METABOLIC ALTERATIONS IN WOMEN WITH PCOS

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PCOS IS A GENERAL HEALTH PROBLEM, AND NOT AN ISSUE ONLY INVOLVED IN INFERTILITY OR MENSTRUAL DISTURBANCE.

In 1935, Irving Stein and Michael Leventhal firs described a group of patient presenting with amenorrhea, bilateral polycystic ovaries, and masculinizing changes.

Diagnostic criteria

PCOS is suspected in patients with irregular menses and clinical signs of hyperandrogenism such as acne, seborrhea, hirsutism, irregular menses, infertility, and alopecia

Diagnostic criteria of PCOS

NIH (1990) : Chronic anovulation & clinical or biochemical hyperandrogenism & exclusion of other diseases

ESHRE-ASRM / Rotterdam 2003: Presence of at least two of the three criteria: Clinical or biochemical hyperandrogenism, Oligo-anovulation, Polycystic ovaries

AES (2009) : Hyperandrogenism (hyperandrogenaemia and/ or hirsutism) & ovarian dysfunction (oligo-anovulation & polycystic ovaries) & exclusion of other diseases

PCOS: Polycystic ovary syndrome; NIH: National Institutes of Health Conference; ESHRE: European Society of Human Reproduction and Embryology; ASRM: America Society of Reproductive Medicine; AES: Androgen Excess Society

Prevalence : Estimation of the prevalence of PCOS depends on which criteria are used to define it and varies from 5% to 10%

Presenting Features of 1097 Patients with Polycystic Ovaries

Finding	Mean Incidence (%)	Range (%)
Infertility	74	35-94
Hirsutism	69	17-83
Amenorrhea	51	15-77
Obesity	41	16-49
Biphasic basal temp	15	12-40
Cyclic menses	12	7-28

Adapted from Goldzieher and Axelrod [73]

Etiology

Genetic factors associated with PCOS

Genome-wide association studies (GWAS) have shown a higher frequency of genetic polymorphisms of the LHCGR , THADA and DENND1A genes in women with PCOS .
(Chen et al. 2011 , Shi et al. 2012 , Louwers et al. 2013)

A GWAS study conducted by a Korean group failed to confirm these results and found that only the glycogen synthase 2 (GYS2) gene could be linked to PCOS and its metabolic complications.
(Hwang et al. 2012)

Another GWAS study conducted in the USA that analysed genes that code for proteins associated with metabolic and cardiovascular abnormalities also did not demonstrate a hereditary component of PCOS .
(Jones et al. 2012)

