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Shang Y, Zhou H, Hu M, Feng H. Effect of Diet on Insulin Resistance in Polycystic Ovary Syndrome. *Journal of Clinical Endocrinology and Metabolism*. 2020;105(10):dgaa425.

What We Know, Think We Know, or Are Starting to Know

That polycystic ovary syndrome [PCOS] is an incredibly complex condition is beyond debate, but most of our current understanding of PCOS relates to the pathophysiology, i.e., the disordered physiological processes of the condition; the aetiology, i.e., the origins and causes of the condition, remain unclear [(1)].

Within the complexity of the pathophysiology, one of the more consistent characteristics that is observed across a range of PCOS phenotypes, including both lean and PCOS women with abdominal obesity, is insulin resistance [(2,3)].

It is important to remove the generic framing of "insulin resistance" from the equation here, which is that popularised by Quacks like Mark Hyman and frames "insulin resistance" as something purely acquired through diet [as per, the culprit is sugar].

While insulin resistance can absolutely be acquired through deterioration in skeletal muscle and hepatic glucose tolerance, an early hallmark of type-2 diabetes pathophysiology [(4)], the insulin resistance in PCOS is more layered because of its intricate connection to hypothalamic-adrenal-ovarian axis function [(5,6)].

In particular, elevated insulin levels drive elevated androgen levels in PCOS*, with potential consequences for ovarian dysfunction, menstrual irregularities and fertility issues, hirsutism, central adiposity, and other presentations of PCOS [(1,5,6)]. The study we Deepdive into now is the most recent synthesis of evidence for dietary interventions and insulin resistance in PCOS.

*Geek Box: Insulin and Androgens in PCOS

It is important to reiterate that insulin resistance in PCOS is observed in both lean PCOS phenotypes and PCOS phenotypes with obesity, particularly visceral/central adiposity. This is important because it indicates that the defective functionality of insulin and androgens, as elements of the pathophysiology of PCOS, have some internal origins.

In women, androgens are secreted by the adrenal glands and the ovaries and stimulated by adrenocorticotropic hormone [ACTH] and luteinizing hormone [LH], respectively. Both ACTH and LH are released from the pituitary gland. Generally, when LH levels are high, the ovaries become desensitised to LH. However, insulin acts to counterbalance this desensitising effect, thus maintaining responsiveness of the ovaries to the stimulatory actions of LH. In the context of elevated LH, this potentiates the synthesis of androgens by the ovaries.

It has long been established that elevated insulin drives ovarian androgen production, and that elevated androgens adversely affect ovulatory function. Typically, this is looked at as a causal chain, i.e., insulin>androgens>ovarian function, with an emphasis on the stimulatory effect insulin has on LH promoting androgen ovarian production. We could consider this an indirect effect of insulin on ovarian function.

Yet there is also evidence of a direct effect of insulin stimulating ovarian cells [theca and granulosa cells] through insulin receptors on these cells, i.e., that hyperandrogenic anovulation may be caused be elevated insulin and insulin binding with these cells. However, currently there is stronger evidence for the chain of elevated insulin > LH > ovarian androgen secretion > ovarian/ ovulatory dysfunction.

