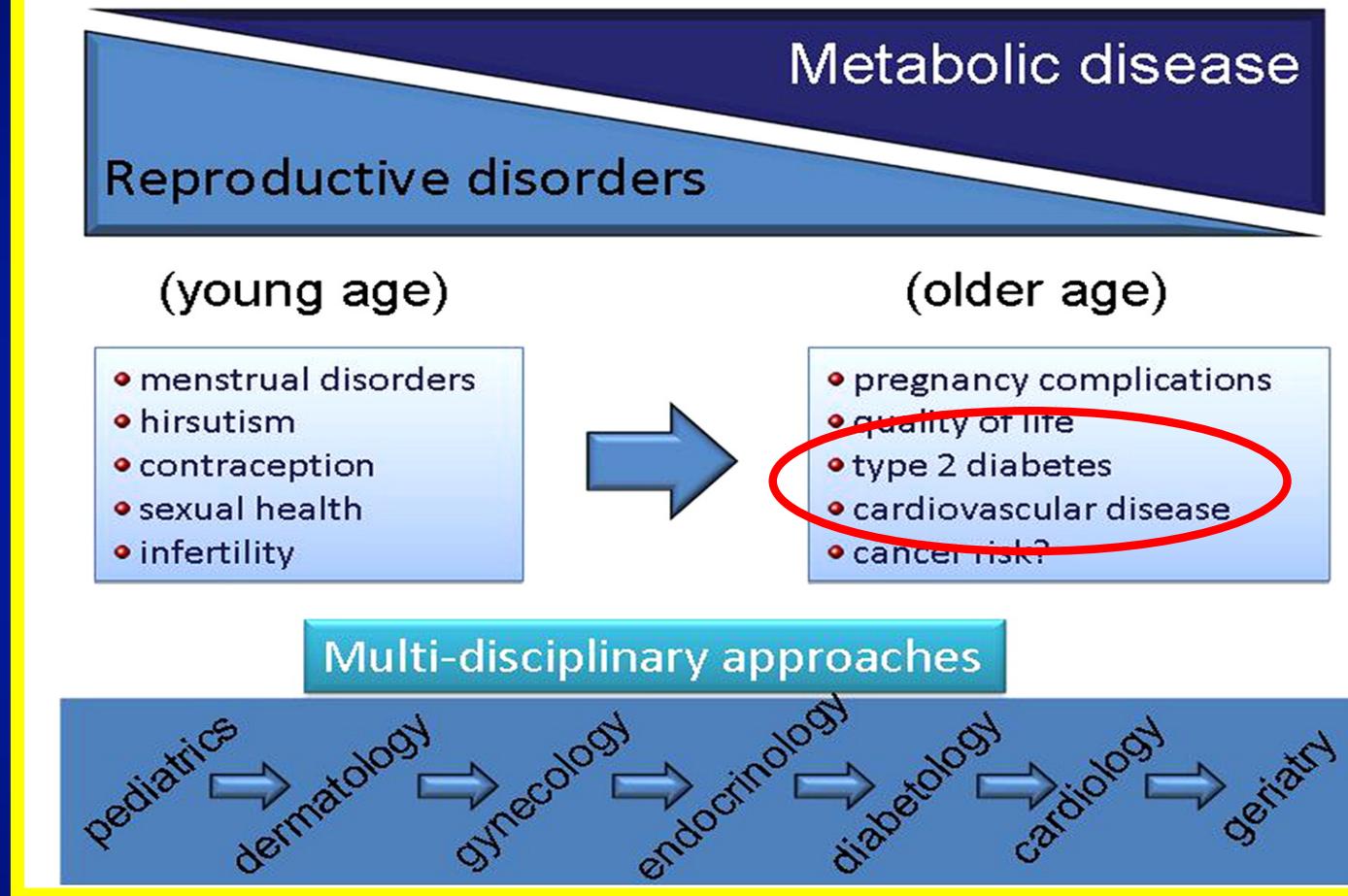
- Polycystic ovary syndrome
- Congenital adrenal hyperplasia
- Ovarian hyperthecosis
- Obesity
- States of insulin resistance
- Endocrinopathies
 - Cushing's syndrome
 - Acromegaly
 - Testosterone/DHEA supplementation
 - Antiepileptics (valproic acid and oxcarbazepine)
 - Danazol
- Iatrogenic

Tumorous hyperandrogenism

- Adrenal tumors
 - Androgen-secreting carcinomas
 - Androgen-secreting adenomas
 - Sertoli–Leydig cell tumors (androblastomas)
 - Hilus cell tumors
 - Granulosa theca cell tumors
 - Metastatic neuroendocrine/gastrointestinal tumors
- Ovarian tumors
 - Cystadenomas

Marios C Markopoulos

PCOS: changing women's health paradigm



Hsu MI Changes in the PCOS phenotype with age. Steroids.2013;78:761-6

PCOS and CVD risk factors

- Obesity (30-80% prevalence in PCOS women)
- Dyslipidemia (low HDL, high TG – prevalence 70%)
- Hypertension
- Insulin resistance – metabolic syndrome
- Defective glucose metabolism
 - Fasting hyperglycemia
 - IGT
 - DM
- Chronic inflammation

Roe A et al. J Clin Endocrinol Metab. 2014 Feb (e-pub)

Tzeng CR et al. Fertil Steril 2014 Feb 14 (e-pub)

Cobin RH et al. Intern Emerg Med. 2013;8 Suppl 1:S61-4.

Wild RA et al. J Clin Endocrinol Metab. 2010;95: 2038-2049.

Subclinical CVD and PCOS

- Increased IMT
- Endothelial dysfunction
- Increased coronary atherosclerosis

Table 3. Surrogate outcomes for cardiovascular disease in women with polycystic ovarian syndrome (PCOS) versus controls.

Surrogate outcomes	Pooled risk estimate
Flow-mediated dilation: systematic review ²²	$n = 908$ vs. 566 Pooled mean difference: -3.021 (95% CI 3.315–2.727); $p < 0.0001$
Intima media thickness: systematic review ²⁵	$n = 1123$ vs. 923 Pooled OR: 0.072 (95% CI 0.040–0.105), $p < 0.0001$
Coronary calcium score: individual study ²⁹	$n = 61$ vs. 85 Any CAC: 45.9% vs. 30.6%, OR 2.31; 95% CI 1.00–5.33, $p = 0.049$ CAC >10: 19.7% vs. 7.1%, $p < 0.033$
Coronary calcium score: individual study ³¹	$n = 24$ vs. 24 Any CAC: 33% vs. 8%, $p < 0.03$; OR 5.5; 95% CI 1.03–29.45
Coronary calcium score: individual study ³⁰	$n = 149$ vs. 166 Any CAC: 63.1% vs. 41%, $p < 0.05$, adjusted $p = 0.037$ CAC >10: 35.5% vs. 12.2%, $p < 0.05$, adjusted

CAC, coronary artery calcium; n , number of patients; OR, odds ratio; CI, confidence interval.

PCOS and metabolic risk

- PCOS women: 4-fold increase in risk of developing diabetes independently of obesity

Table 2. Unfavorable cardiometabolic risk factors in women with polycystic ovarian syndrome (PCOS) compared to controls: a systematic review of 35 studies involving a total of 14 887 PCOS women and 62 865 controls¹³.

Metabolic feature	Pooled risk estimate	
	PCOS vs. non-PCOS controls	PCOS vs. BMI-matched non-PCOS controls
Impaired glucose tolerance	n = 835 vs. 568 pOR: 2.48 (95% CI 1.63–3.77)	n = 347 vs. 319 pOR: 2.54 (95% CI 1.44–4.47)
Type 2 diabetes mellitus	n = 12 105 vs. 56 959 pOR: 4.43 (95% CI 4.06–4.82)	n = 441 vs. 1175 pOR: 4.00 (95% CI 1.97–8.10)
Metabolic syndrome	n = 2256 vs. 4130 pOR: 2.88 (95% CI 2.40–3.45)	n = 273 vs. 276 pOR: 2.20 (95% CI 1.36–3.56)

BMI, body mass index; n, number of patients; pOR, pooled odds ratio; CI, confidence interval.

Hyperandrogenemia persists in women with PCOS after menopause

Hormone	PCOS (n = 20)	Controls (n = 20)	P
FSH (mIU/ml)	72.8 (47.2–90.3)	77.1 (41.3–88.6)	NS
LH (mIU/ml)	37.8 (26.1–42.2)	19.3 (18.9–39.7)	NS
Estradiol (pg/ml)	24 (20–26)	29 (26–39.6)	NS
Prolactin (ng/ml)	8.2 (6.6–12.3)	7.1 (4.9–9)	NS
Progesterone (ng/ml)	0.3 (0.3–0.4)	0.2 (0.1–0.2)	<0.05
17-OHP (ng/ml)	0.5 (0.48–0.55)	0.33 (0.23–0.4)	<0.05
Δ ₄ A (ng/dl)	205 (145–349)	107 (80–144)	<0.05
DHEAS (ng/ml)	1430 (591–1560)	602 (390–889)	<0.05
Total T (ng/ml)	0.47 (0.39–0.59)	0.37 (0.18–0.42)	<0.05
SHBG (nmol/liter)	43.2 (25.1–51.1)	67.7 (54.5–98.3)	<0.01
FAI	3.94 (3.3–5.4)	1.48 (1.05–1.6)	<0.001

Markopoulos M, Mastorakos G et al. J Clin Endocrinol Metab. 2011;96:623-31
 Markopoulos M, Mastorakos G et al. Eur J Endocrinol. 2012;168:83-90.