Environmental factors associated with PCOS

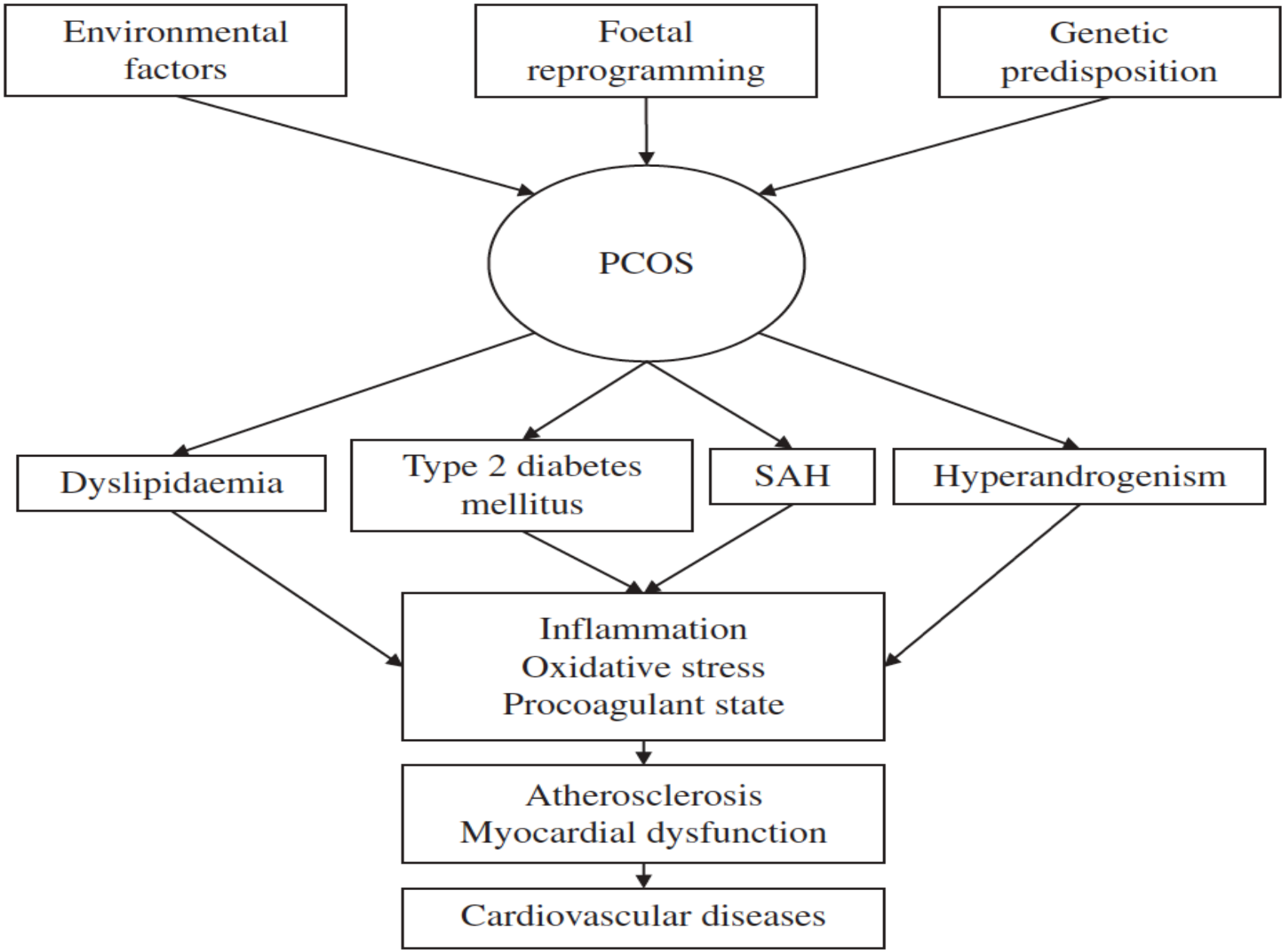
- The ethnic and geographic heterogeneity of PCOS demonstrates that this disorder is associated with environmental factors (Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group 2012)

- Dietary habits, exercise and cultural, social and economic factors might modify environmental exposure.

Role of developmental programming in the pathogenesis of PCOS

- The presence of excess glucocorticoids and/or androgens during fetal organogenesis and growth might promote changes in gene expression, and these changes might be related to an increase in the risk of PCOS-like reproductive and metabolic disorders in postnatal life

- Developmental programming by androgen excess during pregnancy could occur in women with obesity, type 2 diabetes mellitus (DM), insulin resistance (IR), excessive weight gain during pregnancy, PCOS and/or any other situation associated with hyperandrogenism (Sir-Petermann et al. 2009)


Environmental factors
Foetal reprogramming
Genetic predisposition
PCOS
Dyslipidaemia
Type 2 diabetes mellitus
SAH
Hyperandrogenism
Inflammation
Oxidative stress
Procoagulant state
Atherosclerosis
Myocardial dysfunction
Cardiovascular diseases