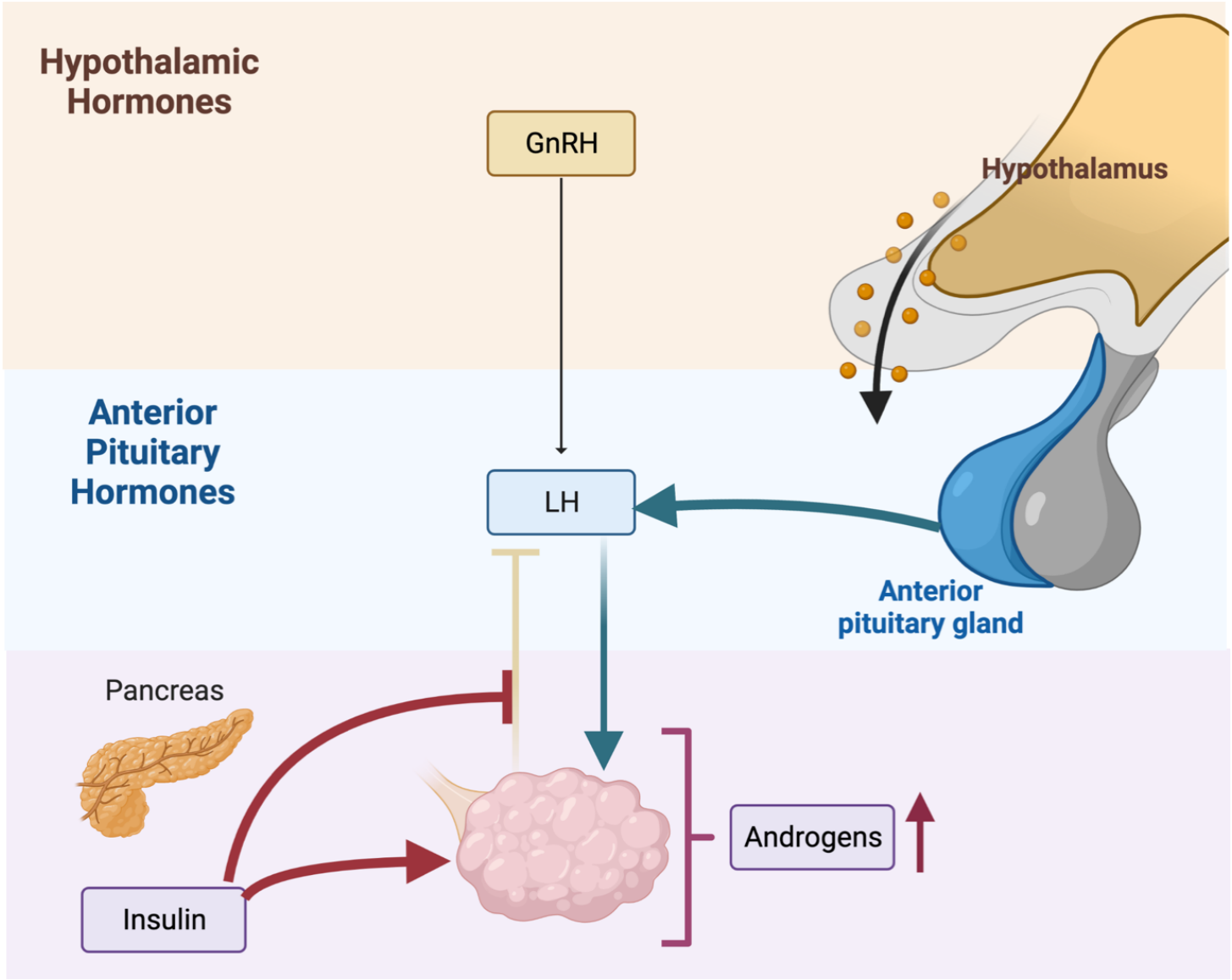


Figure *illustrating the relationship between insulin and ovarian androgens in PCOS. The turquoise arrow lines from the pituitary through the LH label and down to the ovaries indicate the normal release and stimulation of ovarian androgen production by LH. The orange inhibitor line that is parallel to the green LH-Ovaries arrow indicates the feedback regulation that would occur normally with elevated LH, where the ovaries become less responsive to the stimulating effect of LH. However, the red inhibitor arrow against this from insulin indicates the moderating effect that insulin has in counteracting the normal desensitisation of the ovaries to LH, which has the effect of potentiating the effects of LH in stimulating ovarian androgen production. As highlighted in the Geek Box, above, there is some evidence that insulin receptors in ovarian cells may also provide a mechanism through which insulin more directly stimulates ovarian androgen production. Cumulatively, the interactions between insulin and androgenic pathways results in ovarian androgen excess, with consequences for ovulatory function and other aspects of PCOS pathophysiology.*