The adverse cardiometabolic profile of women with PCOS persists after menopause

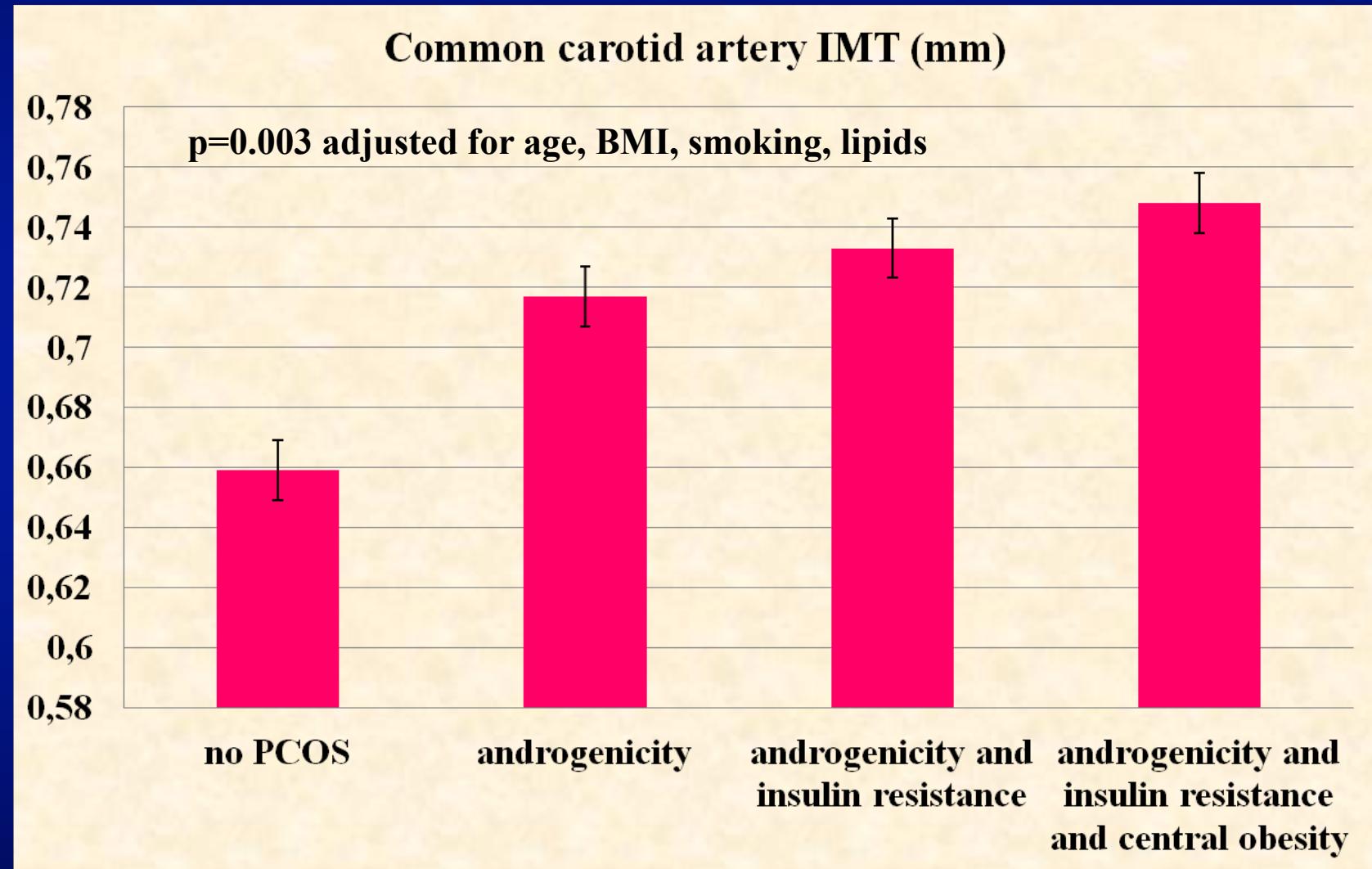
<i>Variables</i>	<i>Postmenopausal PCOS</i>	<i>Postmenopausal Controls</i>	<i>ANOVA P-value</i>
<i>Mean±SD or Frequency (%)</i>			
<i>Biochemical and anthropometric Characteristics</i>			
Age (years)	55.6±7.8	55.3±5.5	0.785
YSM (years)	7.26±5.98	6.60±5.61	0.485
BMI (kg/m ²)	31.2±4.2	25.7±3.8	<0.001
Waist (cm)	96.4±9.2	83.2±9.8	<0.001
WHR	0.88±0.06	0.83±0.07	<0.001
SBP (mmHg)	127.0±20.5	118.3±15.3	0.001
DBP (mmHg)	78.7±11.8	74.4±10.2	0.014
FBG (mg/dl)	98.7±9.5	90.8±8.0	<0.001
HOMA-IR	2.65±1.08	1.36±0.73	<0.001
Total cholesterol (mg/dl)	223.5±34.0	227.9±38.0	0.492
Triglycerides (mg/dl)	105.7±45.0	86.2±39.5	0.004
HDL-Cholesterol (mg/dl)	55.2±10.1	63.9±15.2	<0.001
LDL-Cholesterol (mg/dl)	145.3±30.9	139.9±36.7	0.380
Insulin (μU/ml)	10.9±4.4	5.9±2.9	<0.001

YSM = years since menopause; BMI = body mass index; WHR = waist-to-hip ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure; HOMA-IR = homeostasis model assessment of insulin resistance

Armeni E*, Stamatelopoulos K*, Lambrinoudaki I. J Hypertension 2013; 31:1998-2004

*Equal contribution

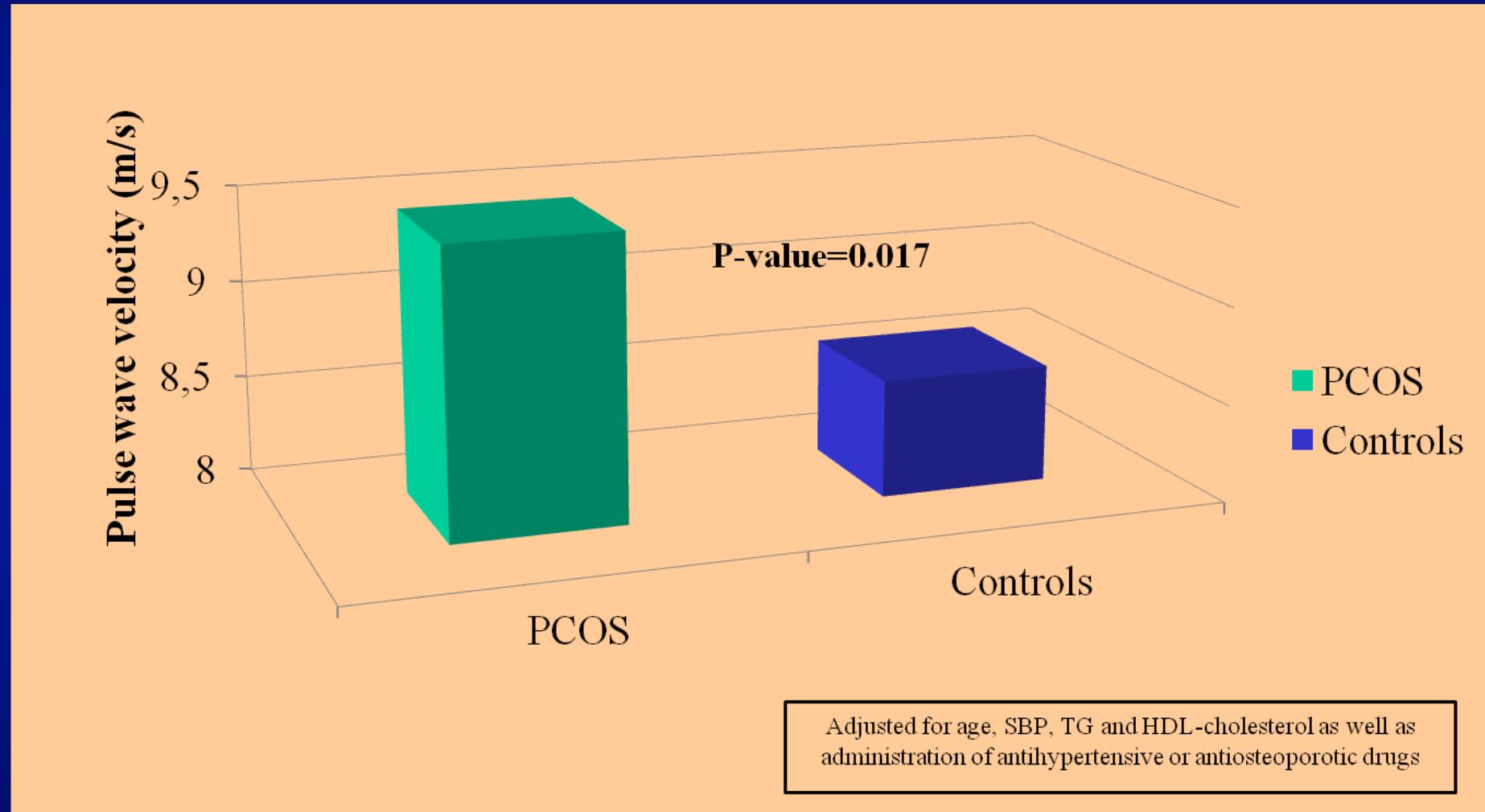
IMT increases linearly with increasing features of PCOS in postmenopausal women



Armeni E*, Stamatelopoulos K*, Lambrinoudaki I. J Hypertension 2013; 31:1998-2004

*Equal contribution

Postmenopausal women with the PCOS phenotype have stiffer arteries compared to women without the PCOS phenotype.

