ALINEA

NUTRITION

NOVEMBER 2021

www.alineanutrition.com

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Kazemi M, Hadi A, Pierson RA, Lujan ME, Zello GA, Chilibeck PD. Effects of Dietary Glycemic Index and Glycemic Load on Cardiometabolic and Reproductive Profiles in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Adv Nutr. 2021;12(1):161-178.

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

It is now well-established that insulin resistance and elevated androgens are the defining metabolic characteristics of most Polycystic Ovary Syndrome [PCOS] phenotypes [(1)]. The PCOS phenotypes with hyperandrogenism [i.e., elevated androgens] also commonly present with higher bodyweight and fat, particularly central abdominal adiposity [(2)].

Impaired carbohydrate metabolism is a prominent feature of the pathophysiology of insulin resistant PCOS phenotypes, and PCOS is considered as an independent risk factor for the development of glucose intolerance and cardio-metabolic risk [(2,3)].

Carbohydrate intake – and carbohydrate quality – also have a dual role in PCOS: the relationship between insulin and androgen levels [(4)]. Physiological levels of insulin [i.e., 'normal' levels in the body, not jacked up levels in a rat] stimulate pathways of androgen production [(4)]. The relationship between elevated insulin levels and testosterone pathways may be a driver of ovulatory dysregulation that is characteristic of PCOS [(5)].

Although the underlying factors relating insulin resistance, impaired carbohydrate metabolism, and hyperandrogenism may be complex, from the perspective of diet they point to a potentially simple intervention: carbohydrate modification. The present study reviewed and analysed the available evidence for glycaemic index and glycaemic load* on cardio-metabolic outcomes in PCOS.

*Geek Box: Glycaemic Index and Glycaemic Load

Have you ever wondered, where does glucose go? Let's use an example of glucose disposal after a hypothetical meal containing 100g of carbohydrate as glucose. As the 100g enters circulation from the small intestine, the first port of call is the liver where around 30% of that glucose is taken up in liver cells. The remaining 70g goes on to enter general circulation, where around 25-30% is taken up next by skeletal muscle, 5-15% by adipose [fat] tissue, 8-10% by the kidneys, and 15-20% taken up directly by the brain. A further 7-15% continues in circulation and can be taken up again by the liver and other tissues, or stored in adipose tissue, as required. Now, this is just an example of hypothetical disposal; what about the rate of that glucose uptake? And what about the dose of a given food, as it relates to rate of uptake? This is where the development of glycaemic index and glycaemic load come in. The glycaemic index [GI] of a food is based on a comparison of how quickly a food makes blood glucose levels rise, compared to 100g of pure glucose. As a result, the scale is a numeric scale from 0 to 100. In general, foods <55 are considered low GI, 56-69 considered moderate GI, and >70 considered high GI. However, this is quite artificial relative to how much of a given food people would actually consume. This is where glycaemic load [GL] comes in, because the GL of a food considers how much glucose that food would contribute per serving. Watermelon is a commonly cited example of the difference; it has a GI of 80, but its GL is only 5 because the majority of the fruit would be water, fibre, and other factors that mean its net glucose value is low. Both the GI and GL have critics, particularly GI given it does not reflect actual food intake. One thing to keep an eye out for is the fact that low GI/GL diets are often a proxy for diets containing minimally processed carbohydrates, fibre-rich foods, wholegrains, and veg and fruit; there are multiple components to these foods that would contribute to long-term health benefits, independent of the mere quantification of impacts on blood sugar using GI/GL.

The Study

The present study was a systematic review and meta-analysis. The primary research question was whether a low GI and GL [LGI/LGL] diet improves cardio-metabolic and reproductive health outcomes in PCOS compared to higher GI/GL diets, in studies over 8-weeks duration.

Relevant studies were searched up until October 2019, with no restrictions on language of publication. To be included, studies had to be randomised controlled trials [RCTs] in which the difference in the effects of the GI/GL diets were reported between the intervention and control group.

The primary outcome was homeostatic model of insulin resistance [HOMA-IR], which calculates insulin resistance based on fasting glucose and insulin measures. Secondary outcomes included blood glucose and insulin, cholesterol, testosterone, and the free androgen index [FAI].

Subgroup analyses were also conducted to determine whether there was any effect of age, energy restriction, or the duration of the study, on the relevant outcomes.

