Polycystic Ovarian Syndrome

Hirsutism

- Normally and abnormally distributed excessive hair growth on biologically defined females[21]
  - A condition caused by hyperandrogenism: excess production and secretion of sex hormones
- 1921: “Diabéte de femmes á barbe”[21]
  - The first link between insulin and hyperandrogenism was recorded by Archard and Thiers in their description of a bearded lady with diabetes mellitus
- PCOS was first described in 1935 as Stein-Leventhal syndrome[2]
  - Original diagnostic criteria: Pathognomonic ovary with the clinical triad: obesity, amenorrhea, and hirsutism
- Though hyperandrogenism displayed through hirsutism had been associated with diabetes, the role of insulin in PCOS was not investigated

Clémentine Delait Clattaux (1865–1934)

Diagnostics in history

- 1960s & 1970s: Endocrine dysfunction became a diagnostic focus[2]
  - Deranged hypothalamus-pituitary axis discovered in PCOS women
    - Focus on high serum LH and LH:FSH
- 1970s & 1980s[2]
  - Ultrasonographic imaging convoluted diagnostics and PCOS definition
  - Some believed presentation of polycystic ovaries alone to be enough for diagnosis,
    - This excluded endocrine associations
- 1980: the relationship between insulin resistance and late complications of PCOS reported[2]
  - Yet still excluded from clinical analysis and diagnostic criteria
- 1988: 23% of women with PCOS present with polycystic ovaries[3]
  - Realization that ultrasonographic imaging alone does not suffice for diagnosis

Experts attempt to meet to define PCOS

- 1990: National Institute of Health formed a group[2]
  - The definitive naming of the disorder and diagnostic criteria remained inconclusive
  - Diagnostics criteria suggested
    - Reasonable diagnosis after other endocrine disorders have been ruled out
      - Presentation of hyperandrogenism and chronic anovulation
        - Still omitting evidence of insulin related metabolic dysfunction and excluding sonographic imaging of polycystic ovaries
  - Though consensus was not reached, the information served PCOS researchers in further exploration of prevalence and metabolic associations
- 1992: 70% of women with PCOS presented with polycystic ovaries[3]
- PCOS remained a diverse, idiopathic disorder[3]
  - featuring irregular ovulation, polycystic ovaries, hirsutism, hyperandrogenemia, disturbed serum gonadotropins, insulin resistance, and hyperinsulinemia

Experts attempt to meet to define PCOS

- The single consistent feature of PCOS remained to be hyperandrogenism[3]
  - Limitations of diagnosis based on hyperandrogenemia
    - When treated by way of hormonal suppression, serum levels decline rapidly
      - Normalization requires a significant amount of time after treatment discontinuation
    - Serum concentrations are altered by age and obesity
  - Limitations of diagnosis based of hirsutism
    - Less prevalent in younger and older women with PCOS
    - Prevalence varies across ethnic groups
- 2003: Experts meet in Rotterdam to discuss the broadening of diagnostic criteria and the inclusion of ultrasonography[3]
  - Recommended diagnostic criteria
    - After exclusion of other etiologies, presentation of at least two of the following
      - Oligo- or anovulation, clinical and/or biochemical hyperandrogenism, or sonographic evidence of polycystic ovaries

The Importance of Diagnosing the Polycystic Ovary Syndrome

- 2000: Systematic literature review of 52 peer reviewed articles[2]
  - Authors provide a historical overview of PCOS diagnostics and focus
  - The consistent overlooking of impaired glucose tolerance (IGT) and insulin resistance (IR) is heavily acknowledged
- A call for early diagnosis, thorough clinical analysis, and long-term follow ups as preventative care for PCOS women[2]
  - Authors present research-based evidence of the prevalence of obesity, IGT, IR and abnormal lipoprotein profiles in PCOS women, in addition to reproductive morbidity associations
- Association between obesity and insulin resistance in PCOS is limiting[2]
  - Obesity is 40-50% prevalent in PCOS women
    - IGT is 31% and 10.3% prevalent in obese and non-obese PCOS women respectively
    - Diabetes Mellitus is 7.5% and 1.5% in obese and non-obese PCOS women respectively

The Importance of Diagnosing the Polycystic Ovary Syndrome

- Insulin resistance in PCOS women[2]
  - 1980 reported relationship to late complications confirmed by several research groups
    - In the presence of overt glucose intolerance, normal diagnostic criteria of insulin resistance is invalid
    - Anovulation is suggested as a major indicator of insulin resistance in PCOS women
      - Serine phosphorylation of IGF-1 receptor may be responsible for 50% prevalence
      - Possible □-cell dysfunction makes PCOS women at risks for type 2 diabetes mellitus
        - 16% of PCOS women treated with wedge resection to promote fertility developed type 2 diabetes mellitus by menopause
  - Obesity worsens insulin resistance, increases risks for diabetes, and cardiovascular disease[2]
    - Weight loss in PCOS patients is difficult due to impaired lipolysis, another associated risk factor for insulin resistance