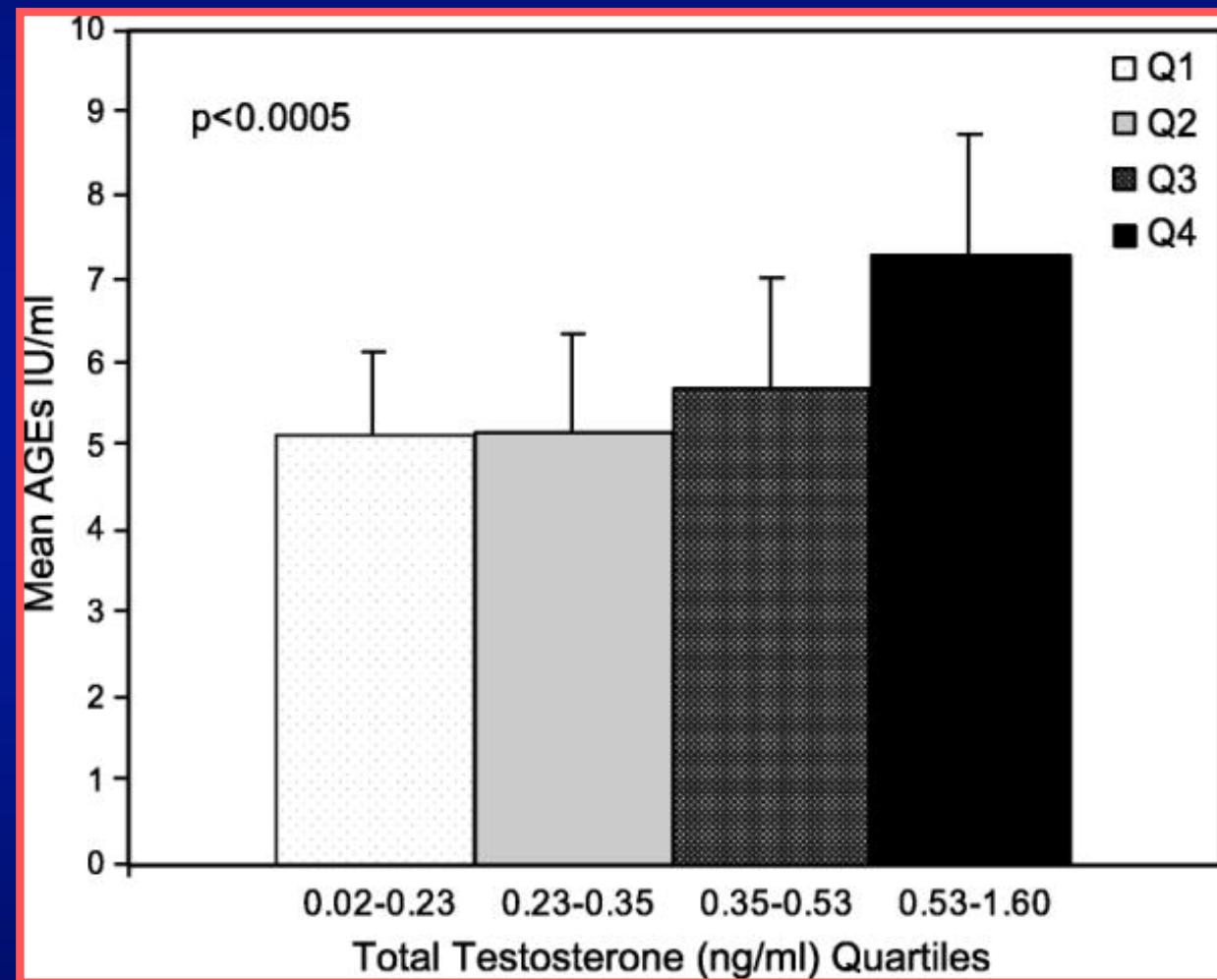


Armeni E*, Stamatelopoulos K*, Lambrinoudaki I. J Hypertension 2013; 31:1998-2004

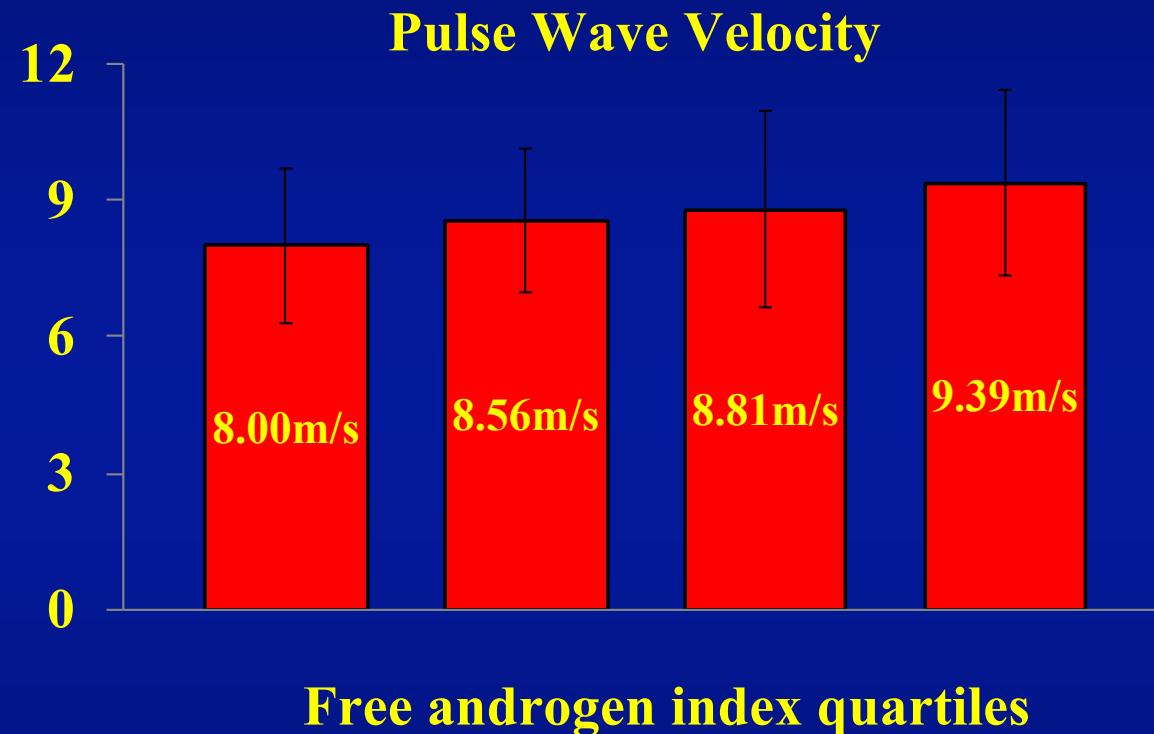
*Equal contribution

High androgen levels are associated with increased serum AGES in postmenopausal women

Serum AGEs
(advanced
glycation
end-products)

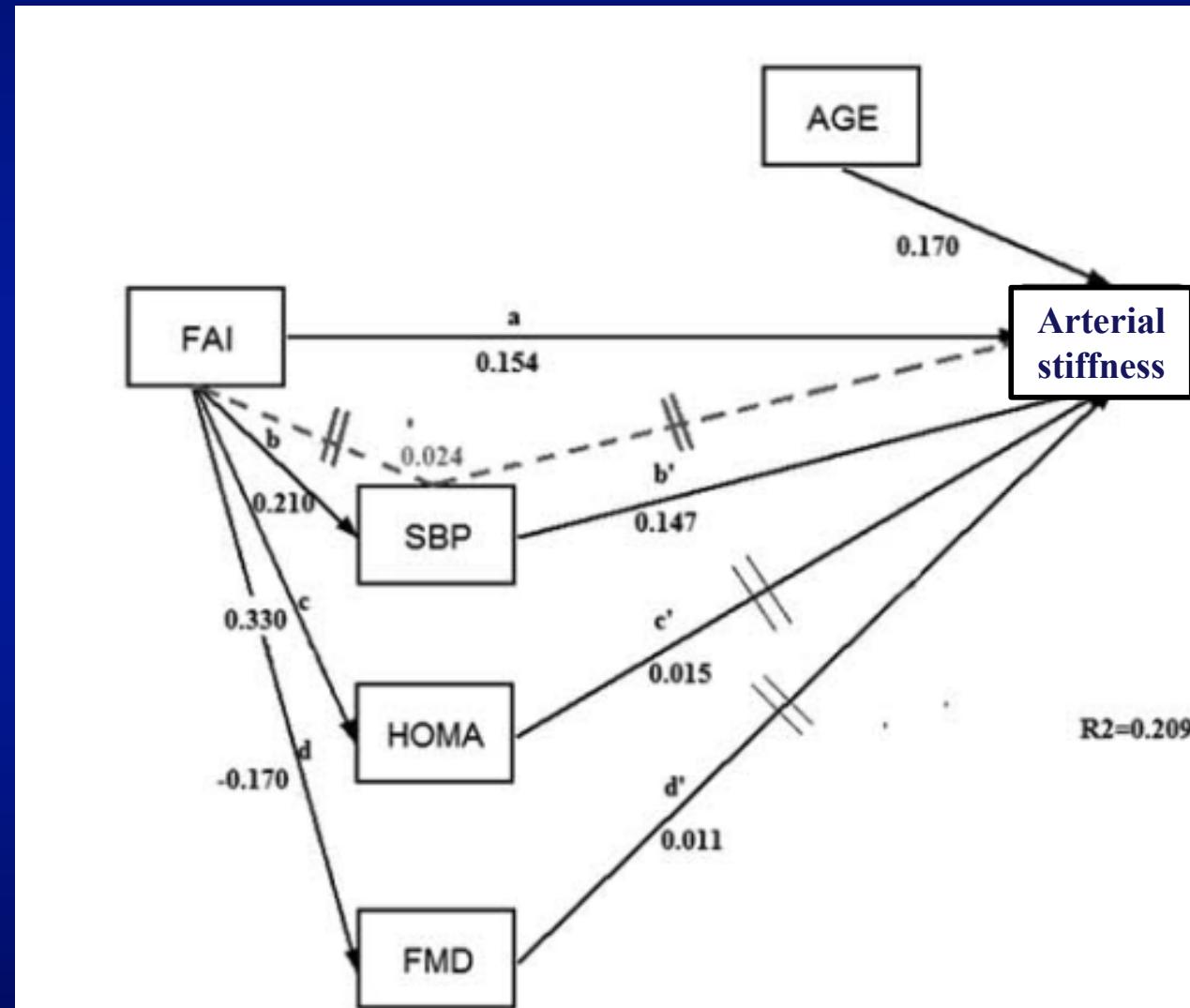


High androgen levels are associated with increased arterial stiffness in postmenopausal women



P-value =0.038 in multiple regression model including age, BMI, smoking, insulin, HDL-cholesterol

Direct and indirect effects of androgens on arterial stiffness in postmenopausal women



Free androgen index as a predictor of blood pressure progression and accelerated vascular aging in menopause

- ❖ 180 postmenopausal women free of CVD, diabetes, renal disease, chronic inflammatory disease, cancer
- ❖ Baseline evaluation of serum androgens
- ❖ Baseline and annual follow-up of subclinical arterial disease (median follow-up 29 months)

