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Effect of whole foods and dietary patterns on markers of subclinical inflammation in weight stable overweight and obese adults – A Systematic Literature Review

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Reduction of subclinical inflammation is a potential target for chronic disease management. Adiposity is a known modifier of meta-inflammation, however the influence of dietary factors is less clear. This review examines the evidence from human trials evaluating effects of wholefoods or dietary patterns on circulating inflammatory markers in weight stable overweight and obese adults. It is the first review to investigate the effect of diet on inflammation, independent of changes in adiposity. This review was conducted using the Cochrane Collaboration Handbook for Systematic Reviews of Interventions, and data sources included Ovid MEDLINE, EMBASE, CINAHL and Cochrane. Quality of studies was evaluated using the Cochrane Collaboration's Risk of Bias Assessment tool. Twenty-eight studies were included assessing the effect of 17 different foods and dietary patterns over 38 inflammatory markers. Overall, wholefoods and dietary patterns were not found to have significant effects on inflammatory markers in weight stable overweight and obese adults. While wholegrains, soy, dairy, citrus fruits, nuts and chocolate, ginger and high total antioxidant capacity diets showed potential to improve inflammatory profiles, inconsistent findings made it difficult to produce definite conclusions. Study design characteristics contributing to these inconsistencies are discussed and recommendations for future research in this area are presented.

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Periodontal bone loss is not modulated by weight gain in an experimental mouse model of periodontitis

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Obesity is a risk factor for poor oral health. Here we test the hypothesis that weight gain due to high carbohydrate diets affects the inflammatory response in a mouse model of periodontitis.

300 male C57BL/6 mice (8 wk old) were fed ad libitum one of 15 isocaloric diets composed of differing percentages of total net metabolisable energy: protein (5, 10, 15%), carbohydrate (75, 70, 65%), fat was fixed at 20%. Mice were maintained on experimental diets for 18–19 weeks. The maxilla were dissected, stained and dried before taking standardised photographs. Periodontal bone loss was assessed by measurements of 3 positions of the second molar on both sides of the maxilla. Data were analysed, and 'Geometric Framework' surfaces generated using two generalised additive mixed models (GAMMs). In all models, the response variable was alveolar bone loss, and the identity of the animal from which the measurement was fitted as a random effect.

Increasing intake of total carbohydrates was associated with a linear increase in alveolar bone loss in mice ($p < 0.01$). On the other hand, protein intake had no effect on bone loss ($p = 0.29$). The mean concentration of IL-1β in gingival tissues was 1.046 ± 0.565 ng/mg total protein. There was a positive correlation between dietary carbohydrate content and pro-inflammatory cytokine IL-1β, although the effect was not statistically significant ($p = 0.08$). There was no evidence that weight moderates the effect of diet on bone loss (linear mixed model, $p = 0.47$).

This is the first study to explore macronutrient composition and types of carbohydrate on the development of natural occurring periodontitis. In the experimental model used an association between weight gain and the periodontitis associated bone loss was not found. However, increased carbohydrate intake significantly increased bone loss. Further research needs to show if weight gain is a risk factor for inflammatory diseases.

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The designer cytokine IC7Fc improves metabolic homeostasis in *db/db* mice

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Background: gp130 receptor ligands represent a therapeutic strategy for the treatment of type 2 diabetes (T2D) [1,2]. Accordingly, we have generated a novel chimeric cytokine, termed IC7Fc, and previously demonstrated it improves metabolic homeostasis in diet-induced obesity and insulin resistance. Whether IC7Fc improves glycemia in a mouse model of human T2D is unknown. Accordingly, in this study, we administered IC7Fc to the leptin receptor-deficient (*db/db*) mouse, which is an appropriate pre-clinical model to study the efficacy of anti-diabetic drugs.

Basic methodologies: Male diabetic *db/db* mice and their lean controls (*db/+*) received a single dose of IC7Fc (1 mg/kg i.p.) or saline in the fed state at 7, 13 and 17 wk of age as the animals transitioned from β-cell compensation (7 wk) to β-cell failure (17 wk). Blood glucose, plasma insulin and body composition were measured.

Major findings: The acute administration of IC7Fc reduced ($P < 0.001$) blood glucose in 7 wk old *db/db* mice within 90 min compared to saline treated *db/db* mice. The actions of IC7Fc progressively diminished along with the age-dependent progression of the disease such that at 17 wk of age, IC7Fc was ineffective in reducing blood glucose. Remarkably, we observed that a single dose of IC7Fc decreased ($P < 0.05$) total body mass, fat mass and fasting insulin 10 d post injection, effects not observed in age-matched lean (*db/+*) control mice.

