Metabolic health, vascular function and cognition

SUMMARY

The number of individuals suffering from type 2 diabetes is rapidly rising with more than 537 million cases worldwide in 2021. Prediabetes is an intermediate condition of insulin resistance resulting in temporary glucose excursions, but not yet as pronounced as in type 2 diabetes. Together with obesity, dyslipidemia, and hypertension, this condition is part of the metabolic syndrome. Individuals with the metabolic syndrome have a predisposition for development into type 2 diabetes, but also have an increased risk for cardiovascular diseases, and cognitive decline. This great health impact can be influenced by lifestyle. A healthy diet is a cornerstone in maintaining metabolic, vascular, and cognitive health, which is shown to be effective in delaying or even preventing the onset of non-communicable diseases such as type 2 diabetes, cardiovascular disease, and cognitive disorders. The research in this thesis aimed to investigate the effects of different dietary components or foods on metabolic health, vascular function, and cognition in humans.

Brain-derived neurotrophic factor (BDNF) is an important protein for neuronal plasticity as well as energy metabolism. Therefore, it seems to be an attractive target to improve both cognitive health and metabolic health. Various controlled human intervention studies have been conducted aiming at elevating BDNF concentrations. In Chapter 2, a systematic review provided an overview of the effects of these dietary interventions on BDNF concentrations in human adults. In total, 48 dietary interventions were selected after a systematic literature search and clustered based on dietary patterns or foods, diets based on energy intake, and supplements. The supplements cluster was further divided into vitamins and minerals, polyphenols, long-chain omega-3 polyunsaturated fatty acids, probiotics, and miscellaneous food supplements. In particular, interventions with whole foods and interventions with polyphenols showed the possibility to significantly increase peripheral BDNF concentrations, whereas for the other interventions no clear effect could be found. Regarding polyphenols, phenolic acids, and other phenolic compounds were responsible for the positive effect on BDNF. We concluded that dietary interventions have potential to elevate circulating BDNF concentrations.

Upon these review results, we speculated that the effects of dietary factors on fasting BDNF concentrations could be mediated by changes in insulin and/or glucose concentrations. In Chapter 4 the postprandial effects of the three dietary macronutrients fat, carbohydrates, or protein on BDNF concentrations were investigated side by side. This enabled us to differentiate between the role of insulin and

glucose in BDNF changes, since each macronutrient triggers a different insulin and glucose response. In total, 18 healthy, but overweight/obese men participated in this randomized, double-blind, controlled cross-over trial. Three postprandial tests were performed with either a high-fat, high-carbohydrate, or high-protein meal with a wash-out of one week in between. As expected, postprandial insulin and glucose concentrations changed upon consumption of the dietary macronutrients and were significantly different between meals. However, postprandial BDNF concentrations were not significantly different between meals. Chapter 2 already highlighted differences in BDNF concentrations when measured in serum compared to plasma due to the predominant storage of BDNF in platelets. Again, BDNF concentrations were higher in serum than in plasma. We concluded that macronutrients do not differently influence postprandial serum and plasma BDNF concentrations, indicating that there is no effect of acute changes in insulin and glucose on BDNF. More research is needed to investigate the role of insulin and glucose on BDNF in a long-term situation.

Previous research showed beneficial effects of the egg protein hydrolysate NWT-03 on peripheral cardiovascular risk factors. As the small peptide fragments might be able to transfer to the brain, we speculated that NWT-03 consumption might also have beneficial effects on central risk factors. In Chapter 3 we investigated the effects of a daily intake of 5 g NWT-03 for 4 weeks on parameters reflecting cognitive function, as well as serum BDNF concentrations. In total, 79 men and women with the metabolic syndrome participated in this randomized, double-blind, placebo-controlled study. Cognitive function was assessed by the anti-cue reaction time test measuring impulse control, and the psychomotor vigilance test measuring sustained attention three times each period with a wash-out of 2-8 weeks in between. We evaluated the change in cognitive performance between the start and end of each experimental period. NWT-03 consumption significantly decreased response times of the anti-cue reaction time test compared to placebo, but not of the psychomotor vigilance test. No effects were found on serum BDNF concentrations. We concluded that, regardless of stable BDNF concentrations, NWT-03 has potential to improve cognitive function within the executive domain.