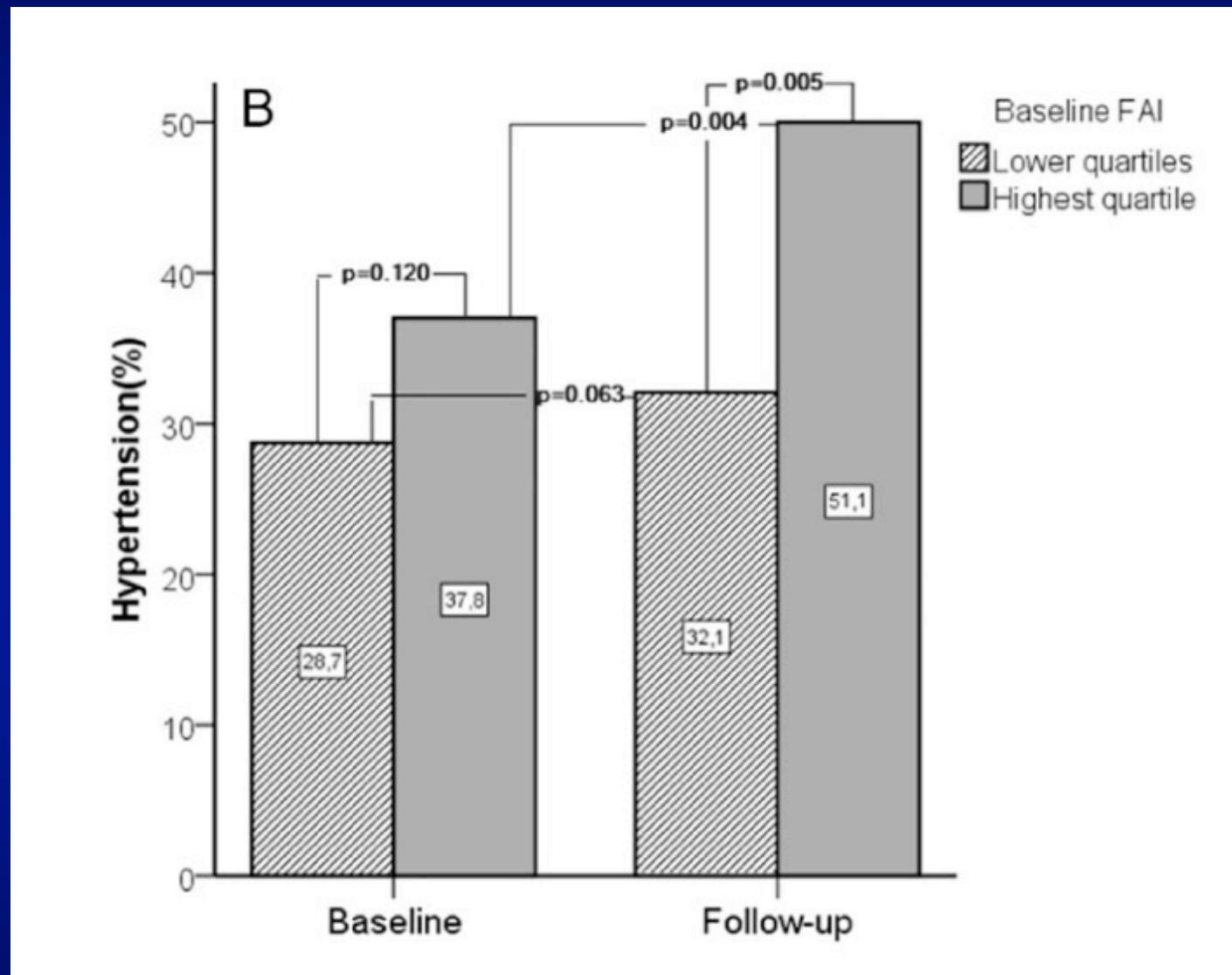
- Blood pressure
- New-onset hypertension
- PWV (arterial stiffness)
- FMD (endothelial function)

Free androgen index as a predictor of blood pressure progression and accelerated vascular aging in menopause

At the end of 3-y follow up women in the highest quartile of baseline free androgen index:

- Higher PVW
- Lower FMD (endothelial dysfunction)
- Higher peripheral and central BP

New-onset hypertension according to baseline free androgen index



Androgen excess and cardiovascular risk in menopause

- States of premenopausal androgen excess persist after menopause
- Association with high BMI, central adiposity and insulin resistance
- Evidence of subclinical arterial disease
- No solid evidence regarding CV events
- Effect may be mediated by the adverse metabolic profile associated with androgen excess

Postmenopausal hyperandrogenism: Differential diagnosis

Most common



Table 1 Causes of hyperandrogenism in women after menopause.

Non tumorous (functional) hyperandrogenism

- | | |
|--------------------------------|---|
| Polycystic ovary syndrome | |
| Congenital adrenal hyperplasia | |
| Ovarian hyperthecosis | |
| Obesity | |
| States of insulin resistance | |
| Endocrinopathies | Cushing's syndrome
Acromegaly |
| | Testosterone/DHEA supplementation |
| Iatrogenic | Antiepileptics (valproic acid and oxcarbazepine)
Danazol |

Very rare

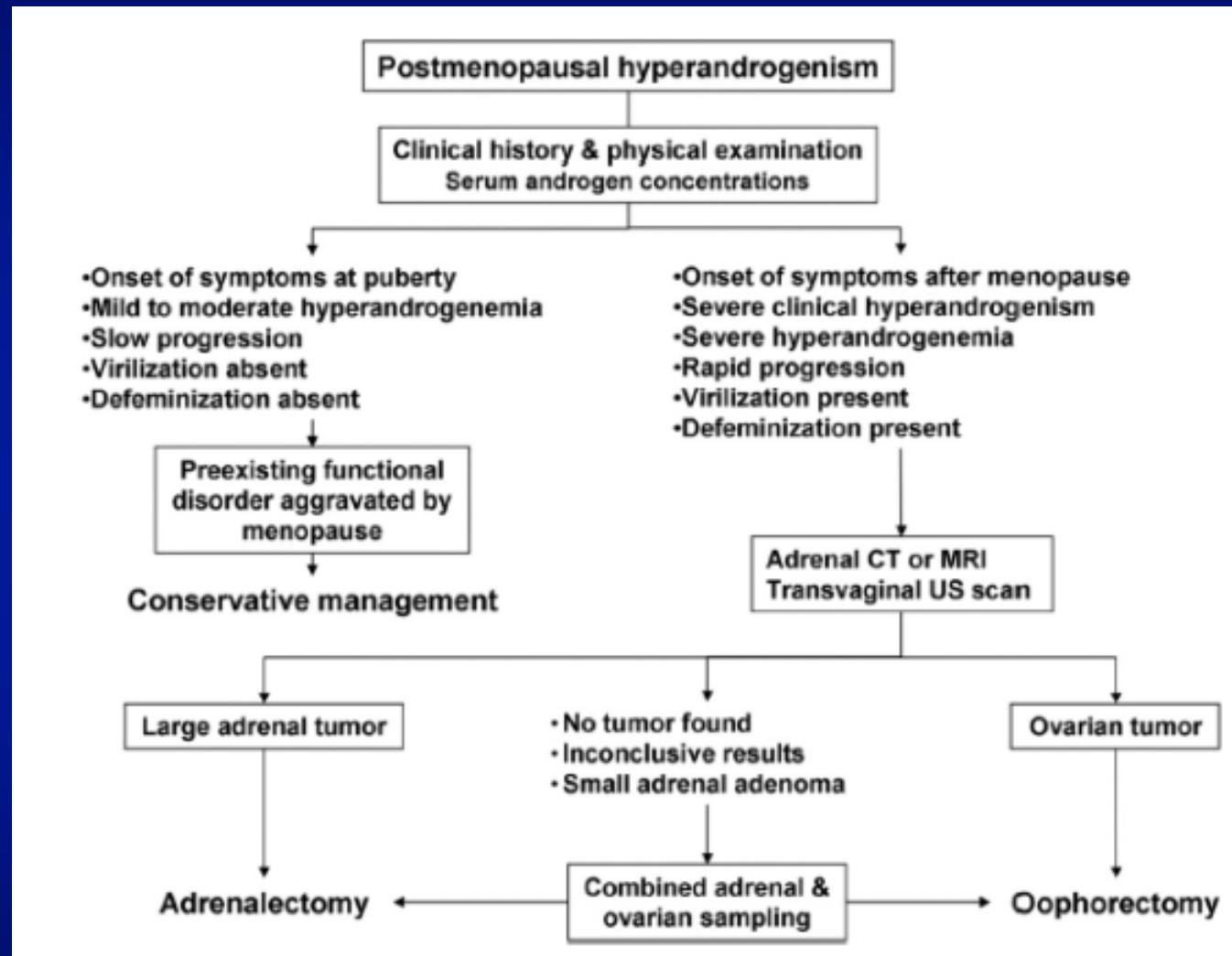


Tumorous hyperandrogenism

- | | |
|----------------|---|
| Adrenal tumors | Androgen-secreting carcinomas |
| Ovarian tumors | Androgen-secreting adenomas
Sertoli-Leydig cell tumors (androblastomas)
Hilus cell tumors
Granulosa theca cell tumors
Metastatic neuroendocrine/gastrointestinal tumors
Cystadenomas |

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Postmenopausal hyperandrogenism: Differential diagnosis