The Importance of Diagnosing the Polycystic Ovary Syndrome

- 2000: Cardiovascular disease is the leading cause of death in women[2]
- CVD risk factors for PCOS women[2]
  - Prevalence of lipid and lipid profile abnormalities is dependent on weight, diet, and ethnicity
    - Elevated cholesterol, triglycerides, and LDL
    - Low HDL and apoA-I
  - Impaired fibrinolysis in PCOS women
    - Closely associated with insulin resistance
    - Increases risks of vascular lesions
  - 40% increase in prevalence of hypertension in perimenopausal PCOS women
  - Atherosclerosis has a higher prevalence in PCOS women
  - PCOS women have an estimated sevenfold increased risk for myocardial infarction
- Increased cardiac risk profile[2]
  - Principally related to insulin resistance and dysglycemia

The Prevalence of Glucose Intolerance in Women with PCOS[4]

An Experimental control study assess IGT as an asymptomatic prediabetic state of PCOS comparative to normal women

Inclusion Criteria	Exclusion Criteria	Control Criteria
Three or more of Rotterdam PCOS diagnostic criteria present	Other causes of hirsutism: Cushing's syndrome, congenital adrenal hyperplasia, androgen-secreting tumor	Regular menses, no evidence of hirsutism, and no hyperandrogenemia

Methods

- All participants had OGTT
- Researchers measured baseline blood samples and glucose and insulin serum levels in 30-minute intervals over two hours after oral ingestion of 75 grams of glucose.
- Evaluation of glucose tolerance with use of ADA criteria
- OGTT glucose and insulin response expressed under the curve (AUC)

Mann-Whitney U test comparison of results

	PCOS Women	Control	P Value
Age (year)	24.6 1.1	27.1 1.2	NS
BMI	27.1 1.2	26.1 0.9	NS
Hirsutism score	16.1 2	4.1 o.2	<0.0005
FPG (mg/dl)	80.2 2.8	72.9 1.4	NS
AUC glucose (mg/dlx120min)	14816.2 787.2	12358.9 484.1	NS
Fasting insulin (IU/ml)	23.5 3.4	6.1 1.7	<0.005
AUC insulin (IU/mlx120min)	12218.7 1224.8	2411.8 261.7	<0.005

Results[4]

Two women (4.3%) had undiagnosed DM, 17.4% of patients had IGT. Previous showed DM prevalence of 6.9% and an IGT prevalence of 9% in subjects over 30 within the same region and 2.3% and 5.3% in a young population, ages 30-39. IGT prevalence presented in this study is notably higher than what was expected is indicative that women with PCOS have higher prevalence of IGT.

Published literature and the presented data suggest that PCOS women need to be monitored closely for the presentation of IGT, as women with PCOS have a 5 to 10-fold accelerated conversion of IGT to Type 2 DM.

Determinants of Impaired Fasting Glucose Versus Intolerance in PCOS[5]

A 2010 cross-sectional study

143 patients with PCOS underwent OGTT, and 68 patients had additional intravenous glucose tolerance test (IVTT) performed to determine insulin response and resistance, normal glucose tolerance (NGT), impaired fasting glucose (IGF), IGT, and combined glucose intolerance (CGI)

Inclusion criteria: diagnosed by NIH criteria aged 18-45

Ethnicity	
White	76%
African American	12%
Hispanic	6%
American Indian	3%
Asian	3%

Exclusion criteria:

Recipients of insulin sensitivity treatment within two months of the study
DM, hypothyroidism, systemic illness
smoking or drinking (> 2 servings/week)
pregnant, postpartum, or lactating

Methods

In the OGTT, patients received oral administration of 75 grams of glucose. Researchers recorded serum levels for 120 minutes at 30-minute intervals. During the IVGTT, researchers drew serum samples at -20, -10, and 0 minutes. Patients received intravenous glucose at 0 minutes and injected insulin at 20 minutes. Researchers took 30 serum samples at varying intervals for 180 minutes and analyzed them for acute insulin response (AIRg), b-cell function, insulin sensitivity index (Si), and disposition index. In assessing CVD risks, researchers measured serum levels of triglycerides, cholesterol, LDL cholesterol, HDL cholesterol, and high-sensitivity C-reactive protein (hs-CRP).

Determinants of Impaired Fasting Glucose Versus Intolerance in PCOS[4]

Table 2—Clinical and biochemical variables of the NGT group divided into tertiles based on degree of insulin resistance