Concluding statement: IC7Fc is an effective and potent therapy in *db/db* mice with a functional pancreas. Thus, IC7Fc may be a viable new treatment for T2D, provided patients still maintain β-cell function.

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Cognitive control of reward neurocircuitry in the activity-based anorexia rat model

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Anorexia nervosa (AN) has the highest mortality rate of any psychiatric disease, yet available treatments are largely ineffective, in part due to a lack of insight into the neurobiological drivers that underpin the condition. Functional neuroimaging in AN patients suggests that the interplay between underactive reward and overactive cognitive neurocircuits may underscore pathological body weight loss. Utilising the activity-based anorexia (ABA) rodent model, we have previously shown that chemogenetic activation of the ventral reward circuitry prevents and rescues precipitous body weight loss by increasing food intake. Here, we hypothesised that reducing activity in neurons of the prefrontal cortex with direct projections to ventral reward circuits would similarly improve body weight maintenance in ABA.

Female Sprague-Dawley rats ($N = 36$) underwent bilateral stereotaxic injections of a retrogradely-transporting Cre (AAV-pmSyn1-EBFP-Cre) into the nucleus accumbens (NAc) and coincident injections of either inhibiting [AAV-hSyn-DIO-hM4D(Gi)-mCherry] or activating [AAV-hSyn-DIO-hM3D(Gq)-mCherry] DREADD viruses into the prefrontal cortex (PFC). This dual viral strategy allows for precise modulation of only those PFC neurons that project to the NAc. Rats injected with the blank viral construct (AAV-hSyn-DIO-mCherry) were used as controls. During exposure to the ABA paradigm, which involves unhindered access to a running wheel and time-limited (90 min/day) access to food, all rats were administered CNO daily (0.3–3 mg/kg i.p.) at the onset of the dark phase for a maximum of 10 days.

Contrary to our hypothesis, chemogenetic inhibition of PFC-NAc projection neurons increased susceptibility to body weight loss in ABA ($\chi^1 = 6.33$, $p = 0.012$), by exacerbating running wheel activity compared to controls ($F = 10.16$, $p = 0.009$), with no effect on food intake ($t = 0.47$, $p = 0.65$). Taken together, our data indicate that both ventral reward and executive control circuits respectively impact on food intake and running activity, both essential elements of the ABA phenotype and the AN condition that contribute to pathological body weight loss.

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The role of amyloid beta$_{42}$ in heart disease

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Background: Heart failure is a major cause of mortality in obesity and can occur in the absence of other established risk factors such as hypertension. This is known as obese cardiomyopathy and an alteration in cardiac metabolism is thought to be one of the key drivers of the disease, however, little is known on the contributing factors. Serum levels of the Alzheimer's disease protein amyloid beta 42 ($A\beta_{42}$) increase in obesity and our research group has recently found that mice administered $A\beta_{42}$, to increase levels to those seen in obesity, develop cardiac dysfunction.

Purpose/aims: The aim of our research is to determine the mechanisms of action of $A\beta_{42}$ on cardiomyocytes in order to better understand the pathogenesis of the disease and potentially uncover therapeutical targets to prevent and treat it.

Methods: Hearts from mice administered $A\beta_{42}$ or scrambled peptide were examined using RNA sequencing, western blotting and qPCR. H9C2 cardiomyocytes were used to screen for receptors and signalling pathways mediating the effects of $A\beta_{42}$.

Results/conclusion: Analysis of RNA sequencing data revealed a number of signalling pathways that may be important in $A\beta_{42}$ mediated changes including the nerve growth factor and fibroblast growth factor signalling pathways. Furthermore, mice administered $A\beta_{42}$ and $A\beta_{42}$ treated cardiomyocytes showed evidence of inflammatory and ER stress responses. Inhibition of protein kinase D (PKD) in $A\beta_{42}$ treated cardiomyocytes impaired these responses, suggesting it may be an important signalling molecule.

To further understand these findings, the importance of PKD in $A\beta_{42}$-mediated cardiomyopathy will be examined in mice with a cardiac specific loss of PKD activity. In addition, the effectiveness of drugs developed for the treatment of Alzheimer's disease to preventing obese cardiomyopathy in a mouse model of obesity will be examined.

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Why do some mice resist weight gain on a high caloric diet? An omics approach

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Background: It's known that laboratory mouse strains respond differently to high caloric feeding in terms of their adiposity and glucose tolerance. However, significant inter-individual variability also occurs within strains. What drives this difference given background genetics is controlled is unknown, but may reveal insights regarding maintenance of leanness.

Methods: We screened 30 C57BL6/J mice fed a high fat/high sucrose diet (HFHS) for 8-weeks and identified three mice discordant for adiposity (i.e. they remained lean) compared to their