Hirsutism versus virilization

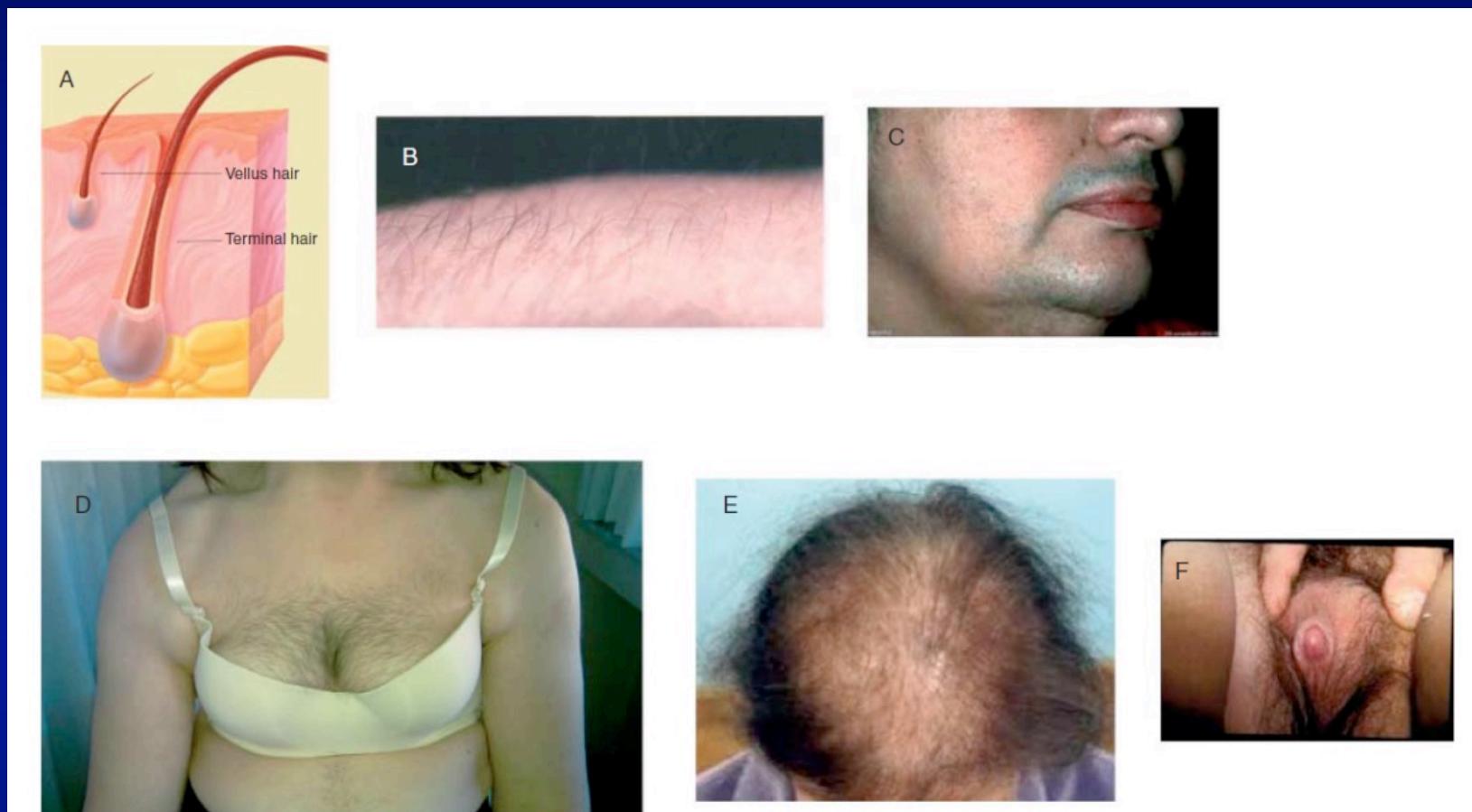


Figure 1

Signs of physiological relative hyperandrogenism ('normal' growth of terminal hair (A and B)) and of true hyperandrogenism and virilization (severe hirsutism (C and D), androgenic alopecia (E), and clitoromegaly (F)) in postmenopausal women.

Table 2 Ovarian androgen-secreting tumors in postmenopausal women.

Histologic type	Age at presentation (years)	Incidence (of all ovarian neoplasms, %)	Hormone secretion	Symptoms	Bilaterality	Malignant potential
Sertoli–Leydig cell tumors (androblastomas)	Range, 2–75	0.5	Androgens, rarely estrogens	Virilization in about one-third of cases	Uncommon (1–2%)	Low
Granulosa cell tumors	40–70	2–3	Estrogens, rarely androgens	Postmenopausal bleeding, mass, rarely virilization	About 5%	Low
Sertoli cell tumors	Range, 7–79	0.1	Androgens, rarely estrogens	Virilization in about 30% of patients	Rare (1–2%)	Low
Hilus cell tumors	Peak at 6th decade	0.02	Androgens	Hirsutism and virilization in 50–75% of cases	Rare	Very rare

Marios C Markopoulos

Steroid cell tumor of the ovary

- 67y old woman
- Rapidly progressing virilization
- Androgens in the male ref range
- Adrenal CT and transvaginal US negative
- 20mm adnexal mass in MRI

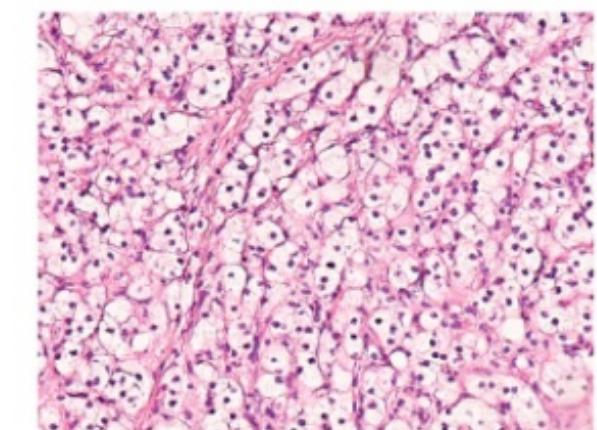


Figure 2. The typical appearance of ovarian steroid cell tumor (large cells with vacuolar cytoplasm and small nuclei), detailed presentation for the section in Figure 1 [hematoxylin-eosin ($\times 220$)].

Table 1. Biochemical profile of the patient at baseline and after the surgery.

Hormone	Post-menopausal reference range	Baseline	After ACTH stimulation test	After overnight dexamethasone suppression test	After LHRH analogue (triptoreline 3.75 mg monthly)	3 months after surgery	8 months after surgery	24 months after surgery
Total testosterone (ng/dl)	5–40	340		380	10	8	11	15
FSH (mIU/ml)	23–110	16			3.8	30.5	33.1	28.8
LH (mIU/ml)	16–54	14			0.9	16.9	23.5	19.7
Estradiol (pg/ml)	<45	48				12.2	5	5
DHEAS (mg/dl)	12–150	95		74		27	29	26
$\Delta 4$ -Androstenedione (ng/ml)	0.20–3.40	4.1		3.9		2	1.9	
17-Hydroxyprogesterone (ng/dl)	0.1–1	9.3	11.6	12.5	0.8	0.6	2	1
Prolactin (ng/ml)		8				7.9	13.6	6
TSH (μ IU/ml)	0.3–4.5	3.8						1.7
Urinary free cortisol (mg/24 h)	3.5–4.5	23.4						
Cortisol (mg/dl)		16.8	31.1	1.3			21.6	
SHBG (nmol/l)	20–130	43.5					30.2	

FSH, follicle stimulating hormone; LH, luteinizing hormone; DHEAS, dehydroepiandrosterone sulfate; TSH, thyroid-stimulating hormone; SHBG, sex-hormone binding globulin.

Management of functional hyperandrogenism in menopause

- Life-style modification
- Medical treatment

- Weight control
- Physical activity

- OC (perimenopausal women)
- Metformin
- Antiandrogens (spironolactone, flutamide)
- 5a-reductase inhibitors (T \rightarrow DHT, finasteride)
- Glucocorticoids (CAH)
- Gn-RH analogues (ovarian hyperthecosis)

Management of androgen excess in perimenopausal women

Oral Contraceptives

D. Lizneva et al. / Best Practice & Research Clinical Obstetrics and Gynaecology 37 (2016) 98–118

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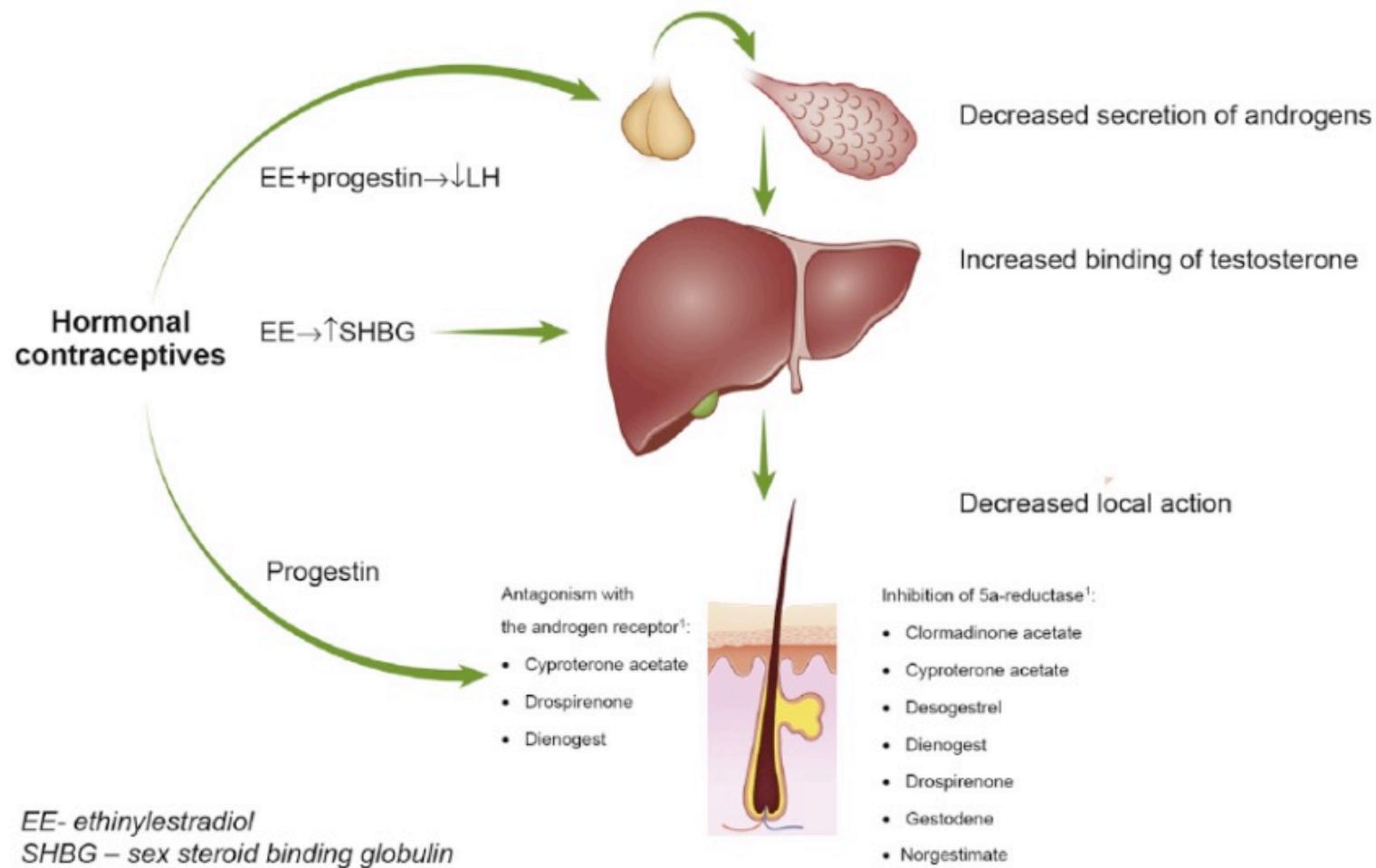


Fig. 5. Action of hormonal contraceptives on the secretion and action of androgens. ¹ Androgen action blockade can be the result of either competitive binding for the androgen receptor (AR) or inhibition of 5 α -reductase activity.

