Abstract

**Background:** Dysregulation of one-carbon metabolism (OCM) is related to metabolic syndrome (MetS) through various mechanisms including epigenetics. Diet plays a central role in ensuring normal OCM regulation by supplying multiple nutrients. Foods such as whole grains and fish have been proposed to regulate OCM and thereby potentially affecting MetS via OCM. Whole grain is rich in several OCM nutrients and higher whole grain intake has been associated with lower plasma homocysteine (Hcy) concentrations. Furthermore, fish are rich in vitamin B12 and choline as well as the fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) which might also play a role in OCM regulation and epigenetics.

**Aim:** This PhD thesis investigates the role of diet in OCM regulation and the potential association between OCM and MetS. We further investigated whether a dietary intervention with high whole grain intake can affect OCM metabolites in plasma. Finally, we explored whether a fish oil supplement can induce epigenetic changes and whether these are related to MetS features.

**Methods:** In two cross-sectional studies using the 3G-cohort, we investigated associations between plasma OCM metabolites, \(s\)-adenosylmethionine (SAM), \(s\)-adenosylhomocysteine (SAH) and Hcy, and diet. Associations between OCM metabolites and MetS features were also investigated. In an 8-week human cross-over intervention study we investigated whether a diet rich in whole grain compared to a diet rich in refined grain could affect OCM metabolites. Finally, we investigated whether supplementing 9-month old infants with fish oil compared to sunflower oil could elicit epigenetic changes, through DNA methylation, and whether this was related to changes in MetS features.

**Results:** OCM metabolites were associated with MetS features, with higher concentrations of SAM, SAH and Hcy being associated with a more adverse risk profile. Different OCM metabolites were independently associated with different MetS features. In the cross-sectional analysis of foods and OCM metabolites, higher whole grain was associated with lower Hcy and higher fish intake was associated with lower Hcy and SAH. No associations were found between EPA, DHA and OCM metabolites. In contrast to the findings in the cross-sectional study, the whole grain intervention trial did not lead to changes in plasma OCM metabolites despite betaine and choline intake being higher in the whole grain period. Supplementing fish oil to infants lead to changes in DNA methylation in multiple genes, and some of these methylation changes were associated with changes in MetS features, such as blood pressure and insulin resistance.
**Conclusion:** OCM is associated with MetS features, however, it is still not known whether this is a cause or a consequence of MetS. Specific foods such as whole grain and fish are associated with OCM metabolites, suggesting that OCM could be manipulated by dietary interventions. However, a whole grain intervention did not change OCM metabolites suggesting that alternative interventions should be considered. We found that supplementing with fish oil lead to epigenetic changes, but we did not find any evidence that this was linked to OCM. More studies are needed to link foods, OCM, epigenetics and MetS in order to find possible preventive and therapeutic possibilities.