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Metabolism

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New research developments and insights from *Metabolism*

In a field of great importance to daily life and clinical care, metabolic-related research covers a wealth of information and knowledge. This broad field encompasses a number of physical states that are increasingly critical to study, including obesity, type 2 diabetes, metabolic syndrome, and cardiovascular disease. Additionally, the impacts of diet, nutrition, and exercise on these physical states are an area of ever-important and expanding research. With the latest advances in metabolic research, much knowledge has been gained. Here, we present the newest findings from research published in *Metabolism*. We hope that these results provide not only critical knowledge needed for clinical care and daily life, but also a platform for the continuing expansion of research into metabolic-related issues.

1. Diet and nutrition

1.1. *Carbohydrate influences on body composition in polycystic ovary syndrome*

In order to target healthy weight loss, diet composition may require special consideration for women with poly-cystic ovary syndrome. Goss et al. [1] demonstrated in a crossover study of 30 women with poly-cystic ovary syndrome (aged 31 ± 5.8 years) that consumption of a reduced-carbohydrate diet as compared to a standard diet significantly decreased the amount of adipose tissue without changing total calories consumed over the course of eight weeks. While on the low carbohydrate diet, loss of fat mass occurred from subcutaneous-abdominal, intra-abdominal, and thigh-intermuscular adipose tissues (−4.6%, −7.1%, and −11.5%, respectively). Furthermore, the reduced-carbohydrate diets were also associated with decreased insulin levels. In contrast, the "standard" diet may have decreased lean mass by converting it to fat. Therefore, women with polycystic ovary syndrome who consume a diet lower in carbohydrates may preferentially lose fat mass from unhealthy areas of the body. Future studies could be focused on whether altering fat or protein content has a similar effect on the loss of fat mass in women with polycystic ovary syndrome.

1.2. *Impacts of ginsenosides on hyperlipidemia and GLP-1*

Ginsenosides, found in Panax Ginseng, help to ameliorate hyperlipidemia, but the mechanism by which they act is still not yet completely understood. Liu et al. [2] investigated whether glucagon-like peptide-1 (GLP-1) release mediated by ginseng total saponins (GTS), in addition to exerting anti-diabetic properties, have effects on hyperlipidemia in 20 obese male Sprague–Dawley rats (weighing 100–200 g). After the rats were randomized to receive either a high-fat diet (HFD) intervention or a chow control diet for four weeks, rats on the HFD were further randomized to a treatment of low-dose (150 mg/kg/day) or high-dose (300 mg/kg/day) GTS for an additional four weeks. Liver weight in rats fed a HFD decreased by 6.8% and 7.8% after the low- and high-dose treatments, respectively. As measures of body fat content, epididymal fat and retroperitoneal fat decreased 21% and 16%, respectively, in rats treated with high-dose GTS as compared to HFD control rats. Similarly, plasma levels of triglycerides, total cholesterol, and free fatty acids decreased by 39%, 15% and 16%, respectively, with high-dose treatment. Lastly, plasma levels of Apo-B48 and LDL-C decreased by about 38% and 28%,

Abbreviations: GLP-1, glucagon-like peptide 1; 25OHD, 25-hydroxyvitamin D; RDA, recommended daily allowance; IGF-1, insulin-like growth factor 1; HDL, high density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; HbA1c, glycated hemoglobin; HFD, high-fat diet; BMI, body mass index; AMPK, AMP-activated protein kinase; PBMCs, peripheral blood mononuclear cells; OXPHOS, oxidative phosphorylation; OGTT, oral glucose tolerance test; LV, left ventricular; VO_2peak, peak oxygen uptake; KLAKS, Concept Leipzig: Adiposity therapy for school aged children; STAT3, signal transducer and activator of transcription 3; DPP-4, dipeptidyl peptidase-4; IL, interleukin; PKC, protein kinase C; MODY, maturity onset diabetes of the young; ISI, insulin sensitivity index; VLDL, very low density lipoproteins; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; TCR, T cell receptor; FGF21, fibroblast growth factor 21; PET, positron emission tomography; DUAL-SPIR, dual echo spectral presaturation inversion recovery; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy.

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respectively, again with high-dose GTS treatment. Moreover, treatment with ginsenosides improved insulin resistance and leptin sensitivity and increased GLP-1 levels. Although it was determined that oral ginsenosides may mediate the anti-hyperlipidemic effects through greater GLP-1 secretion, future research should consider whether oral ginsenosides may have a direct effect on lowering lipid profiles.

