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DEEPA DIVE SUMMARIES

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Melatonin and Insulin Resistance: What is the Link?

Lauritzen ES, Kampmann U, Pedersen MGB, et al. Three months of melatonin treatment reduces insulin sensitivity in patients with type 2 diabetes-A randomized placebo-controlled crossover trial. *J Pineal Res.* 2022;73(1):e12809.

Background

- Although melatonin is primarily known for its role in regulating the sleep-wake cycle, melatonin in fact participates in a range of biological functions by acting through melatonin receptors in different tissues throughout the body.
- A genetic variant in melatonin receptor 1b [*MTR1B*] is associated with higher fasting glucose, impaired responses to glucose tolerance tests, and higher type-2 diabetes [T2D] risk.
- However, the effects of both supplemental melatonin and the most common *MTR1B* genetic variant in individuals with T2D is not well researched.

The Study

- A randomised, double-blind, placebo-controlled, crossover [participants underwent both arms of the study] intervention trial in participants with T2D. 10mg/d melatonin was consumed at night for 12-weeks and compared to placebo.

Findings, Strengths & Limitations

- After 12-weeks of melatonin supplementation, insulin sensitivity decreased by 12% compared to the placebo, and insulin levels over 2-3 h after a glucose tolerance test were 24% higher.
- However, there was no interaction with the melatonin receptor genotypes and insulin outcomes.
- The strengths of the study were its design and use of the gold-standard for assessing insulin sensitivity. Limitations include the small [$n = 17$] sample size in males only, and potential for “false negatives” in relation to the melatonin receptor genotypes.

Context

- Several recent cross-sectional studies have indicated a relationship between the timing of the nocturnal rise in melatonin [“melatonin onset”], as an approximate start of the biological night, and adiposity.
- A large trial of 845 participants found that glucose tolerance 1 h before bed was significantly impaired compared to 4 h before bed, which was worse in individuals with the *MTNR1B* gene.
- Currently, interventions have shown decreased insulin sensitivity correlated with both higher *endogenous* plasma melatonin and of higher *exogenous* supplemental melatonin.

Application

- The supplemental dose used in the present study was 10mg per day; this is very high considering that the minimum effective dose for supplemental melatonin is 0.5mg.
- It is prudent advice to try to avoid large intakes of energy later into the night, which would be in close proximity to the nocturnal rise in melatonin levels.

Weight Status and Stress Eating in Children

Miller AL, Riley H, Domoff SE, Gearhardt AN, Sturza J, Kaciroti N, Lumeng JC. Weight status moderates stress-eating in the absence of hunger associations in children. *Appetite*. 2019 May 1;136:184-192.

Background

- Generally, “flight or fight” nervous system responses in the body decrease appetite and food intake.
- However, we know from the literature that humans respond *both ways*, i.e., some people respond to stress by *over-eating* while some respond to stress by *under-eating*, and the precise reasons for these divergent responses are not well understood.
- However, very little is known about the potential impacts of stress, and the interaction with sex and weight status, in children.

The Study

- The study was a non-randomised experimental intervention in 223 children who participated in an experimental stress protocol to investigate the effects of stress induction on eating in the absence of hunger [EAH].

Findings, Strengths & Limitations

- There was a significant interaction between anxiety and weight status, i.e., children with overweight increased EAH as anxiety increased. Conversely, children without overweight decreased EAH as anxiety increased.
- The effect of child sex did not moderate the associations between either observed anxiety or subjective distress and EAH.
- Strengths include the large sample size for a study in this age group, specifically focused on children from low-income families, and the balance between both male and female children. The main limitation is that the study was a non-randomised trial with no control groups.

Context

- It is a known feature of the research on stress and eating that humans may respond to stress by both over-eating and under-eating. However, previous research has also shown that having overweight or obesity predicts greater energy intake in response to stress.
- The fact that children without overweight consumed less may reflect the anticipated effect of acute stressors on appetite, i.e., a downregulation of appetite.
- However, weight status acted as a moderator of the stress response, i.e., children with overweight/obesity were more likely to eat more in response to stress.
- The experiment in the present study involved social stress, and this type of “threat stress” involving public embarrassment or failure may provide a plausible explanation for the interaction of weight status and anxiety/stress on increasing EAH in the present study.

Application

- It is crucial for practitioners to understand, and have empathy for, the fact that food in the context of stress is a coping mechanism to respond to the stressor.
- From a nutrition perspective, encouraging brief mindfulness interventions may improve enjoyment of palatable foods while also regulating overall intake.
- In effect, help to provide your clients with tools to better respond to the effect of stress on eating behaviour.

The Effects of Genetically Higher Blood Levels of Polyunsaturated Fats on Heart Disease

Park S, Lee S, Kim Y, et al. Causal Effects of Serum Levels of n-3 or n-6 Polyunsaturated Fatty Acids on Coronary Artery Disease: Mendelian Randomization Study. *Nutrients*. 2021;13(5):1490.