The Study

The study was a systematic review and meta-analysis of randomised controlled trials [RCTs] investigating the effects of dietary interventions on insulin resistance in women with PCOS. The inclusion criteria were as follows:

- RCTs with parallel arms [i.e., treatment and control run concurrently]
- Evaluated parameters of insulin resistance as outcomes [e.g., HOMA-IR]
- Women in the trials had a clear diagnosis of PCOS

The study did allow for either exercise and/or medications to be used as part of the intervention, if this was similar in the control group [i.e., diet was then the only difference between groups].

Results: A total of 19 RCTs were included in the final study, which encompassed 1,193 participants.

6 studies were each conducted in China and Iran, 2 each from the U.S. and Australia, and 1 each from Egypt, Jordan, and Denmark.

Of the included trials, 11 used the Rotterdam Criteria for diagnosis of PCOS, while 6 used the NIH Criteria.

Of the dietary interventions used in the trials, 10 used low-carb diets, 4 used the DASH diet, 3 used calorie-restricted diets, 2 used low-fat diets, and 1 used a Mediterranean diet.

- ***HOMA-IR*:** Based on 5 trials with 266 participants, dietary interventions led to a decrease in insulin resistance [assessed by HOMA-IR, which is calculated from fasting glucose and fasting insulin measures] of 0.78 [95% CI 0.65 to 0.92]. Depending on the cut-off points used, HOMA-IR of >2.0 is often considered insulin resistant, so this finding would have some clinical meaningfulness. The DASH diet was more effective than the low-carb diets in lowering HOMA-IR [more under ***Interesting Finding***, below].
- ***Fasting Insulin*:** Based on 9 trials with 500 participants, dietary interventions led to a decrease in fasting insulin of 4.24mIU/L [95% CI 3.10 to 5.37mIU/L]. Subgroup analysis indicated that the effect was greater in trials >12-weeks duration compared to <12-weeks. Both DASH and low-carb diets were similarly effective.
- ***Fasting Plasma Glucose*:** Based on 6 trials with 272 participants, dietary interventions led to a decrease in fasting glucose of 0.11mmol/L [95% CI 0.04 to 0.17mmol/L]. This effect was primarily observed in trials of <12-weeks, but in trials >12-weeks there was no significant effect. The DASH diet was the only diet that significantly lowered fasting glucose.
- ***Weight-Related Outcomes*:** Dietary interventions led to an average decrease in BMI of 1.01kg/m^2 [95% CI. 0.64 to 1.38kg/m^2], a decrease in weight of 1.74kg [95% CI 1.05 to 2.42kg], and a decrease in waist circumference of 3.25cm [95% CI 1.22 to 5.29cm]. These effects were greatest with calorie restricted diets and with longer duration of intervention >12-weeks.

The Critical Breakdown

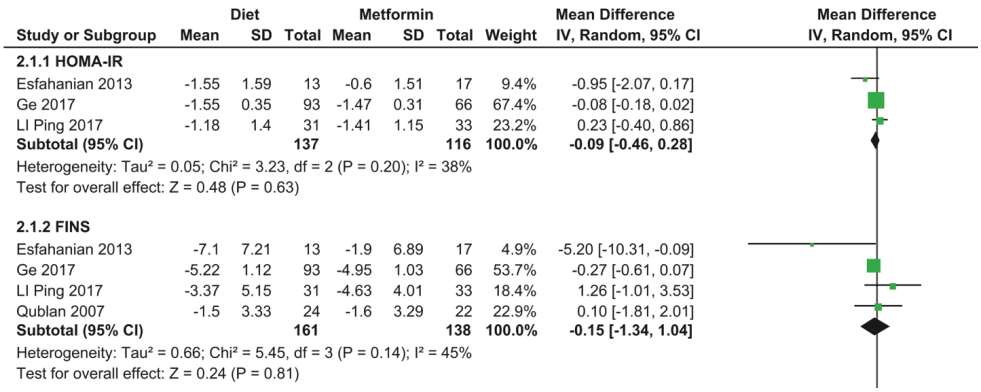
Pros: The review was pre-registered on the National Institutes of Health database of systematic reviews, and thus the criteria were all pre-specified. Relevant databases were searched for included studies and the inclusion criteria were clearly defined. The included studies covered a range of regions and background populations. The diagnostic criteria used for the primary studies was defined. The analysis separately analysed whether a dietary intervention was compared to another diet or to treatment with metformin. The results and data are clearly reported and presented.