Clinical eligibility of OCs according to age and CV risk factors

Table 1

WHO-Medical Eligibility Criteria (MEC) for women with age-related important cardiovascular risk factors (modified according [2]).

	CO _C	P/R	PO _P	DM _{PA}	ETG	Cu-IUD	LNG-IUD
Age							
<18 years	1	1	2	2	1	2	2
18–40 years	1	1	1	1	1	1	1
≥40 years	2	2	1	2 ^a	1	1	1
Obesity							
BMI ≥ 30	2	2	1	2	1	1	1
Smoking							
age < 35 years	2	1	1	1	1	1	1
age ≥ 35 years							
<15 cic	3	1	1	1	1	1	1
≥15 cic	4	4	1	1 ^a	1	1	1
Hypertension							
systolic 140–159 or	3	3	1	2	1	1	1
diastolic 90–99 mmHg							
systolic > 159 mmHg	4	4	2	3	2	1	2
or diastolic > 99 mmHg							
including vascular							
diseases	3/4	3/4	2	3 ^a	2	1	2
>2 cardiovascular risk	3/4	3/4	2	3 ^a	2	1	2
factors							

CO_C: combined oral contraceptives, P: patch, R: vaginal ring, PO_P: progestogen-only pill, DM_{PA}: depot-MPA, ETG: etonogestrel implantat, IUD: intrauterine device, LNG: levonorgestrel.

^a Authors would recommend one higher MEC category.

MEC category:

1: method can be used in any circumstances.

2: method can be generally used.

3: use of method not recommended unless other more appropriate methods are not available or not acceptable.

4: method not to be used.

Xiangyan Ruan^{a,b}, Alfred O. Mueck^{a,b,*}

Effect of physical activity on androgen levels in women

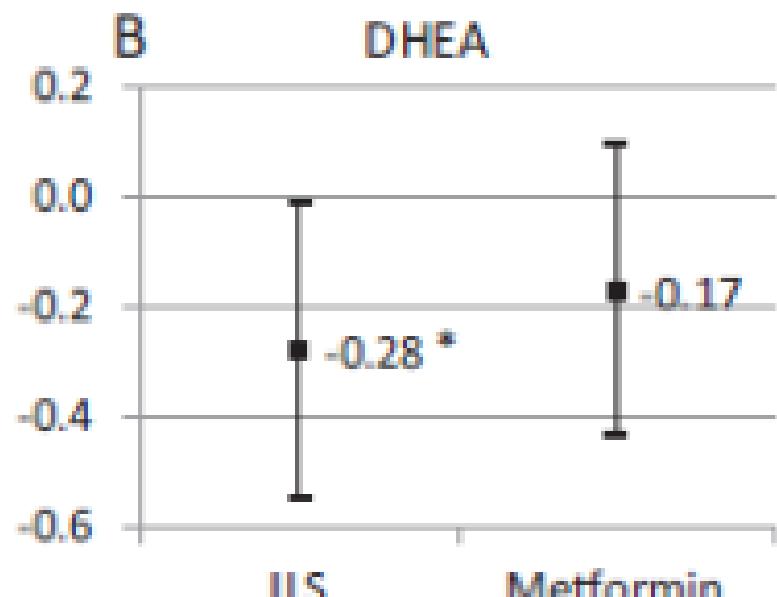
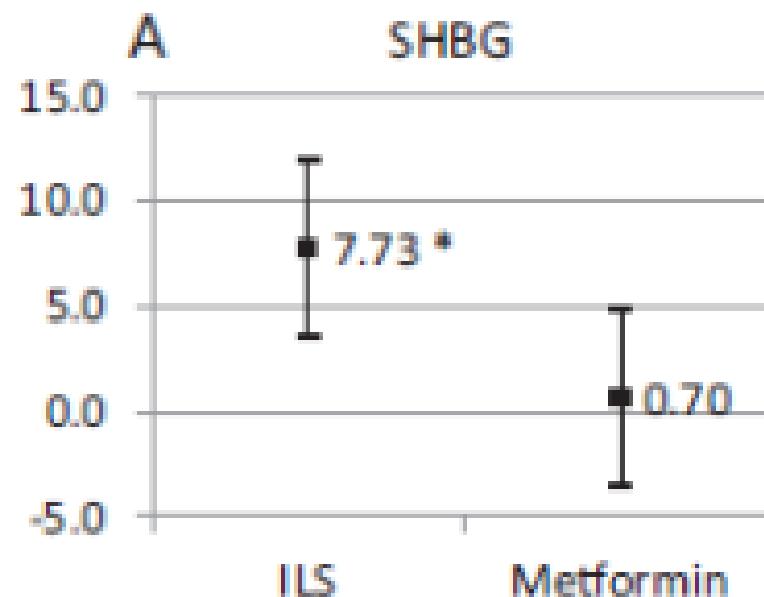
Table 2 Meta-analysis of secondary outcomes

Outcome or subgroup	Studies (n)	Participants (n)	Effect estimate	95 % CI	I^2 (%)
Other estrogens (mean difference)					
Estrone (pg/ml)	4	973	-1.67	-3.62, 0.28	0
Estrone sulfate (ng/ml)	2	393	-0.02	-0.19, 0.14	0
Estriol (NR)	1	79	123.90	-249.69, 497.49	NA
Estrogens – not otherwise specified (pg/ml)	2	89	27.80	-9.76, 65.36	94
Estrogen metabolites (standardized mean difference)					
2-OHE1	3	512	-0.03	-0.20, 0.15	0
16 α -OHE1	3	512	0.03	-0.15, 0.20	1
Total estrogen metabolites concentration (2-OHE1 + 16 α -OHE1)	1	32	0.37	-0.33, 1.07	NA
2-OHE1:16 α -OHE1 ratio	2	195	-0.08	-0.36, 0.21	0
Androgens (mean difference)					
Total testosterone (ng/dl)	21	1939	-1.36	-3.83, 1.11	61
Free testosterone (pg/ml)	9	1369	-0.18	-0.29, -0.07	0
Androstenedione (pg/ml)	7	1187	-33.87	-64.44, -32.9	9
DHEA (ng/ml)	4	304	-0.08	-0.50, 0.35	0
DHEA sulfate (μ mol/l)	8	697	-0.31	-0.57, -0.06	0
Sex hormone binding protein (mean difference) (nmol/l)	14	1634	3.93	0.98, 6.87	75
Anthropometric factors (mean difference)					
Body weight (kg)	16	1737	-1.83	-2.86, -0.81	45
Body mass index (kg/m ²)	20	1976	-0.45	-0.87, -0.03	65
Total body fat (kg)	10	1552	-2.11	-3.71, -0.52	92
Percent fat mass (%)	13	1563	-1.28	-1.95, -0.61	54
Waist circumference (cm)	11	1274	-2.23	-2.97, -1.49	34

CI confidence interval, DHEA dehydroepiandrosterone, NA not applicable, NR not reported, OHE1 hydroxyestrone

Effect of lifestyle intervention on sex hormones in postmenopausal, glucose – intolerant women

J Clin Endocrinol Metab, August 2012, 97(8):2853–2861



12 month RCT, n=235 50-75y postmenopausal women

Intervention: hypocaloric diet 1200-2000 Kcal / day

3 supervised 45min aerobic sessions + 2 at home

Outcome: sex hormone levels

Reduced-Calorie Weight Loss Diet, Exercise, and Sex Hormones

Table 3. Change in Sex Hormones by Study Group, Geometric Means, and 95% CI (continued)

Biomarker	Baseline		12 Months		Δ*	%Δ	P†
	Mean	95% CI	Mean	95% CI			
Free testosterone, pg/mL							
Control	4.9	4.4 to 5.6	5.1	4.6 to 5.7	0.13	2.6	
Diet	5.1	4.7 to 5.6	4.6	4.2 to 5.1	-0.51	-10.0	$P_C < .001\ddagger$ $P_E = .02\$$ $P_{D+E} = .02\$$
Exercise	5.1	4.7 to 5.5	4.9	4.5 to 5.3	-0.23	-4.5	$P_C = .20\ddagger$ $P_D = .02\$$ $P_{D+E} < .001\$$
Diet + exercise	5.3	4.9 to 5.7	4.5	4.1 to 4.8	-0.82	-15.6	$P_C < .001\ddagger$ $P_D = .02\$$ $P_E < .001\$$

Abbreviations: SHBG, sex hormone–binding globulin; Δ, change.

*Change at 12 months from baseline.

†P values for comparing the change from baseline to 12 months between groups. There are six between-group comparisons ($P < .05/6$; .008 is the critical value).

‡ P_C , P values for comparing the changes between control group and three intervention groups.

§ P_D or P_E , P values for comparing the changes between exercise group and diet group; P_{D+E} , P values for comparing the changes between diet + exercise group and two other intervention groups (exercise group or diet group).

||Free estradiol, not calculated for individuals with estradiol below the level of detection (N = 420; n = 79 for control; n = 115 for diet; n = 110 for exercise; n = 116 for diet + exercise groups).