Results: The systematic review included 10 RCTs, with a total of 20 intervention and control groups [202 total participants from intervention groups and 201 from control groups]. Of these 10 studies, 7 were had sufficient data to include in the meta-analysis. Only two of the included studies focused specifically on glycaemic load, the remainder focused on glycaemic index.

- ***HOMA-IR*:** Compared to the HGI control groups, on average LGI diets led to a 0.78 lower HOMA-IR [more on the context of these numbers under ***Relevance***, below]. However, the subgroup analysis indicated that this effect was only evident in trials prescribing energy restriction, which showed a 1.02 lower HOMA-IR.
- ***Fasting Insulin and Glucose*:** Compared to the HGI control groups, fasting insulin levels were significantly lower in the LGI diet groups, however this was only evident in younger participants [<30yo], trials with energy restriction, and trials of <16-weeks duration. There was no significant change in fasting glucose levels comparing LGI to HGI diets.
- ***Blood Lipids*:** There was a significant reduction in LDL-C by 0.16mmol/L [6.27mg/dL] in the LGI diet groups, compared to the HGI control groups. There was also a significant reduction in triglycerides, 0.16mmol/L [14.85mg/dL; this appears higher than the mmol/L value for triglycerides because the multiplier to convert to mg/dL is different than that for LDL-C!].
- ***Androgens*:** Compared to the HGI control groups, LGI diets led to a 0.21nmol/L lower total testosterone level. Subgroup analysis indicated that this lower total testosterone was only evident in participants <30yrs, in trials with energy restriction, and in trials <16-weeks duration.

The Critical Breakdown

Pros: The study addressed an important research question for clinical practice. The study was pre-registered on the National Institute for Health Research database, and there are no obvious deviations from the protocol in the final paper. All studies were relatively recent, published between 2009 and 2020. Many of the included studies used similar interventions, e.g., the DASH diet, which is rare to have similarity in a nutrition meta-analysis.

Cons: It is not uncommon for dietary interventions to have small sample sizes, and so it is the case here; even with all data combined in the meta-analysis, the total sample size is <200 people in either the intervention or control groups. Only two of the included studies focused specifically on glycaemic load, the remainder focused on glycaemic index, so the meta-analysis was confined to LGI diets. With certain outcomes, subgroup analysis could not be conducted due to a lack of studies which investigated that particular outcome.

Key Characteristic

One can never stress the importance of well-thought out subgroup analysis, particularly for meta-analyses of nutrition studies, given that the design of trials often varies substantially from study to study. What makes the subgroup analysis in the present study more robust is that it was a *priori*, meaning that it was using prior knowledge to declare which factors it would investigate; this was all declared in the pre-registration, so there is no 'fishing' going on.

One such factor was energy balance, i.e., whether the trial used a maintenance energy or energy restricted diet. In the subgroup analysis of the effects of LGI diets on the primary outcome of HOMA-IR, it emerged that LGI diets only led to reductions in HOMA-IR in studies that used energy-restricted diets. Thus, the improvements in insulin resistance were more related to energy restriction that the LGI diets in isolation. A similar outcome was observed for fasting insulin, were decreases in fasting insulin were only observed in trials using energy-restricted diets, in participants under 30yrs of age, and in studies under 16-weeks duration.

Interesting Finding

Given the mechanistic understanding of the relationship between insulin and androgens in PCOS, the findings in relation to total testosterone are interesting. Bear in mind that normal levels for women are in a range of 0.5 to 2.4nmol/L; thus, a change of 0.21nmol/L could be clinically meaningful. However, the evidence for an effect of carbohydrate modification on androgens in PCOS has been inconsistent [(6)]. A previous meta-analysis showed that diets with a range of 41-45% carbohydrate had little effect on testosterone [(6)].

In the present meta-analysis, the one study which found a a significant reduction of androgens was, like most included studies, a traditional DASH diet, but it was also an energy-restricted diet. Thus, is the effect on androgens mediated more by total carbohydrate intake in insulin-resistant women with PCOS, or by total energy intake? And what is the relationship between the two [total carb and energy]? There are no quality studies yet answering this question, possibly because most of the PCOS research community seems more interested in finding some Unicorn random supplement than dietary interventions.

I understand the Unicorn's name is "spearmint tea".