In Chapter 5 our target population shifted from the metabolic syndrome to prediabetes. In total, data of 34 men and women with prediabetes was used in a cross-sectional correlation analysis. We investigated whether the insulin resistant condition in prediabetes was already linked to disturbed cognitive performance as seen with type 2 diabetes, and whether this was linked to disturbances in peripheral and brain vascular function. In more detail, we evaluated the associations between insulin sensitivity and

peripheral vascular function, brain vascular function, and cognitive performance. Insulin sensitivity was measured by the hyperinsulinemic euglycemic clamp and expressed as the M-value, or as HOMA-IR. Peripheral vascular function was evaluated with PWA or PWV as a measure of arterial stiffness, whereas brain vascular function was evaluated with gray matter CBF. Finally, cognitive performance was evaluated using a set of neuropsychological tests by CANTAB. Insulin sensitivity did not show a clear correlation with cognitive performance or brain vascular function, but significantly correlated with peripheral vascular function. In turn, brain vascular function significantly correlated with cognitive performance. The correlation between peripheral and brain vascular function remains speculative. We concluded that disturbances in peripheral vascular can already be observed with prediabetes. However, potential disturbances in the periphery and the brain are not clearly linked. Whether this is due to the fact that it is too early in the development of diabetes or that these processes are epiphenomena occurring side by side needs further investigation.

The cross-sectional data in Chapter 5 was obtained as part of a dietary intervention study evaluating the effects of almonds on glucose metabolism, which is described in Chapter 6. Nuts are part of the dietary guidelines for cardiovascular prevention because of their lipid lowering effects. In addition, improvement of insulin sensitivity and glucose metabolism could prevent the development of prediabetes into type 2 diabetes. However, findings on such health effects of almonds are inconclusive, which could be related to fluctuations in body weight. Therefore, we investigated the effects of long-term almond consumption on glucose metabolism under free living conditions, *i.e.*, without detailed dietary instructions on how to incorporate the almonds into the habitual diet. Glucose metabolism was assessed by a hyperinsulinemic euglycemic clamp to measure insulin sensitivity, a mixed meal test to measure postprandial glucose concentrations, and a continuous glucose monitor to measure free-living glucose profiles. In total, 34 prediabetic men and women consumed 50 g almonds daily for 5 months in this randomized controlled trial with a wash-out of 2 months. No detailed instructions were provided related to consumption of the almonds, mimicking real life conditions. At the end of each experimental period, the different methodologies to evaluate effects on glucose metabolism were assessed side by side. Almond consumption significantly decreased insulin sensitivity, and increased postprandial glucose concentrations, and fasting insulin concentrations, as compared to the control period. Continuous glucose profiles just did not reach statistical significance. In the almond period, BMI and waist circumference also increased significantly, as well as the energy intake as derived from the food frequency questionnaires. This suggests that without additional dietary guidelines, almonds were consumed on top of the habitual

diet, not fully replacing other energy-dense food items. We concluded that long-term almond consumption under free living conditions has adverse effects on glucose metabolism.

Based on a systematic review, a cross-sectional study, and three human intervention trials in this thesis, we conclude that dietary interventions are able to influence fasting BDNF concentrations in favor of metabolic and cognitive health, but not postprandial BDNF concentrations. NWT-03 consumption is an additional measure to improve cognitive health. Regarding prediabetes, correlations indicated that concomitant disturbances in peripheral vascular function can already be observed, but insulin sensitivity and glucose metabolism cannot be improved by adding almonds to the diet.