	Sensitive	Intermediate	Resistant	ANOVA* P_1	ANOVA* P_2
n	33	32	32		
Anthropometric					
Age (years)	26.4 ± 1.23	25.9 ± 1.5	25.9 ± 1.5	0.9641	0.449
BMI (kg/m^2)	27.4 ± 1.0	31.6 ± 1.2†	39.9 ± 1.2†‡	<0.0001	—
Fasting					
Glucose	4.8 ± 0.02	5.0 ± 0.002†	5.1 ± 0.02†‡	<0.0001	<0.0001
Insulin	41 ± 2	79 ± 2†	146 ± 2†‡	<0.0001	<0.0001
HOMA	1.44 ± 0.10	2.9 ± 0.1†	5.6 ± 0.3†‡	<0.0001	<0.0001
QUICKI	0.37 ± 0.004	0.33 ± 0.002†	0.30 ± 0.002†‡	<0.0001	<0.0001
OGTT					
$\Delta Glucose_{0-30}$	2.2 ± 0.3	2.3 ± 0.2	2.6 ± 0.2†	0.3,801	0.4358
$\Delta Insulin_{0-30}$	235 ± 23	391 ± 32†	736 ± 73†‡	<0.0001	<0.001
Insulinogenic index	134 ± 26	221 ± 45§	421 ± 130†§	0.0355	0.3425
$AUC_{Glucose\ 0-120}$	11.6 ± 0.4	13.0 ± 0.3†	14.2 ± 0.3†§	<0.0001	0.0006
$AUC_{Insulin\ 0-120}$	463 ± 32	781 ± 29†	1,689 ± 129†§	<0.0001	<0.0001
$ISI_{Matsuda}$	8.12 ± 0.6	3.71 ± 0.12†	1.90 ± 0.09†§	<0.0001	<0.0001
CVD risk factors					
Triglyceride (mmol/l)	0.91 ± 0.07	1.18 ± 0.09	1.51 ± 0.17†	0.0006	0.1873
Cholesterol (mmol/l)	4.76 ± 0.14	5.04 ± 0.17	4.86 ± 0.18	0.4407	0.1721
LDL cholesterol (mmol/l)	2.73 ± 0.19	3.25 ± 0.17	3.14 ± 0.14	0.0671	0.1361
HDL cholesterol (mmol/l)	1.43 ± 0.07	1.25 ± 0.05†	1.03 ± 0.05†‡	<0.0001	0.0359
hs-CRP (mg/l)	1.9 ± 0.3	5.9 ± 2.1†	10.6 ± 1.9†‡	<0.0001	0.1055
Androgens					
Testosterone	2.25 ± 0.14	2.53 ± 0.14	2.60 ± 0.21	0.2176	0.3996
SHBG (nmol/l)	57.9 ± 7.7	37.9 ± 7.0	25.0 ± 3.3†	0.0025	0.0661
FAI	6.6 ± 1.0	10.1 ± 1.4†	12.8 ± 1.7†‡	0.0010	0.0741
DHEAS (μmol/l)	0.61 ± 0.0.6	0.61 ± 0.06	0.54 ± 0.07	0.4783	0.8567

Data are means ± SEM. *P_1, significance by ANCOVA; P_2, significance by ANCOVA after adjustment for BMI. †$P < 0.05$ compared with the NGT group. ‡$P < 0.05$ compared with the IFG group. §$P < 0.05$ compared with the IFG group shown in Table 1, analyzed using the Bonferroni multiple-comparisons procedure in ANCOVA. DHEAS, dehydroepiandrosterone sulfate; FAI, free androgen index.

Distribution of glucose abnormalities

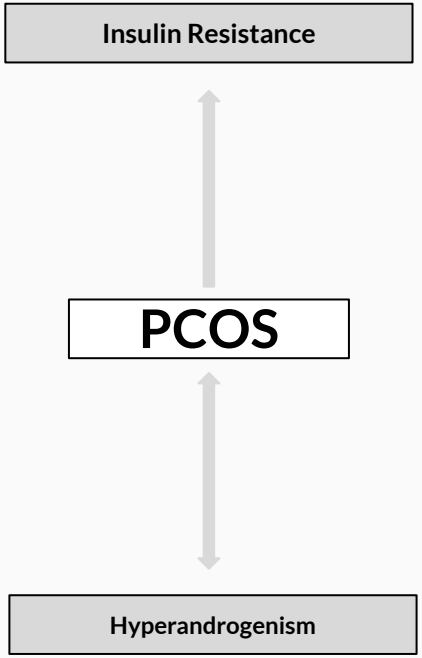
Ethnic groups are similarly distributed amongst NGT, IFG, IGT, and CGI.

GT abnormalities	IFG	IGT	CGI	NGT
32%	11%	7%	14%	68%

Results

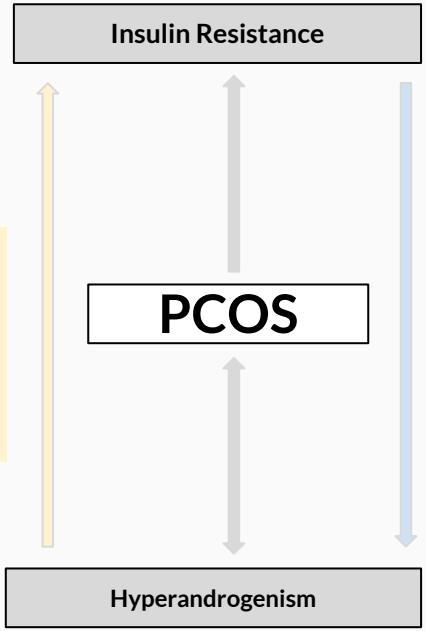
IFG and peripheral insulin resistance were positively correlated. Normal OGTT glucose levels did not correlate with normal glucose sensitivity or lower CVD risks. BMI, sex hormone-binding globulin (SHBG), HDL, and hs-CRP appeared to have value in the assessment of IR in NGT patients. AUCinsulin-120 values indicated that PCOS patients can develop both IFG and CGI during hyperinsulinemia. Researchers reported a positive correlation between weight and both IR and IGT, and both age and obesity with diabetes risks. The data suggest that PCOS patients with NGT may still present with severe insulin resistance. CVD risks and hyperandrogenemia are likely to become worse before hyperglycemia.