1.3. *Vitamin D influences diabetic outcomes*

Vitamin D deficiency often accompanies type 2 diabetes, but the potential role of vitamin D in the pathogenesis of diabetes, if any, remains unclear. Kampmann et al. [3] sought to determine whether administration of vitamin D in 16 subjects with type 2 diabetes who had a vitamin D deficiency would positively affect insulin and inflammatory markers. In a randomized double-blind trial with 16 participants, 8 adults (aged 61.6 ± 4.4 years) received oral cholecalciferol (280 μg/day for two weeks and 140 μg/day the following 10 weeks) and 8 additional adults (aged 57 ± 4.5 years) were given placebo. Plasma 25-hydroxyvitamin D (25OHD) significantly increased 238% ($p = 0.01$) in the supplemented group, whereas 25OHD decreased 7.8% in the placebo group ($p = 0.02$). Serum-1,25 $(OH)_2$ also increased by about 40% in the treatment group. C-peptide levels, incremental AUC insulin and insulin secretory burst mass showed a trend towards improvement, which, however, did not reach the level of statistical significance ($p = 0.05$–0.10), indicating a potential improvement in insulin secretion. Insulin sensitivity and inflammation, however, did not improve with vitamin D replacement therapy. Future research with larger sample sizes and longer treatment duration could help elucidate further benefits of vitamin D supplements for type 2 diabetes.

1.4. *Fish-based diets and endothelial function*

To test whether a fish-based diet with high n-3 polyunsaturated fatty acids (>3.0 g/day) may improve endothelial function as compared to a control diet, Kondo et al. [4] enrolled 23 postmenopausal women with type 2 diabetes (aged 69.7 ± 6.6 years) in a randomized, crossover trial to consume either the fish-based or control diet for 4 weeks followed by the opposite for the next four weeks. Determinants of endothelial function improved with the fish-based diet: peak forearm blood flow by 63.7%, duration of reactive hyperemia by 27.9% and flow debt repayment by 70.7%. While the fish-based diet as compared to the control diet resulted in improvements in endothelial function, these observations did not correlate with n-3 polyunsaturated fatty acid levels, suggesting that something else in the fish diet may be causing these improvements. Future studies should examine this in more general populations, as well as more broadly seek to discover the beneficial component in the fish-based diet.

1.5. *High protein diets influences on hormones*

Henning et al. [5] sought to determine whether a diet high in protein during an energy deficit may attenuate the typically observed fat-free mass loss through insulin-like growth factor 1 (IGF-1) signaling. Using a block-randomized design, 33 adult participants were assigned to a diet with protein levels of either the recommended daily allowance (RDA) (aged: 22 ± 1 years), twice the RDA (aged: 21 ± 1 years) or three times the RDA (aged: 22 ± 1 years; 0.8, 1.6, or 2.4 g kg^{-1} day^{-1}, respectively) for 31 days. Hormone levels were measured and compared after 10 days of a weight-maintaining diet and 21 days later after a 40% energy-deficient diet. Energy deficit decreased IGF-1 levels (14%) and testosterone levels (total: 16%, free: 23%) and increased IGF binding proteins (63%), regardless of protein level intake. Changes in these molecules did not correlate with changes in fat-free mass seen after energy deficit, suggesting that they may not play a role in mediating the relationships between energy-deficient diets and fat-free mass regardless of high protein intake. Future studies should examine other potential mechanisms to prevent loss of fat-free mass during energy deficient diets.

1.6. *Influences of maternal diet on insulin resistance in the offspring*

To determine whether a mother's HFD during pregnancy or lactation would affect insulin resistance in their offspring, Melo et al. [6] examined newborn or recently weaned mice (6 animals per litter) from ten mothers who were randomly assigned to receive a HFD or control diet. Recently weaned (28 days old), but not newborn mice (0 days old), showed elevated markers for endoplasmic reticulum stress and triglycerides. Thus, these results suggest that maternal diet may have more influence over offspring metabolic dysfunction during lactation rather than pregnancy. Future studies should examine how this may continue into adulthood risk of obesity and metabolic comorbidities.

1.7. *Balanced high fat diets improve cardiometabolic risk*

Silver et al. [7] hypothesized that a balanced high fat diet (9 g/day) for 16 weeks, containing equal amounts of saturated, monounsaturated, and polyunsaturated fats, would lessen cardiovascular disease risk and inflammation. The 144 obese, premenopausal women (aged 36.7 ± 6.8 years) stabilized on the HFD for 2 weeks were subsequently randomized to supplement their diet with either encapsulated stearate (18:0), oleate (18:1), linoleate (18:2) or placebo for 12 weeks. Body fat mass decreased by about 2.5 ± 2.1% while lean mass increased by about 2.5 ± 2.1%. Additionally, multiple inflammatory marker levels decreased in all groups. HFD supplemented with stearate most effectively reduced the inflammatory marker interferon gamma by 74%, while HFD supplemented with linoleate most markedly decreased plasminogen activator inhibitor-1, a measure of vascular function, by 31%. These results may suggest that balancing fats would improve cardiovascular disease risk in women. However, future studies should expand these results by testing the effects on broader populations, including men and postmenopausal women, and studying any potential long-term effects.

1.8. *Walnuts may help improve metabolic risk factors*

In a controlled crossover study comparing a walnut-enriched diet to a control diet, Wu et al. [8] examined whether walnuts may improve biomarkers for metabolic risk, including lipids, inflammatory markers, and adipokines. Forty participants