Cons: Although it is a meta-analysis, many of the subgroup analyses only included 1 study, leaving the effect size shown at the mercy of a single study which could exaggerate the observed effect. By definition, the "low-carb" diets were not really such, with most containing a minimum of 40% carbohydrate [this is not a fault of the researchers *per se*, they're playing the hand they've got with the literature]. 4 of the included studies had dropout rates of >20%, and only 2 trials included had used intention-to-treat analysis, i.e., analyse all participants included whether they completed the trial or not [using the last data point if not], to maintain balance between groups and reduce risk of bias. Many of the analyses had a small number of trials and participants, and may lack statistical power to detect more robust estimates of effect. Nearly all included studies involved total energy restriction, so the effects of diet are not necessarily independent of lower total energy intake.

Key Characteristic

With PCOS interventions, the definition of the intervention and the comparison matter due to the potential for adjuvant use of diet and medications. In this meta-analysis, the researchers separately analysed trials where the comparison was diet treatment only or where the comparison included metformin. And, while specific dietary intervention was superior to standard diets in this analysis, when the comparison was against metformin there was no longer any significant effect of diet on HOMA-IR, fasting insulin or glucose, but there was a significant effect of diet in lowering BMI, weight, and waist circumference.

However, I wouldn't be too quick to call this settled science. Another recent meta-analysis of 12 trials that compared diet + metformin vs. diet alone found that energy-restricted diets *per se* lowered fasting insulin and glucose independent of whether metformin was added on top [7]. Ultimately, this is an example of where creating a false dichotomy between "lifestyle or drugs" becomes self-defeating. As we covered in a previous Deepdive, for PCOS it appears that combinations of interventions are likely more superior to any one approach in isolation.



Study or Subgroup	Diet Mean	Diet SD	Diet Total	Metformin Mean	Metformin SD	Metformin Total	Weight	Mean Difference IV, Random, 95% CI
2.1.1 HOMA-IR								
Esfahanian 2013	-1.55	1.59	13	-0.6	1.51	17	9.4%	-0.95 [-2.07, 0.17]
Ge 2017	-1.55	0.35	93	-1.47	0.31	66	67.4%	-0.08 [-0.18, 0.02]
LI Ping 2017	-1.18	1.4	31	-1.41	1.15	33	23.2%	0.23 [-0.40, 0.86]
Subtotal (95% CI)			**137**			**116**	**100.0%**	**-0.09 [-0.46, 0.28]**
Heterogeneity: Tau² = 0.05; Chi² = 3.23, df = 2 (P = 0.20); I² = 38%								
Test for overall effect: Z = 0.48 (P = 0.63)								
2.1.2 FINS								
Esfahanian 2013	-7.1	7.21	13	-1.9	6.89	17	4.9%	-5.20 [-10.31, -0.09]
Ge 2017	-5.22	1.12	93	-4.95	1.03	66	53.7%	-0.27 [-0.61, 0.07]
LI Ping 2017	-3.37	5.15	31	-4.63	4.01	33	18.4%	1.26 [-1.01, 3.53]
Qublan 2007	-1.5	3.33	24	-1.6	3.29	22	22.9%	0.10 [-1.81, 2.01]
Subtotal (95% CI)			**161**			**138**	**100.0%**	**-0.15 [-1.34, 1.04]**
Heterogeneity: Tau² = 0.66; Chi² = 5.45, df = 3 (P = 0.14); I² = 45%								
Test for overall effect: Z = 0.24 (P = 0.81)								