Metabolic Changes & PCOS



Metabolic Changes & PCOS

High androgens lead to android adiposity, decreased adipocyte lipolysis leading to insulin resistance



High insulin levels stimulate theca cells to produce more androgens, decrease amounts of SHBG

Ye, W., Xie, T., Song, Y., & Zhou, L. (2020). The role of androgen and its related signals in PCOS. *Journal of Cellular and Molecular Medicine*, *25*(4), 1825–1837. https://doi.org/10.1111/jcmm.16205

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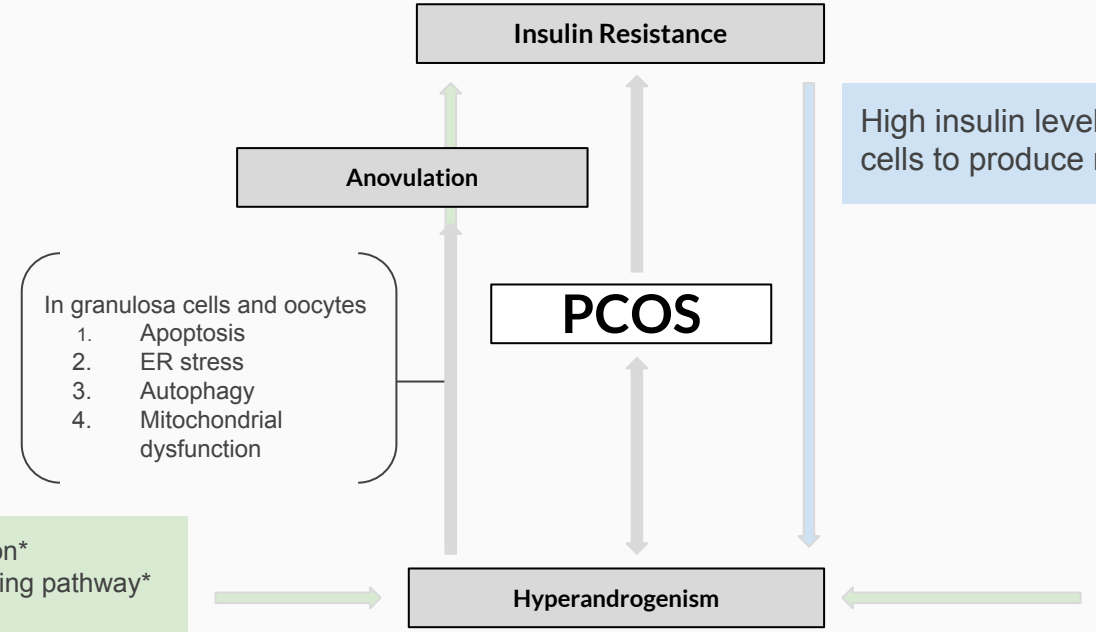
Metabolic Changes & PCOS