Relevance

The primary outcome of the study was a reduction in HOMA-IR of 0.78, which was 1.02 in trials using energy-restricted diets. For HOMA-IR, a score of 1.0 and range of 0.5-1.4 indicates normal insulin sensitivity; above 1.9 indicates early insulin resistance, while over 2.9 indicates significant insulin resistance. Thus, the magnitude of change from the present study would be clinically meaningful, with a greater clinical benefit in the context of an energy deficit.

The included studies targeted LGI and LGL diets, however, this does not say anything about total carbohydrate content of the diets. And this may be important, because previous research has suggested that the biggest impact on metabolic outcomes and androgen levels in PCOS may be observed with diets of less than 35% total fat and less than 45% total carbohydrate [(6)].

Most of the LGI studies used the standard DASH diet, so total carbohydrate intake was often in a range of ~45-55% energy. For improvements in insulin and androgen levels in PCOS, despite the GI content of the diet being low, this may be a level of total carbohydrate at which there is no meaningful effect. Thus, there is still low hanging fruit to be picked on macronutrient manipulations for improving the hormonal milieu of PCOS.

In particular, one of the included studies in the present meta-analysis used a 30% protein diet, in conjunction with low glycaemic load, and found significant improvements in metabolic and androgenic outcomes [(7)]. The other studies included in the present analysis all averaged 15-20% protein, so there is scope to examine the beneficial effects of higher dietary protein in women with PCOS.

It should be noted that there may be other benefits to LGI diets in women with PCOS, in particular evidence for improved menstrual regularity [(8)]. However, irrespective of macronutrient composition, weight loss improves metabolic and androgen outcomes in women with PCOS [(8,9)].

Application to Practice

Where do we stand on macronutrient manipulations for improving the insulin resistance and hyperandrogenism characteristic of certain PCOS phenotypes? Like many areas of nutrition, we stand on a body of evidence consisting of small trials, low statistical power, and varying consistency in effects, and the size of those effects.

However, there are still meaningful findings to apply. The first is that, in the phenotype characterised by central abdominal adiposity, energy restriction and weight loss improves endocrine outcomes. The second is that dietary modification can be effect at also improving these outcomes, and the evidence for LGI diets includes improved insulin sensitivity, menstrual regularity, blood lipids, and general quality of life indices [(8)]. The final point is that total carbohydrate intake does appear to be relevant, and under at least 45% of daily energy may lead to more meaningful improvements in these outcomes.

To what extent there may be a benefit to replacing that carbohydrate with protein, and whether it is preferable to also have a lower total fat intake, remain to be fully investigated in future research.

References

1. Westerveld HE, Hoogendoorn M, de Jong AWF, Goverde AJ, Fauser BCJM, Dallinga-Thie GM. Cardiometabolic abnormalities in the polycystic ovary syndrome: Pharmacotherapeutic insights. Pharmacology and Therapeutics. 2008;119(3):223–41.
2. Diamanti-Kandarakis E. Polycystic ovarian syndrome: Pathophysiology, molecular aspects and clinical implications. Expert Reviews in Molecular Medicine. 2008;10(3):1–21.
3. Diamanti-Kandarakis E, Christakou C, Marinakis E. Phenotypes and Enviromental Factors: Their Influence in PCOS. Current Pharmaceutical Design. 2012;18(3):270–82.
4. Baptiste CG, Battista MC, Trottier A, Baillargeon JP. Insulin and hyperandrogenism in women with polycystic ovary syndrome. Vol. 122, Journal of Steroid Biochemistry and Molecular Biology. 2010. p. 42–52.
5. Balen A. The pathophysiology of polycystic ovary syndrome: Trying to understand PCOS and its endocrinology. Best Practice and Research: Clinical Obstetrics and Gynaecology. 2004;18(5 SPEC. ISS.):685–706.
6. Zhang X, Zheng Y, Guo Y, Lai Z. The Effect of Low Carbohydrate Diet on Polycystic Ovary Syndrome: A Meta-Analysis of Randomized Controlled Trials. 2019.
7. 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. Journal of the American College of Nutrition. 2012 Apr;31(2).
8. 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.
9. Frary JMC, Bjerre KP, Glintborg D, Ravn P. The effect of dietary carbohydrates in women with polycystic ovary syndrome: a systematic review. Minerva endocrinologica. 2016 Mar;41(1).