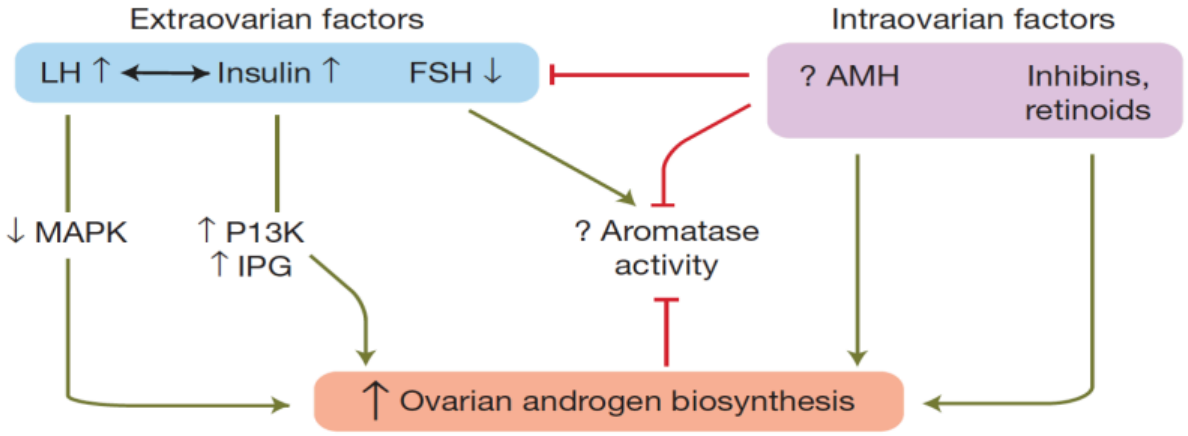
pathophysiology

- Increased androgen synthesis
- disrupted folliculogenesis
- İnsulin resistance

An intriguing concept involves the perpetuation of a vicious circle with endocrine/reproductive and metabolic components.

Hyperandrogenaemia in PCOS
Ovarian hyperandrogenism

Ovarian hyperandrogenism is mainly attributed to an inherent steroidogenic defect of theca cells in PCOS. Increased luteinising hormone (LH) and increased insulin levels appear to amplify the intrinsic abnormality of theca steroidogenesis



Hormonal regulators and intracellular signalling defects contributing to increased ovarian androgen production in PCOS

Adrenal hyperandrogenism

- There is a body of evidence to suggest that adrenal hyperandrogenism by putative dysregulation of CYP17A1 is a genetically determined trait in PCOS .

  Goodarzi, Mark O., et al. *American journal of obstetrics and gynecology* 196.4 (2007): 398-e1.

- Increased peripheral metabolism of cortisol has also been proposed to contribute to the functional adrenal hyperandrogenism .

  Tsilchorozidou, Tasoula, John W. Honour, and Gerard S. Conway *The Journal of Clinical Endocrinology & Metabolism* 88.12 (2003): 5907-5913.

The Role Of Gonadotropins

- Increased LH pulse frequency and amplitude leading to persistently increased LH levels may directly enhance theca androgen synthesis.

- Elevated LH levels result from an impaired negative feedback on LH secretion, due to excessive androgen action on the hypothalamic–pituitary axis

- The relatively reduced FSH levels (in relation to LH) may have an indirect role. The decreased stimulation of aromatase by FSH results in the decreased conversion of androgen to estrogen and aggravates the ovarian androgen excess

The Role Of Insulin

- Insulin appears to be a triggering factor that aggravates the inherent dysregulation of theca steroidogenesis in PCOS.

- Insulin seems to act in synergy with LH to stimulate androgen synthesis in PCOS ovarian theca cells.

- Insulin appears to stimulate ovarian P450c17 (CYP17A1) mRNA expression and enzyme activity through its receptor in theca cells.

The Role Of Intraovarian Factors

- Intraovarian factors of granulosa cell origin, such as anti-Mullerian hormone (AMH) and inhibins, may contribute to the steroidogenic activity of theca cells.