High insulin levels stimulate theca cells to produce more androgens

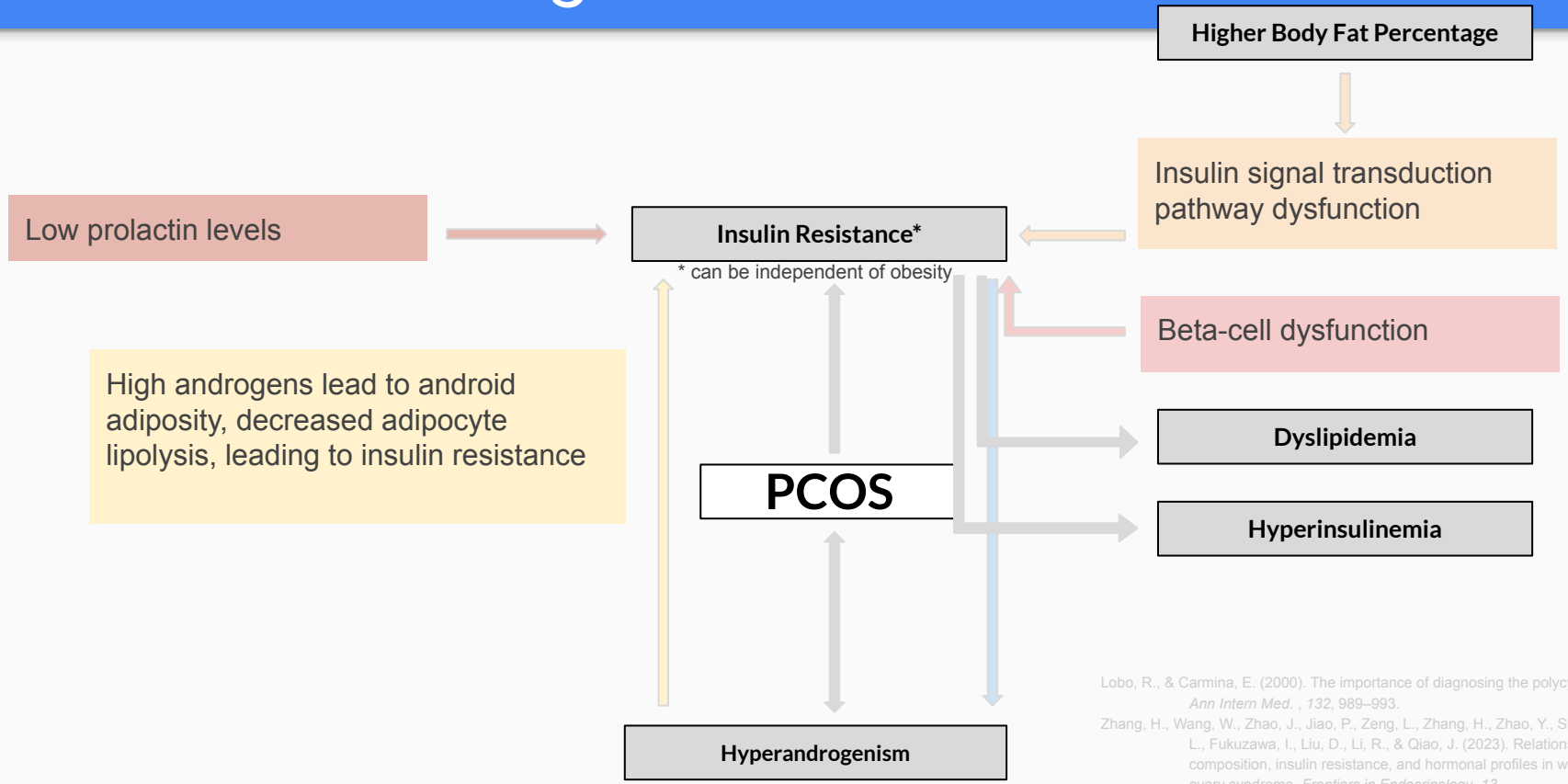
From HPO axis dysfunction, **high luteinizing hormone (LH)** induce changes in:
- **GPCR pathways in adrenals,** stimulating androgen synthesis
- **PI3K/AKT pathway in theca cells,** stimulates ovarian dysfunction and androgen synthesis

- Wnt4 mutation*
- MAPK signaling pathway*

*studies find differing results, need further research to determine correlation

Ye, W., Xie, T., Song, Y., & Zhou, L. (2020). The role of androgen and its related signals in PCOS. *Journal of Cellular and Molecular Medicine*, *25*(4), 1825–1837. https://doi.org/10.1111/jcmm.16205

Metabolic Changes & PCOS



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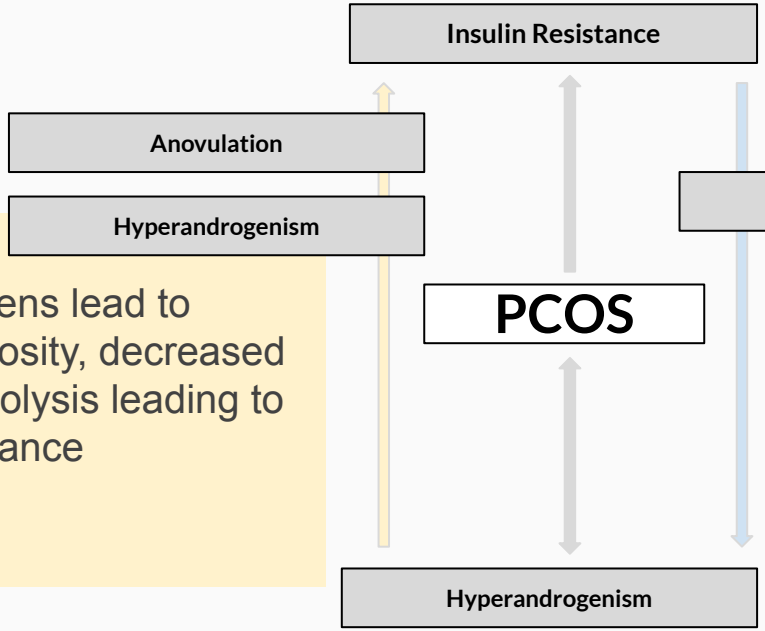
Metabolic Changes & PCOS



High androgens lead to android adiposity, decreased adipocyte lipolysis leading to insulin resistance