Figure *from the paper showing no superior benefit of dietary intervention compared to metformin on HOMA-IR or fasting insulin. This is based off a limited number of included studies.*

Interesting Finding

A subgroup analysis to compare the effects of the type of dietary intervention on HOMA-IR compared the effects of studies using the DASH diet to studies using a low-carb diet. The findings for each were:

- **DASH**: Decreased HOMA-IR by 0.91 [95% CI 0.74 to 1.07]
- **Low-Carb**: Decreased HOMA-IR by 0.70 [95% CI 0.59 to 0.81]

One could have sympathy for the comparison from the perspective of low-carb diets, as only the paper by Sun *et al*. 2017 had carbohydrate intake of <40%; the other two papers had intakes of ~40% on the nose. The DASH diets contained 52-55% carbohydrate. This is interesting because Barbara Gower' s group, one of whose papers is included in this analysis, compared diets of 55% carbs / 18% protein / 27% fat vs. 41% carbs / 19% protein / 40% fat, and found that the lower carbohydrate diet resulted in preferential loss of abdominal fat mass and improvements in insulin response and sensitivity [which also corresponded to decreases in circulating testosterone levels] [8,9].

What is interesting about the two studies on the DASH diet included in this subgroup analysis is that *both* comparison diets contained the same energy and macronutrient profile: the DASH diet contained 52% carbs / 18% protein / 30% fat, and so did the comparison diet. The difference was in the dietary pattern, with the DASH diet enriched in vegetables, fruits, wholegrains, low-fat dairy, etc. So, what could explain the differences?

It could be glycaemic load; the low-carb trials included were also low-GI/GL diets, and the DASH diets were low-GI/GL diets. As we covered in a recent Deepdive, lowering GI/GL appears to provide a benefit in PCOS, supported by meta-analysis of low-GI/GL diets that we covered in another Deepdive. An important caveat here is that energy restriction may often explain much of the benefit.

Relevance

The top-line caveat to the present meta-analysis is that practically all the included studies also involved energy restriction, so the effects of diet composition *per se* may be less relevant overall. Or at least, we don't know. For example, is the greater improvement in HOMA-IR found for the DASH diet compared to low-carb diets related to the composition of diets or to the magnitude of achieved energy restriction?

Bear in mind the Gower *et al*. 2013 paper modified carb intake and GI/GL but in energy-balance diets. The other studies in that subgroup analysis [under ***Interesting Finding***, above] did use energy-restricted diets, and so we still have the open question of which is more important: total carb content, carb quality [GI/GL], dietary pattern, higher protein intake, and/or total energy level.

We don't have answers to those questions because the research in this area has left the 'Big Picture' questions – e.g., are there effects of diet composition independent of energy restriction? – on the table in favour of pursuing random nonsense like *"we tested the combination of a niche probiotic strain and hibiscus tea on glutathione levels"*. Just the scientific community letting women down, again.

Nevertheless, broadly speaking, dietary interventions with a degree of energy restriction and a modification of diet quality improve insulin resistance and fasting glucose levels in women with PCOS. In the present study, dietary intervention was not superior to metformin, but the wider evidence suggests that combination treatments are generally favourable to a range of metabolic and androgenic outcomes in PCOS [10–12].

Application to Practice

It is always helpful when a study of nutrition in PCOS seeks to answer a relevant and focused research question, such as the effect of dietary interventions on insulin resistance. At this juncture in the evidence, it appears that there are several dietary approaches that may benefit, with DASH and low-carb diets showing the most consistent effects.

However, it is crucial to bear in mind that "low-carb" here is seldom less than 40% total carbohydrates, and when we compare the effects of those diets with DASH diets, we see a unifying theme: low glycaemic index and load diets, which consistently improve insulin resistance. The fact that such effects appeared to be enhanced with duration of intervention indicates the importance of adherence, giving rise to the cliché that "the best diet is the one you can stick to".