Background

- For omega-6 polyunsaturated fats [PUFA], there is a comprehensive body of evidence demonstrating benefits to these fats for cardiovascular health.
- For omega-3 PUFA, the evidence requires much more dissection to come to any conclusion, and that conclusion could be debated.
- The challenges of teasing out cause-effect relationships in science, particularly in nutrition science, has led to an explosion in the popularity of genetic studies known as Mendelian randomisation [MR] as a research design.

The Study

- The study conducted an MR analysis of the effects of omega-6 and omega-3 on coronary artery disease [CAD] and myocardial infarction [MI].
- The “exposure” was genetic variants associated with higher levels of omega-3 and omega-6 in the serum [the fluid portion of blood remaining after blood has clotted].

Findings, Strengths & Limitations

- Higher serum omega-3 EPA and omega-6 linoleic acid [LA] were each associated with 4% lower odds for MI, and with 22% and 3% lower odds of CAD, respectively.
- Higher serum DHA was not associated with MI or CAD.
- Strengths include the enormous sample sizes in the genetic cohorts, and the replication of the findings in two separate genetic cohorts; limitations include that only 4% of the total UK Biobank cohort experienced an MI, which may reduce some of the statistical power to detect associations, and the use of genetic data only from individuals of White/European ancestry, and thus the findings may not generalise to other ethnic/ancestry population groups.

Context

- The fact that this analysis focused on *serum* levels of PUFA is the critical design factor to be considered in interpreting the findings, as serum as a proxy for diet would only reflect the most immediate intakes of PUFA from diet.
- This could be too short-term and variable a tissue compartment to make causal claims of long-term dietary intake.
- The fact that LA was associated with lower risk may be further vindication against the allegations that LA causes inflammation and *increases* risk for adverse health outcomes.
- Reviews of available evidence show that LA is not associated with inflammatory markers.

Application

- The authors continually referred to the findings as “causal effects of PUFA”, and it is important to temper this language; it is more appropriate to consider these findings as “genetic associations”.
- If we bear in mind that “genetically higher levels” of any fatty acid translate, in interpretation, to “higher dietary intakes”, then nothing really turns on this study because both omega-3 and omega-6 are beneficial fats to include in the diet, which we know from wider evidence.

Can Soy Isoflavones Improve Menopausal Symptoms?

Yoshikata R, Myint KZY, Ohta H, Ishigaki Y. Effects of an equol-containing supplement on advanced glycation end products, visceral fat and climacteric symptoms in postmenopausal women: A randomized controlled trial. *PLoS One*. 2021;16(9):e0257332.

Background

- The primary soy isoflavones may be characterised as “phytoestrogens”, and properties have led to interest in the potential effects of soy isoflavones for women’s health, particularly during the menopausal period, which is characterised by decreases in oestrogen production and associated increases in symptoms associated with menopause.
- While soy is generally recognised for the phytoestrogen activity of its main isoflavones, it is the metabolism of daidzein by gut bacteria into a compound known as “equol” that may be of particular interest for the reported health effects of soy foods.
- Equol is exclusively a product of bacterial metabolism of daidzein, and does not appear in urinary excretion [its elimination pathway] unless soy foods are consumed in the diet. Or, as the present study tested, as a dietary supplement.

The Study

- The study was a randomised controlled trial in 57 postmenopausal women in Japan. Women randomised to the equol supplement intervention group consumed 10mg of equol per day [extracted from fermented soybeans]. The total duration of the intervention was 12-weeks.
- Outcome measures included blood lipid levels, visceral fat, and advanced glycation end products [AGEs], and the Climacteric Scale, a composite scale of menopausal symptoms.

Findings, Strengths & Limitations

- There was no significant difference in blood cholesterol, triglycerides, visceral fat levels, or skin autofluorescence [as a marker of AGEs], between groups.
- There was a significant difference between groups in the Climacteric Scale scores, which decreased from 16.4 to 11.3 in the equol supplement group and were unchanged from 14.7 to 14.7 in the control group over 12-weeks, respectively [between-group difference of 3.4].
- This was quite a poor study overall, and one which in the screening process for Deepdives looked good in the abstract summary.

Context

- The evidence for benefits from equol supplementation specifically is also confined to Japanese peri-menopausal women, and therefore some caution is warranted in extrapolating the findings beyond this population group.
- The Kupperman Index [KI] represents a more comprehensive grouping of 11 menopausal symptoms, meta-analysis suggests that soy phytoestrogens are not superior to placebo for menopausal symptoms assessed using the KI, however, they may reduce hot flushes.

Application

- Currently the data is too inconsistent to recommend either soy isoflavone supplementation, or equol supplementation specifically, for menopausal symptoms.
- Overall soy isoflavones exert a range of biological activity, similar to other flavonoids, that justify inclusion in the diet, but likely not as a supplement.