High insulin levels stimulate theca cells to produce more androgens, decrease amounts of SHBG

PCOS and Diet

- There is no single diet for PCOS
- Diet plans should be individualized and generally healthy
- Nutrition can help related dysfunction of PCOS:
  - Insulin Resistance
  - Weight Management
  - Inflammation
  - Hyperandrogenism
  - Fertility
  - General Health

Teede H, Tay CT, Laven JSE, et al. International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome 2023. Monash University. 2023

Restricted Energy & Low Glycemic Index Diet

- 2019 study on 62 participants in Iran
- 24 week energy restricted LGI diet
- 3-day dietary food record completed twice a month
- Also asked to record menses 6 months before study and during
- Asked to sustain baseline activity level

Image from trans4mind.com

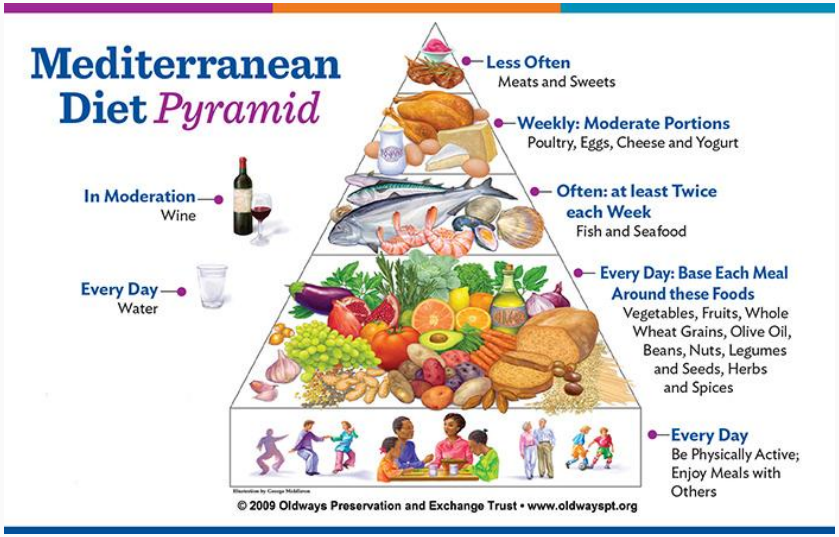
Shishehgar F, Mirmiran P, Rahmati M, Tohidi M, Ramezani Tehrani F. Does a restricted energy low glycemic index diet have a different effect on overweight women with or without polycystic ovary syndrome? *BMC Endocrine Disorders*. 2019;19(1). doi:10.1186/s12902-019-0420-1

Restricted Energy & Low Glycemic Index Diet, results…

- Beneficial effects on anthropometric and metabolic characteristics of overweight women with and without PCOS.
- Decrease in weight and insulin resistance in both groups.
- Improvement in menstrual irregularities
- Greater weight loss and improved IR
- Reduced testosterone
- Notable reduction in acne occurrence

Shishehgar F, Mirmiran P, Rahmati M, Tohidi M, Ramezani Tehrani F. Does a restricted energy low glycemic index diet have a different effect on overweight women with or without polycystic ovary syndrome? *BMC Endocrine Disorders*. 2019;19(1). doi:10.1186/s12902-019-0420-1

Mediterranean Diet and PCOS

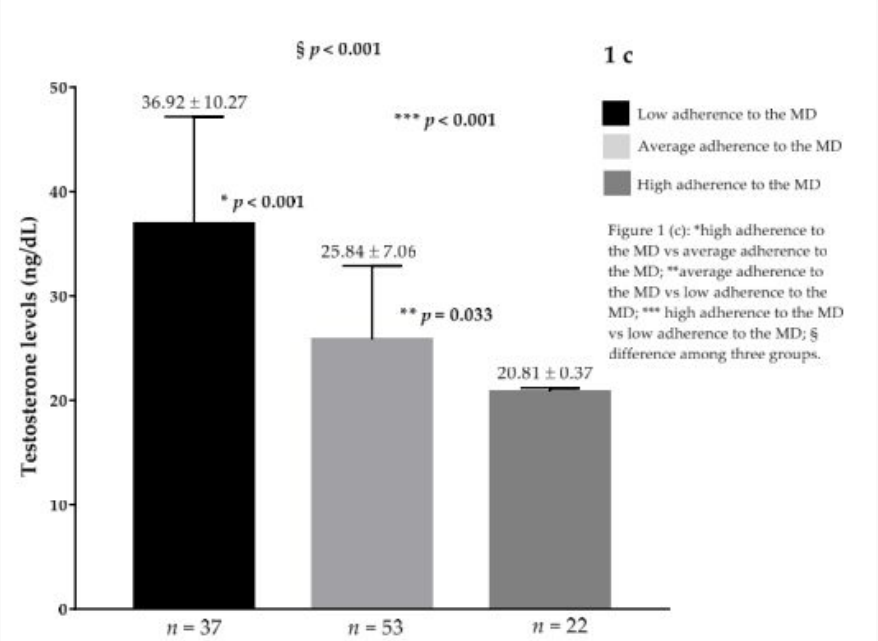


- Cross-sectional study from 2014-2019
- 112 treatment-naive women with PCOS from Naples, Italy compared to a control group of 112 healthy women matched for age and BMI.
- Seven day food records to assess adherence and dietary patterns.
- Measured Body composition & testosterone

Barrea L, Arnone A, Annunziata G, et al. Adherence to the Mediterranean diet, dietary patterns and body composition in women with polycystic ovary syndrome (PCOS). *Nutrients*. 2019;11(10):2278. doi:10.3390/nu11102278

Mediterranean Diet and PCOS, con't.