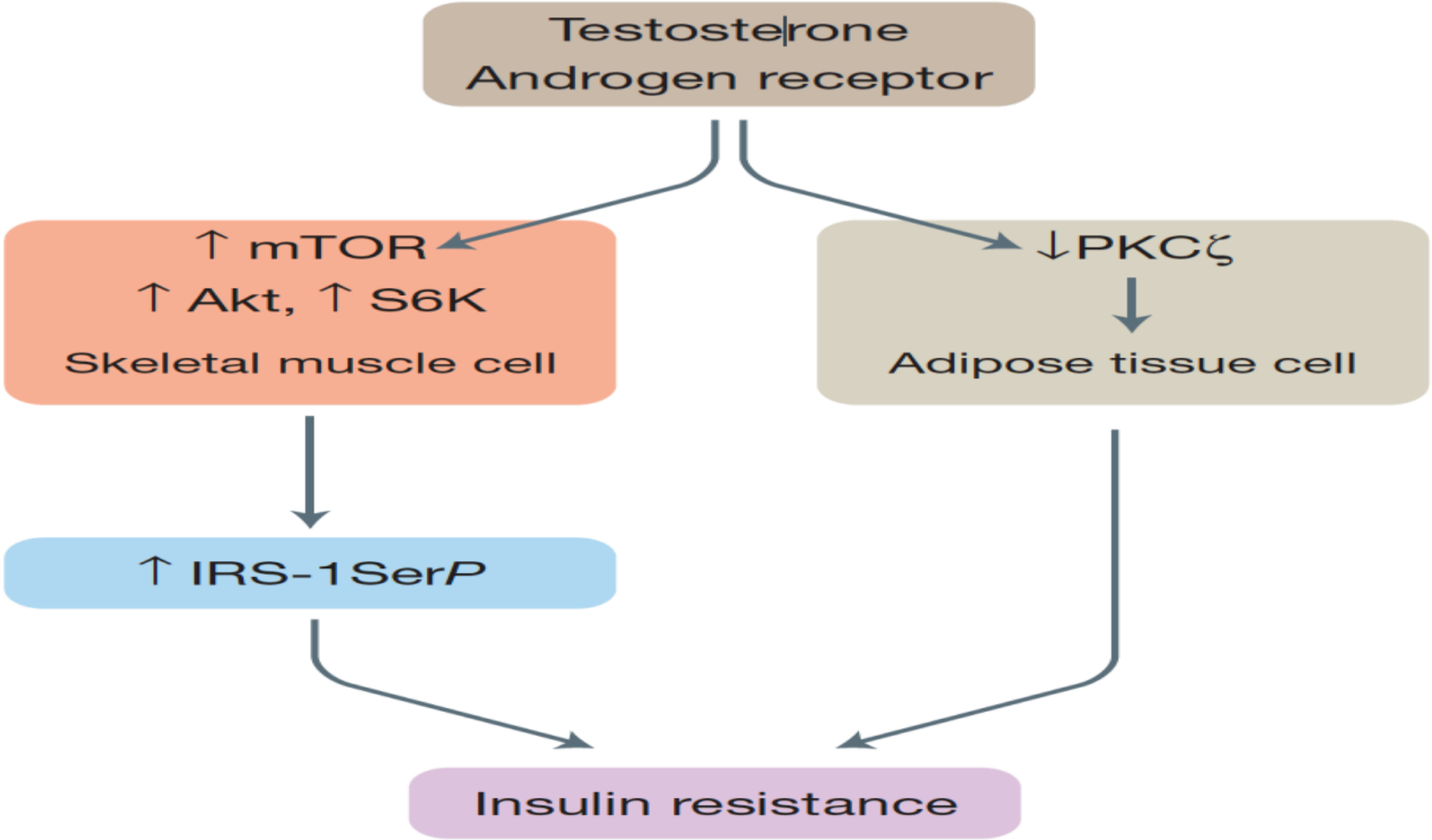
- AMH type II receptors (AMHRII) have recently been detected on theca cell membranes of maturing follicles and could mediate a paracrine effect of AMH on androgen production

The role of androgens in metabolic aberrations in PCOS

Hyperandrogenaemia

- visceral adiposity
- insulin resistance
- lipolysis in visceral adipose tissue

Seow KM, Juan CC, Wu LY, Hsu YP, Yang WM, Tsai YL, Hwang JL, Ho LT. 2004. Serum and adipocyte resistin in polycystic ovary syndrome with insulin resistance. Hum Reprod 19:48–53



The role of androgens in insulin-signalling defects in peripheral tissues in PCOS

Expert Reviews in Molecular Medicine

The growing recognition of the intrinsic linkage of PCOS with metabolic abnormalities has prompted considerations on the long-term sequelae of the syndrome.