Kristin L. Campbell,

Effect of Exercise on Postmenopausal Sex Hormone Levels and Role of Body Fat: A Randomized Controlled Trial
Evelyn M. Monninkhof, Miranda J. Velthuis, Petra H.M. Peeters, Jos W.R. Twisk, and Albertine J. Schuit

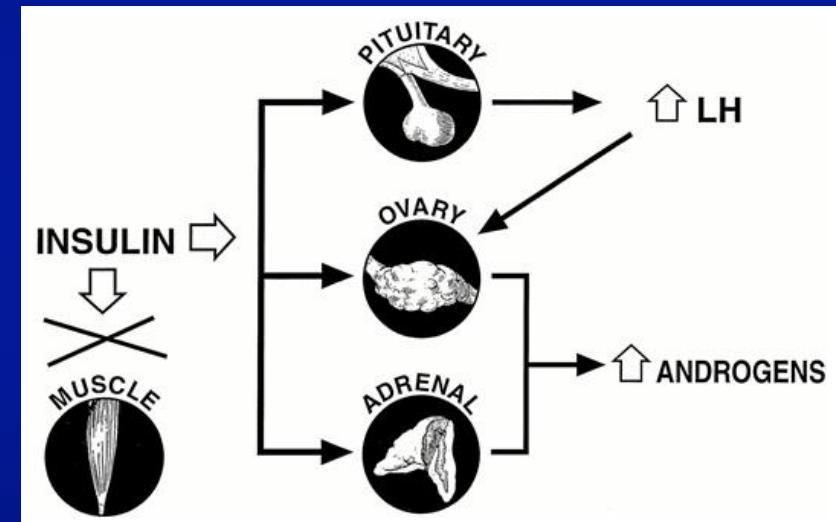
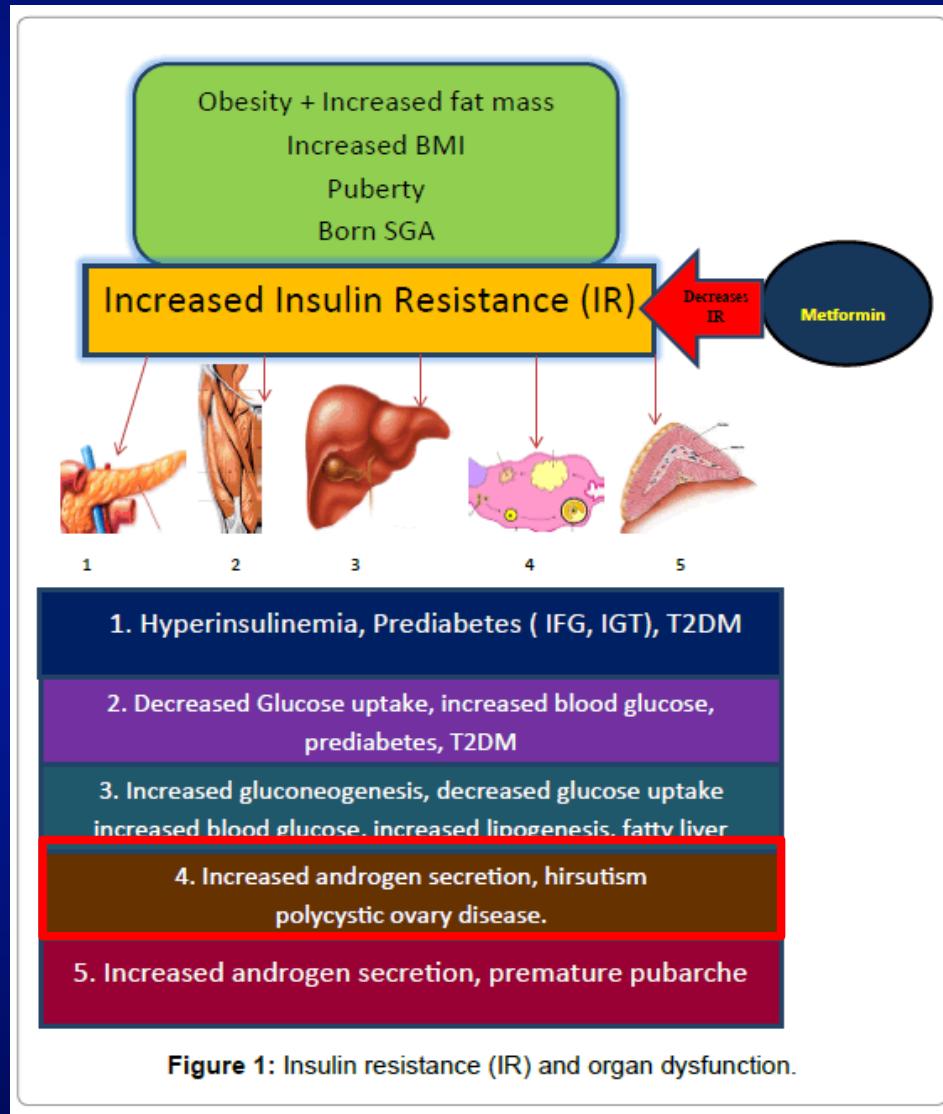
- Two 1-h group sessions, one 30min individual session / week for 12months

Table 3. Hormone Concentrations at Baseline and 4 and 12 Months and Difference Between Intervention and Control Groups for the Subgroup of Women Who Lost > 2% Body Fat

Hormone	Baseline	4 Months	12 Months	% Change From 0 to 4 Months	% Change From 0 to 12 Months	β_{overall}^*	95% CI	P_{overall}^*
No. of patients								
Intervention	39	38	38					
Control	30	29	30					
Androgens								
Free testosterone, pg/mL								
Intervention	8.7	7.6	7.8	-12.8	-10.2	0.94†	0.88 to 0.997	.040
Control	9.7	9.2	8.7	-4.5	-9.9			
Testosterone, pg/mL								
Intervention	517	450	469	-12.9	-9.4	0.92†	0.88 to 0.98	.005
Control	575	577	549	0.2	-4.6			
Androstenedione, pg/mL								
Intervention	1,118	1,003	1,060	-10.4	-5.3	0.90	0.83 to 0.96	.003
Control	1,299	1,308	1,367	0.70	5.3			

Metformin and sex hormones

- Insulin sensitizer: lowers circulating insulin



Metformin

Stimulates AMPK

Inhibits lipogenic enzymes

Activates GLUT-4

Decreases Lipogenesis

Increases Fatty acid oxidation

Increases basal glucose uptake

Activates
Insulin Signalling

Increases insulin-
dependent glucose
uptake

Decreased Insulin Resistance

Metformin enhances insulin signaling in insulin-dependent and - independent pathways.

Figure 2: Mechanism of action of metformin.

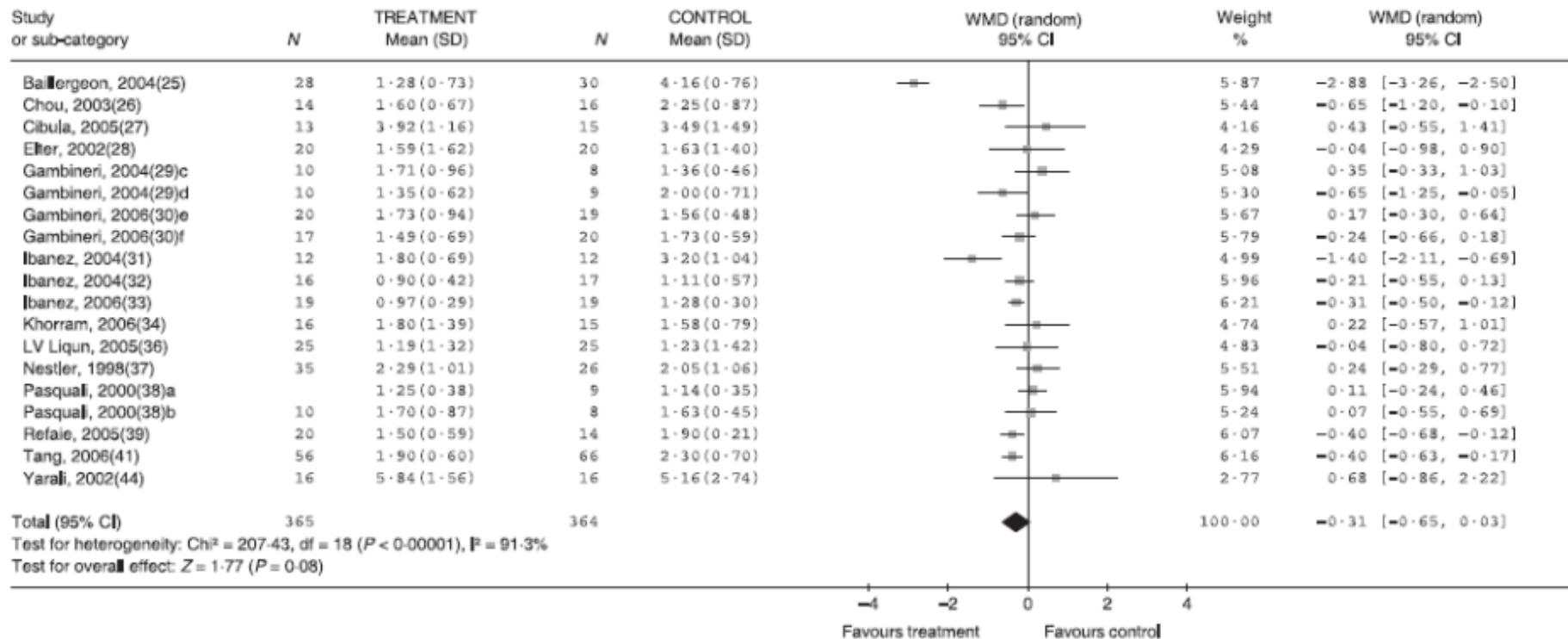
REVIEW ARTICLE

The effects of metformin on endogenous androgens and SHBG in women: a systematic review and meta-analysis

Maddalena Barba*, Holger J. Schünemann†‡, Francesca Sperati*, Elie A. Aklt, Felice Musicco§, Gordon Guyatt‡ and Paola Muti*

Effect of metformin on total testosterone in women

Review: Metformin effects on Endogenous Androgens in Women
 Comparison: TREATMENT vs CONTROL
 Outcome: Total Testosterone