- Women with PCOS had less effective adherence to the MD than controls.
  - Consumed higher simple carbohydrates
  - Low consumption of complex carbohydrates, fiber and MUFA's
- This diet pattern was associated with greater hyperandrogenism, inflammatory status and IR.
- Reported direct association between adherence to the MD and clinical severity of PCOS, suggesting potential therapeutic role of the diet in PCOS.



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The Ketogenic Diet and PCOS

- Systematic Review on effects of ketogenic diet on reproductive hormones on women with PCOS.
  - Also evidence of weight changes
  - 5 studies reviewed from 2020-2022
- Found a significant improvement in reproductive hormone levels
  - Reduced LH/FSH ratio
  - Reduced serum free testosterone
  - Increase serum sex hormone binding globulin (SHBG)
- Significant weight loss in all studies

Barrea L, Arnone A, Annunziata G, et al. Adherence to the Mediterranean diet, dietary patterns and body composition in women with polycystic ovary syndrome (PCOS). *Nutrients*. 2019;11(10):2278. doi:10.3390/nu11102278

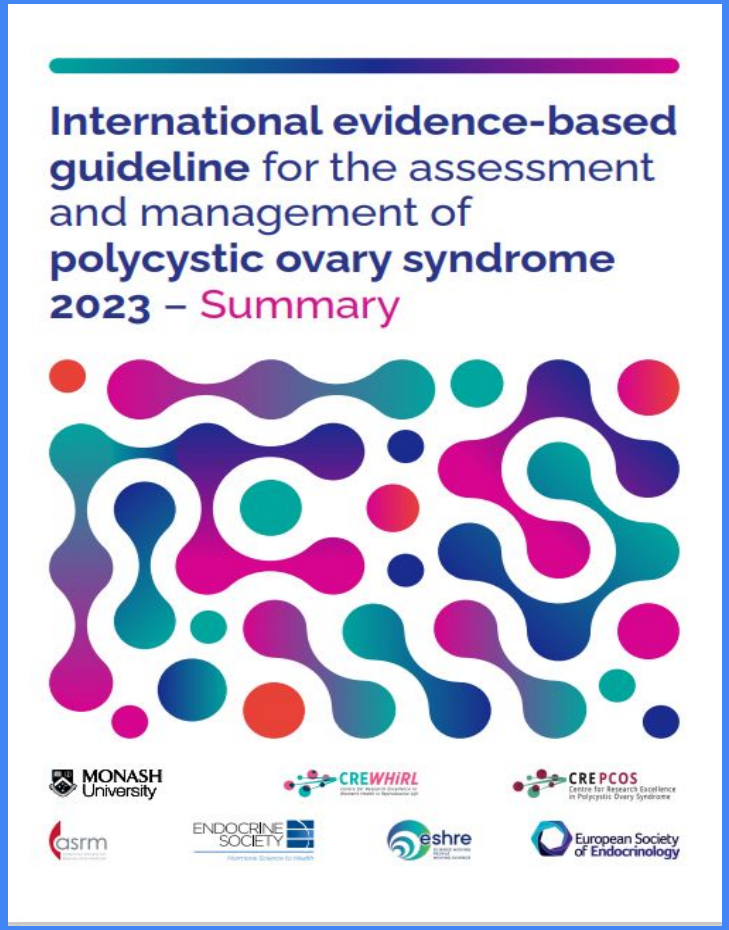

Table 1: Categories of the PCOS guideline recommendations

EBR	Evidence-based recommendations: Evidence sufficient to inform a recommendation made by the guideline development group.
CR	Consensus recommendations: In the absence of adequate evidence, a consensus recommendation has been made by the guideline development group, also informed by evidence from the general population.
PP	Practice points: Evidence not sought. A practice point has been made by the guideline development group where important issues arose from discussion of evidence-based or consensus recommendations.