Hyperinsulinemia, Insulin Resistance, and Dysglycemia

- **Decreased insulin sensitivity in lean women with PCOS (%30)**
- **Decreased insulin sensitivity in obese women with PCOS (%70)**

Impaired Glucose Tolerance (IGT) and Type 2 Diabetes in PCOS

- 31.1% of subjects had impaired glucose intolerance
- 7.5% had diabetes in a prospective study of 254 PCOS women
- There also appears an increased risk of persistent impaired glucose metabolism after gestational diabetes in women with PCOS

this is a 3- to 7-fold greater risk than the age-comparable population

Legro, Richard S., et al. "Prevalence and predictors of risk for type 2 diabetes mellitus ‘
Palomba, Stefano, et al. "The risk of a persistent glucose metabolism impairment after gestational diabetes mellitus

The potential mechanisms leading to insulin resistance in PCOS

no structural abnormality in the insulin receptor has been identified
postreceptor defects in the insulin receptor signal transduction are involved

Increased insulin receptor serine phosphorylation

↓

Decreased protein kinase activity

↓

insulin resistance in PCOS

Dunaif, Andrea, et al. "Excessive insulin receptor serine phosphorylation in cultured fibroblasts and in skeletal muscle.

Obesity In Women with PCOS

40–85% of PCOS women are overweight or obese

increased prevalence of android obesity in PCOS women is particularly common and affects between 50 and 70% of women with PCOS, regardless of BMI

Blood pressure, lipid profile, platelet activity, insulin resistance, impaired glucose tolerance, and type 2 diabetes are all influenced by android obesity

Weight gain in many susceptible women will lead to both the metabolic and hormonal perturbations characteristic of PCOS

Metabolic Syndrome in Women with PCOS

According to the National Cholesterol Education Program (NCEP) criteria, the presence of any three criteria defines metabolic syndrome

central obesity (waist circumference> 88 cm)
serum triglycerides > 150 mg/dl
serum HDL concentration < 50 mg/dl
systemic hypertension > 130/85 mmHg
fasting plasma glucose level > 100 mg/dl

Metabolic Syndrome in Women with PCOS

The prevalence of metabolic syndrome changes between 6.7% and 22% among countries

The prevalence is 3-fold higher in women with PCOS and increases with age

In one cohort study with a 25 year follow-up, it was found that self-reported cardiovascular disease was observed more often (19.4%) in adults who had clinical features of metabolic syndrome than in those who did not (1.5%)

Morrison, J. A., Friedman, L. A., & Gray-McGuire, C. (2007). Metabolic syndrome in childhood predicts adult cardiovascular disease 25 years later: the Princeton Lipid Research Clinics Follow-up Study. *Pediatrics*, *120*(2), 340-345.

Adipokines and PCOS

Abnormal production, release, and/or function of adipocytokines and inflammatory factors in PCOS could be related to the increased incidence of traditional and nontraditional cardiovascular risk factors and metabolic disturbances

- Leptin
- Adiponectin

} cardiometabolic effects

- Vaspin
- Visfatin

} regulation of energy homeostasis

- **Acute-phase serum amyloid A (ASAA)**
- **Chemerin**

Proinflammatory and Macrophage-Derived Factors In PCOS

Resistin : circulating resistin levels and resistin expression in adipocytes are increased.

TNF- alpha : In PCOS, serum TNF-alpha has been reported to be increased irrespective of obesity, potentially implicating TNF-alpha in the insulin resistance of lean PCOS women

Interleukins :IL-6, a proinflammatory adipocytokine, is associated with insulin resistance and human obesity , and elevated levels of IL-6 may predict the development of type 2 diabetes

C-reactive protein and PCOS :CRP have been proposed to predict the risk of cardiovascular events, independent of other risk factors

Dyslipidemia In PCOS

high-density lipoprotein (HDL) ↓

Triglycerides ↑

Very low-density lipoprotein-cholesterol ↑

The lipoprotein profile in PCOS is comparable to that seen in patients with type 2 diabetes

Legro, Richard S., Allen R. Kunselman, and Andrea Dunaif. "Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome." *The American journal of medicine* 111.8 (2001): 607-613.

Cardiovascular Dysfunction In PCOS

(Hypertension, Atherosclerosis, Cardiac dysfunction)

Hypertension : There is a higher prevalence of hypertension among women with PCOS

At menopause, women with PCOS have a risk of developing hypertension that is 2.5- fold higher than age-matched controls

Elting, M. W., et al. "Prevalence of diabetes mellitus, hypertension and cardiac complaints in a follow-up study of a Dutch PCOS population." *Human Reproduction* 16.3 (2001): 556-560.