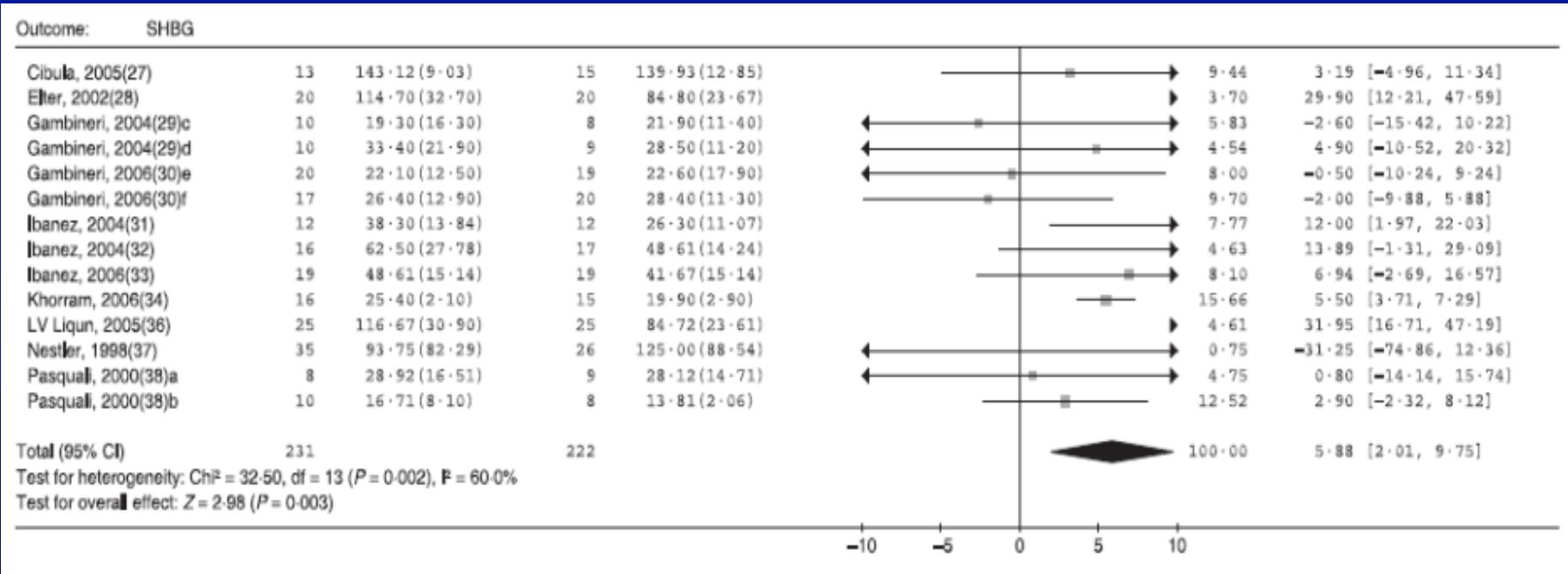


REVIEW ARTICLE

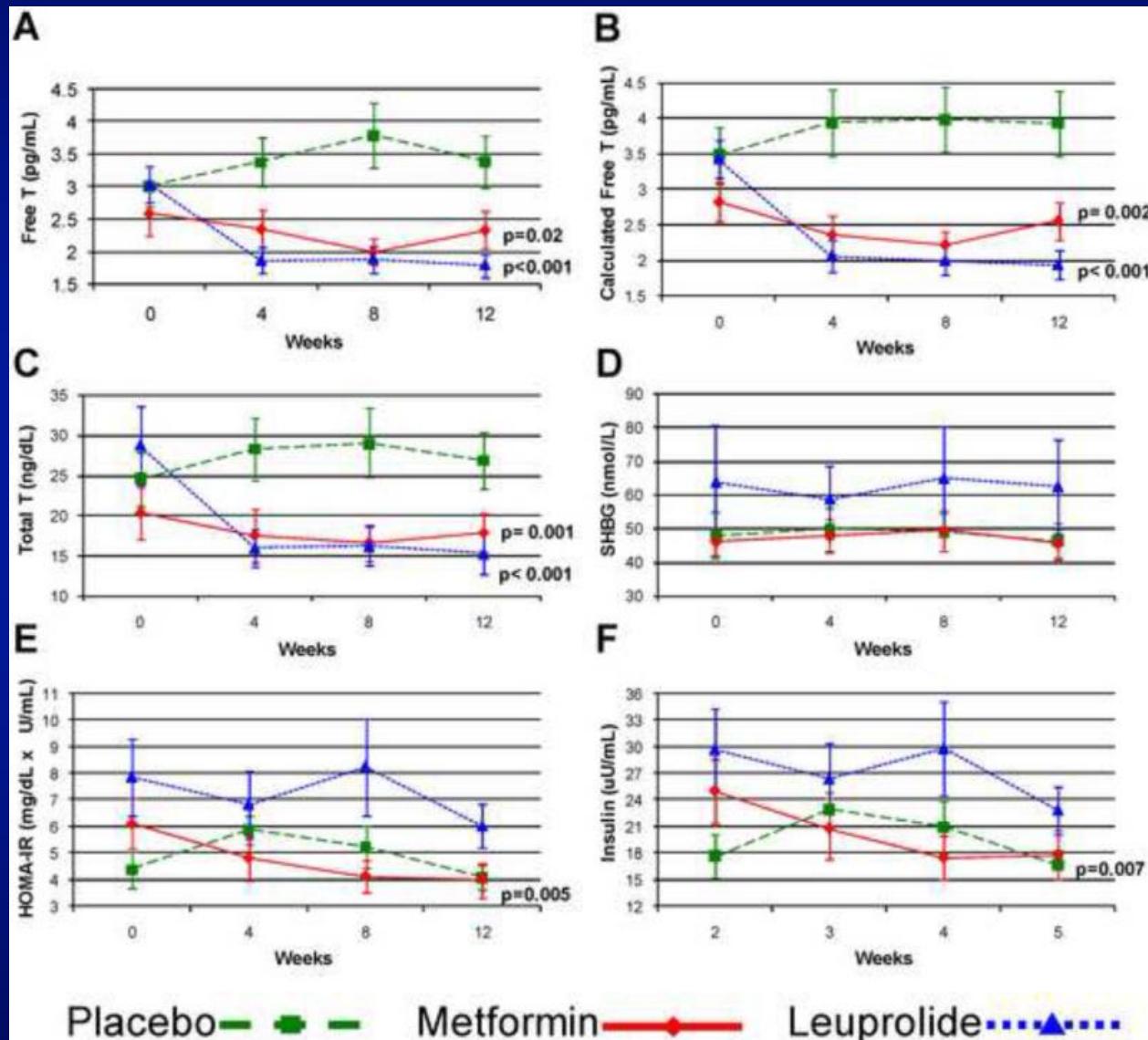
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Effect of metformin on SHBG in women



- Postmenopausal women aged 50-79 yr with insulin resistance and higher testosterone levels
- Metformin 1000mg twice daily



Patel et al. Fertil Steril. 2010 Nov; 94(6): 2161–2166.

Effect of metformin on postmenopausal ovarian hyperthecosis

Table I. Patient characteristics and response to the therapeutic and investigational interventions.

Patient	Age (years)	Final diagnosis	Clinical features						Serum total T (nmol/l)						
			Weight (kg)		BMI (kg/m ²)		Other features of MS	US imaging	BL			GnRH-a	MF	OP	Nadir
			BL	MF	BL	MF			T	fT	DST				
1	31	PCOS	115	110	40	38	dyslipidemia; ↑BP; acanthosis nigricans	PCO – no mass lesion	9.5	202	–	–	2.0	–	2.0
2	27	PCOS	77	77	42	42	–	–	4.8	103	3.3	–	3.2	–	3.2
3	35	PCOS	92	92	33	33	dyslipidemia	PCO – no mass lesion	4.4	131	1.8	–	2.2	–	2.2
4	29	PCOS	88	84	36	32	dyslipidemia	PCO – no mass lesion	7.2	189	4.2	–	2.4	–	2.4
5	38	PCOS	82	79	33	32	T2DM; ↑BP	PCO – no mass lesion	7.6	220	–	–	3.5	–	3.5
6	24	PCOS	101	97	39	38	–	no mass lesion	5.0	81	–	–	2.4	–	2.4
7	35	PCOS	112	114	40	41	dyslipidemia; ↑BP	PCO – bulky right ovary	7.7	157	8.3	<1.0	3.5	2.8 [†]	<1.0
8	23	PCOS	85	79	34	32	dyslipidemia; ↑BP	PCO – no mass lesion	4.9	86	–	–	1.6	<1.0	<1.0
9	62	OH	92	79	38	33	dyslipidemia; T2DM	no mass lesion	5.6	164	–	–	2.1	–	2.1
10	64	OH	136	138	52	53	dyslipidemia; T2DM; ↑BP	–	5.2	96	2.1	–	2.8	–	2.8
11	64	OH	119	103	47	40	T2DM; ↑BP	no mass lesion	7.6	65	5.6 [3.9] [*]	2.3	7.6	–	2.3
12	59	OH	74	–	29	–	↑ BP	1.5 cm right ovarian cyst	4.1	93	–	<0.1	–	–	<0.1
13	64	OH	89	–	36	–	dyslipidemia	5 cm right ovarian cyst	6.2	157	–	–	1.9	–	1.9
14	55	OH	149	143	59	57	dyslipidemia; T2DM; ↑BP	–	6.1	64	3.0	3.9	3.1	–	3.1

BL, baseline value; MF, post metformin; BMI, body mass index; MS, metabolic syndrome; US, ultrasound; T, testosterone; fT, free testosterone (normal range: 0–25 pmol/l); DST, post-dexamethasone suppression test; GnRH-a, post-gonadotropin-releasing hormone analog therapy; OP, post-oophorectomy; Nadir, lowest serum T achieved by any intervention; PCOS, polycystic ovary syndrome; OH, postmenopausal ovarian hyperthecosis; BP, blood pressure; T2DM, type 2 diabetes mellitus; PCO, polycystic ovaries; *value in [] is that after high-dose DST (2 mg every 6 h for 2 days); [†]right salpingo-oophorectomy only, with drilling of preserved left ovary.

Take-home messages

- Androgens decrease gradually with increasing age. Menopause has no effect on the production of androgens.
- Menopause is a state of relative androgen excess.
- Premenopausal hyperandrogenism persists after menopause.
- Androgen excess is associated with an adverse cardiometabolic profile.
- Androgen excess in menopause is usually functional. Newly onset of hyperandrogenism in postmenopausal women merits investigation to rule out a tumorous cause.
- Functional hyperandrogenism usually responds to lifestyle modifications and possibly metformin. For severe cases, antiandrogens, 5a-reductase inhibitors or LHRH analogues can be contemplated.



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