The GRADE of the recommendation is determined by the GDG from structured, transparent consideration of the GRADE framework[16] including desirable effects, undesirable effects, balance of effects, resource requirements and cost effectiveness, equity, acceptability and feasibility and includes:

❖	Conditional recommendation against the option
❖❖	Conditional recommendation for either the option or the comparison
❖❖❖	Conditional recommendation for the option
❖❖❖❖	Strong recommendation for the option

Table 2: Quality (certainty) of evidence categories (adapted from GRADE)[16]

High	⊕⊕⊕⊕	Very confident that the true effect lies close to that of the estimate of the effect.
Moderate	⊕⊕⊕◯	Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different.
Low	⊕⊕◯◯	Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect.
Very Low	⊕◯◯◯	Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Teede H, Tay CT, Laven JSE, et al. International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome 2023. Monash University. 2023. Online resource. doi:https://doi.org/10.26180/24003834.v1

3.3		Dietary interventions	
3.3.1	EBR	Healthcare professionals and women should consider that there is no evidence to support any one type of diet composition over another for anthropometric, metabolic, hormonal, reproductive or psychological outcomes.	❖❖❖ ⊕○○○
3.3.2	CR	Any diet composition consistent with population guidelines for healthy eating will have health benefits, and within this, healthcare professionals should advise sustainable healthy eating tailored to individual preferences and goals.	❖❖❖❖
3.3.3	PP	Tailoring of dietary changes to food preferences, allowing for a flexible, individual and co-developed approach to achieving nutritional goals and avoiding unduly restrictive and nutritionally unbalanced diets, are important, as per general population guidelines.	
3.3.4	PP	Barriers and facilitators to optimise engagement and adherence to dietary change should be discussed, including psychological factors, physical limitations, socioeconomic and sociocultural factors, as well as personal motivators for change. The value of broader family engagement should be considered. Referral to suitably trained allied healthcare professionals needs to be considered when women with PCOS need support with optimising their diet.	

Teede H, Tay CT, Laven JSE, et al. International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome 2023. Monash University. 2023. Online resource. doi:https://doi.org/10.26180/24003834.v1

Treat the Whole Person

- Exercise and mental health care help support body systems:
  - Digestion and nutrient absorption
  - Insulin sensitivity
  - Weight management
  - Hormone regulation
  - Motivation and energy for self-care

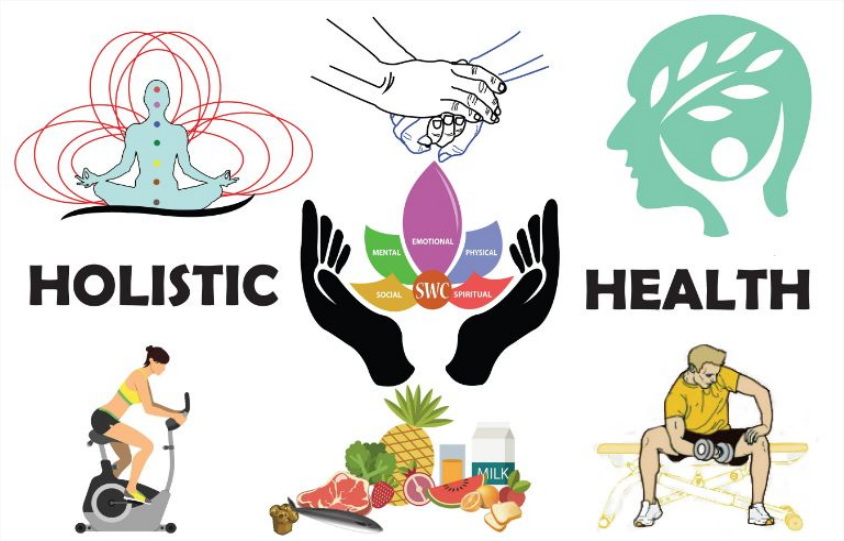

Image from dryatendrayadav.com

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Common Treatments of PCOS

- Insulin Sensitizers[16,20]
  - Metformin
  - Inositol isomers (Myo-inositol, D-chiro-inositol)
    - duel treatment of MYO and DCI, with higher DCI%, is more efficacious[16]
      - 40:1 MYO: DCI, with 550 mg MYO + 150 mg DCI[16]

- Oral Contraceptive Pills[18]
    - oral contraceptive pills used for teen PCOS treatment
    - Increases estrogen and progesterone[18]
    - can lead to later development of insulin resistance[18]
    - are found to be more effective when taken alongside MYO, which reduces risk of insulin resistance development[18]

Experimental Treatments of PCOS

- Botanical derivatives
  - Astaxanthin (ASX)[17]
    - a carotenoid derived from microorganisms and seafoods
    - high antioxidant, indicated in reducing ER stress[17]
    - 12 mg a day was associated with reduced biomarkers indicative of ER stress[17]
    - More research needed
  - Curcumin
    - a polyphenol commonly derived from turmeric (*Curcuma longa*)
    - Previous studies indicate effects on glycemic control, gene expression, cell signalling, hormonal fluctuations, reducing inflammation, and reducing insulin resistance[19]
      - Promotes fatty acid and glucose oxidation[19]
    - 1500 mg a day associated with significant reduction in serum levels of FPG and DHEA, and possible increase in estradiol[19]
    - was not shown to significantly impact other biomarkers associated with PCOS[19]
      - (LH, FSH, FI, WC, BMI)
    - More research is needed

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