Atherosclerosis

PCOS women are at an increased risk of developing early-onset atherosclerosis

- increased carotid intima-media thickness (IMT)
- higher prevalence of coronary artery and aortic calcification
- increased endothelin-1

The presence of both anatomic and functional abnormalities at an early age in women with PCOS predisposes to the development of atherosclerosis.

Cardiac dysfunction

low systolic flow velocity

Reduced left ventricular ejection fraction

left ventricular diastolic dysfunction

increased insulin levels in PCOS are associated with decreased cardiac function

Prelevic, Gordana M., et al. "Cardiac flow velocity in women with the polycystic ovary syndrome." *Clinical endocrinology* 43.6 (1995): 677-681.

Nontraditional CVD Risk Factors

- Impaired nitric oxide generation by the endothelial cells
- The hyperinsulinemia-induced impaired fibrinolysis
- The hyperglycemia-activated coagulation

All these abnormalities are parameters of the so-called endothelial dysfunction that follows states of severe insulin resistance like PCOS

Vinik, Aaron I., et al. "Platelet dysfunction in type 2 diabetes." *Diabetes care*24.8 (2001): 1476-1485.

- Elevated plasminogen activator inhibitor-1 (PAI-1) activity
- Elevated endothelin-1 ,vascular endothelial growth factor and highly sensitive CRP
- Low tissue plasminogen activator

PCOS and Nonalcoholic Fatty Liver Disease (NAFLD)

Obesity and insulin resistance are considered key features of NAFLD

- the excessive free fatty acid flux from the adipose tissue to the liver
- the hyperinsulinemia- promoted hepatic de novo lipogenesis

Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ 2005 Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J Clin Invest 115:1343–1351

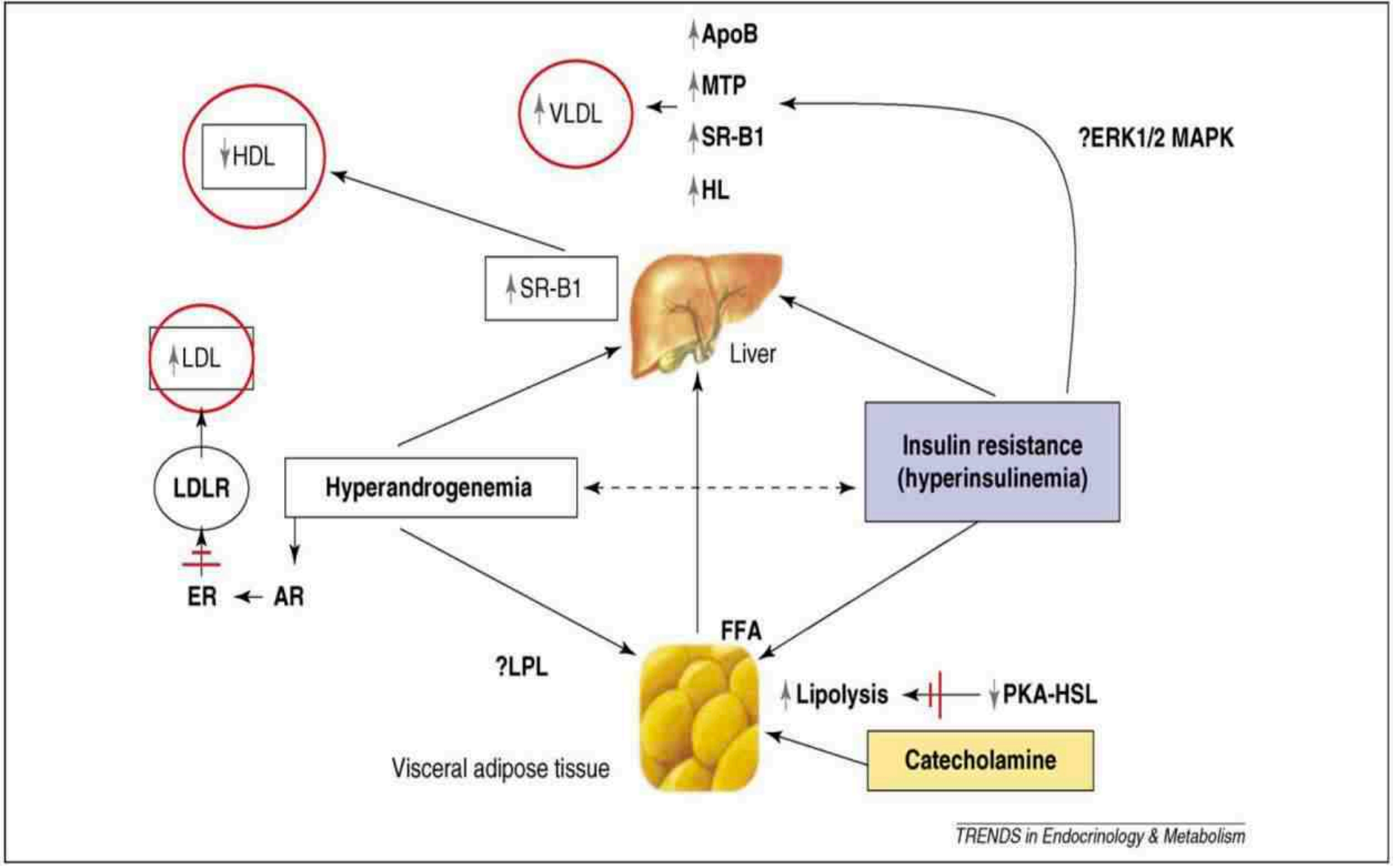
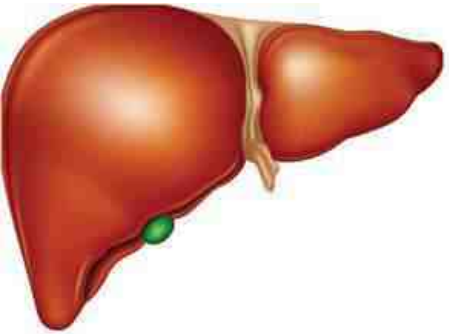