However, where improvements in androgens are sought on top of lowering insulin resistance, there is a case to be made for higher protein and low-GI diets, in the context of energy restriction, which have been shown to significantly improve *both* insulin resistance and androgens [13].

References

1. Rosenfield RL, Ehrmann DA. The Pathogenesis of Polycystic Ovary Syndrome (PCOS): The Hypothesis of PCOS as Functional Ovarian Hyperandrogenism Revisited. Endocrine Reviews. 2016 Oct 1;37(5):467–520.
2. Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound Peripheral Insulin Resistance, Independent of Obesity, in Polycystic Ovary Syndrome. Diabetes. 1989 Sep 1;38(9):1165–74.
3. Morales AJ, Laughlin GA, Bützow T, Maheshwari H, Baumann G, Yen SS. Insulin, somatotropic, and luteinizing hormone axes in lean and obese women with polycystic ovary syndrome: common and distinct features. The Journal of Clinical Endocrinology & Metabolism. 1996 Aug;81(8):2854–64.
4. Gerich JE. Physiology of glucose homeostasis. Diabetes, Obesity and Metabolism. 2000 Dec;2(6):345–50.
5. Kayampilly PP, Wanamaker BL, Stewart JA, Wagner CL, Menon KMJ. Stimulatory Effect of Insulin on 5α-Reductase Type 1 (SRD5A1) Expression through an Akt-Dependent Pathway in Ovarian Granulosa Cells. Endocrinology. 2010 Oct 1;151(10):5030–7.
6. Barbieri RL, Makris A, Randall RW, Daniels G, Kistner RW, Ryan KJ. Insulin Stimulates Androgen Accumulation in Incubations of Ovarian Stroma Obtained from Women with Hyperandrogenism. Journal of Clinical Endocrinology & Metabolism. 1986 May;62(5):904–10.
7. Garcia-Hernandez SC, Porchia LM, Pacheco-Soto BT, López-Bayghen E, Gonzalez-Mejia ME. Metformin does not improve insulin sensitivity over hypocaloric diets in women with polycystic ovary syndrome: a systematic review of 12 studies. Gynecological Endocrinology. 2021 Nov 2;37(11):968–76.
8. Goss AM, Chandler-Laney PC, Ovalle F, Goree LL, Azziz R, Desmond RA, et al. Effects of a eucaloric reduced-carbohydrate diet on body composition and fat distribution in women with PCOS. Metabolism. 2014 Oct;63(10):1257–64.
9. Gower BA, Chandler-Laney PC, Ovalle F, Goree LL, Azziz R, Desmond RA, et al. Favourable metabolic effects of a eucaloric lower-carbohydrate diet in women with PCOS. Clinical Endocrinology. 2013 Oct;79(4):550–7.
10. Moran LJ, Ko H, Misso M, Marsh K, Noakes M, Talbot M, et al. Dietary Composition in the Treatment of Polycystic Ovary Syndrome: A Systematic Review to Inform Evidence-Based Guidelines. Journal of the Academy of Nutrition and Dietetics. 2013 Apr;113(4):520–45.
11. Unfer V, Facchinetti F, Orrù B, Giordani B, Nestler J. Myo-inositol effects in women with PCOS: A meta-analysis of randomized controlled trials. Endocrine Connections. 2017;6(8):647–58.
12. Diamanti-Kandarakis E, Kandaraki E, Christakou C, Panidis D. The effect of pharmaceutical intervention on lipid profile in polycystic ovary syndrome. Obesity Reviews. 2009;10(4):431–41.
13. Mehrabani HH, Salehpour S, Amiri Z, Farahani SJ, Meyer BJ, Tahbaz F. Beneficial Effects of a High-Protein, Low-Glycemic-Load Hypocaloric Diet in Overweight and Obese Women with Polycystic Ovary Syndrome: A Randomized Controlled Intervention Study. J Am Coll Nutr. 2012 Apr;31(2):117-25.