Figure 1. Pathophysiology of dyslipidemia in PCOS and its possible mechanisms. Within adipocytes, insulin resistance and hyperandrogenemia result in increased catecholamine-induced lipolysis and release of fatty acids into circulation. Increased free fatty acid flux to the liver stimulates the assembly and secretion of VLDL resulting in hypertriglyceridemia. The main serum lipid abnormalities in PCOS are indicated in red circles. Broken arrow represents potential interaction. ↑, activation; ↓, deactivation; ≠, inhibition. Abbreviations: ApoB, apolipoprotein b; AR, androgen receptor; ER, estrogen receptor; ERK1/2 MAPK, extracellular signal-regulated kinase 1/2 mitogen-activated protein kinase; FFA, free fatty acids; HL, hepatic lipase; LDLR, low density lipoprotein receptor; LPL, lipoprotein lipase; MTP, microsomal triglyceride protein; PKA-HSL, protein kinase a-hormone sensitive lipase complex; SR-B1, scavenger receptor-b1; VLDL, very low density lipoprotein.

PCOS and Obstructive Sleep Apnea (OSA) Syndrome

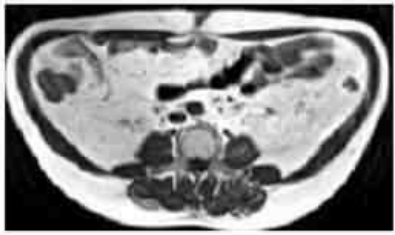
- OSA is related to metabolic disturbances including insulin resistance and diabetes
- OSA is a well-recognized risk factor for CVD and atrial fibrillation

Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M, Young T 2008 Sleep apnea and cardiovascular disease: an American Heart Association/ American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. J Am Coll Cardiol 52:686–717



NASH

Obesity



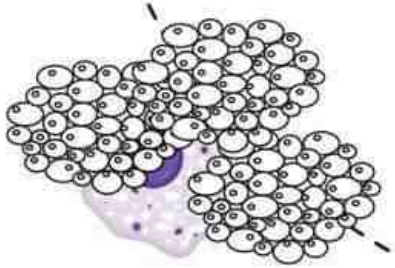
Insulin Resistance

OSA

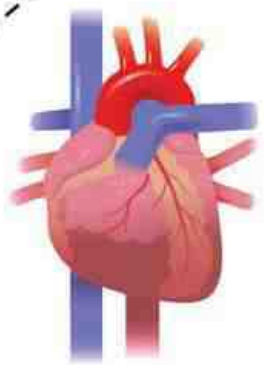
Diabetes

Cardiometabolic disturbances in PCOS

Dyslipidemia



CVD



Adipokines, Gut Hormones and Proinflammatory Factors

Hyperandrogenism

Management

the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society recommends :

BMI, waist circumference, serum lipid/glucose, and blood pressure determinations for all women with PCOS

Oral glucose tolerance testing is recommended in those with obesity, advanced age, personal history of gestational diabetes, or family history of type 2 DM.

Lifestyle management is recommended for primary CVD prevention, targeting LDL and non-HDL-C and adding insulin-sensitizing and other drugs if dyslipidemia or other risk factors persist.

Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, FutterweitW,Lobo R,NormanRJ, Talbott E, Dumesic DA 2010 Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. J Clin Endocrinol Metab 95:2038–2049

- Weight loss
- Diet
- Exercise

Pharmacotherapy

OC pill (OCP)

- OC have been the mainstay of PCOS pharmacological therapy for decades
- OC are more effective in improving menstrual pattern and reducing serum androgen levels

Insulin sensitizers and insulin-lowering agents

- The most extensively studied insulin-lowering drug in the treatment of PCOS is metformin

There are a number of studies that have shown that metformin improves metabolic parameters in PCOS women.

- normalize glucose tolerance in half of these subjects,
- lower total and free testosterone
- decrease BMI and sc adipose tissue
- improve insulin sensitivity

Arslanian SA, Lewy V, Danadian K, Saad R 2002 Metformin therapy in obese adolescents with polycystic ovary syndrome and impaired glucose tolerance: amelioration of exaggerated adrenal response to adrenocorticotropin with reduction of insulinemia/insulin resistance. J Clin Endocrinol Metab 87:1555–155

WeickertMO,Hodges P, Tan BK, RandevaHS2012 Neuroendocrine and endocrine dysfunction in the hyperinsulinemic PCOS patient: the role of metformin. Minerva Endocrinol 37:25–40

Metabolic/reproductive defects in PCOS	Benefits of metformin
Blood pressure	Reduction
Insulin resistance	Reduction
Fasting insulin	Reduction
New onset of IGT	Reduction
New onset of type 2 DM	Reduction
Fasting triglycerides	Reduction
Fasting cholesterol	+/−
Body weight, BMI, and waist circumference	Reduction
Serum androgens	Reduction
Hirsutism scores	No effect
Anovulation	Improvement
Endothelial structure and function	Improvement
IMT	Reduction
Atypical endometrial hyperplasia	Improvement

Long-term treatment
(OCPs versus Insulin sensitisers)

OCPs in PCOS

May worsen insulin resistance
May cause glucose intolerance
May increase triglycerides
May increase the risk of DM
May increase risk of cardiovascular disease

Insulin sensitisers in PCOS

Improves insulin sensitivity
Improves glucose tolerance
May reduce serum triglycerides
Reduces PAI-1
Reduces endothelin-1

Antiobesity agents

Orlistat, a pancreatic lipase inhibitor, limits the absorption of dietary fat, and it has been shown that it significantly reduces body weight and total testosterone levels in PCOS women.

It also had a beneficial effect in reducing elevated advanced glycation end-products after 6 months of treatment, independently of BMI changes.

Jayagopal V, Kilpatrick ES, Holding S, Jennings PE, Atkin SL 2005 Orlistat is as beneficial as metformin in the treatment of polycystic ovarian syndrome. J Clin Endocrinol Metab 90:729–733

Diamanti-Kandarakis E, Katsikis I, Piperi C, Alexandraki K, PanidisD2007 Effect of long-term orlistat treatment on serum levels of advanced glycation end-products in women with polycystic ovary syndrome. Clin Endocrinol (Oxf) 66:103–109

Conclusions

The long-term health consequences of PCOS are a concern particularly in the background of the current obesity pandemic. In simple terms, these women are at greater risk for insulin resistance, type 2 diabetes, and vascular disease as compared with their non-PCOS counterparts. Thus, women with PCOS may require more regular screening for such risks as well as effective and targeted lifestyle advice to prevent weight gain.