Metabolic health, vascular function and cognition

IMPACT

The main objective of this thesis was to examine the effects of diet on metabolic health, vascular function, and cognition in subjects at risk for type 2 diabetes and cardiovascular disease development. We systematically reviewed that dietary interventions can elevate circulating BDNF concentrations, specifically whole foods and polyphenols. We concluded that these effects could be mediated by insulin. However, in our controlled intervention study we showed that macronutrients did not differently affect postprandial BDNF concentrations, regardless of acute changes in glucose and insulin concentrations. The egg protein hydrolysate NWT-03 also did not change serum BDNF concentrations. However, it did have the potential to improve cognitive function within the executive function domain. The impact of NWT-03 supplementation might be of great interest as it appeared to improve not only peripheral cardiovascular risk factors [1-3], but also central risk factors.

In contrast to the well-known lipid lowering effects of almonds, we found that long-term almond consumption did not improve glucose metabolism. This unexpected adverse effect can partly be due to the observed increase in body weight during the almond intervention period, which affects insulin sensitivity. Regarding this risk of weight gain, it should be taking into consideration to extend the dietary guidelines with instructions on how to incorporate nuts in the healthy diet. Overall, lifestyle modifications are key to attenuate or prevent disease development, in particular, disturbances in peripheral vascular function which can already be observed in prediabetes. The potential impact of the research in this thesis will be discussed here from a societal and economic perspective.

Societal relevance

The metabolic syndrome, covering abdominal obesity, insulin resistance, hypertension, and hyperlipidemia, has become a global epidemic [4]. Besides these well-known characteristics, the metabolic syndrome is also associated with cognitive decline and dementia [5] The metabolic syndrome often resembles the prevalence of obesity, and increases the risk of cardiovascular disease and type 2 diabetes. Cardiovascular disease is the number one cause of morbidity and mortality worldwide, with 17.9 million deaths in 2019 [6], whereas type 2 diabetes has prevalence estimates of 463 million in the same year [7]. As with both metabolic syndrome and prediabetes there are no clear signs or symptoms [8, 9], the prevalence is probably even higher than type 2 diabetes. Furthermore, estimates vary based on the criteria used [4]. For clinical diagnosis and

treatment, it is relevant to define pathology thresholds, for example, for prediabetes in terms of glucose concentrations [10]. In contrast to genetic predisposition for disease development, there are modifiable lifestyle risk factors such as obesity, physical inactivity, and an unhealthy diet [11]. Therefore, it is of great importance to examine the health effects of diet to decrease the negative social impact of these diseases.

Based on our systematic review, we posed that dietary interventions can elevate circulating BDNF concentrations. BDNF is a protein involved in neuronal survival and growth [12], but also acts as a metabolic modulator [13]. This makes dietary interventions a potential strategy to improve metabolic and cognitive health. Unfortunately, we did not find changes in BDNF concentrations upon consuming diets enriched in either one of the different macronutrients. However, dietary macronutrient composition is still important to reduce the risk of cardiovascular disease [14]. NWT-03 supplementation also contributes to an improved cardiovascular and metabolic health [3], and in addition to that, we here provided evidence for its contribution to improve cognitive health. The dietary guidelines advise to consume nuts as part of a healthy diet to support cardiovascular risk reduction. Almonds are indeed associated with ameliorations in various factors related to lipid metabolism [15]. However, we found no beneficial effects of almonds on glucose metabolism. This lack of effect could only partly be attributed to the observed weight gain. When body weight is maintained, not just dietary factors, but a balanced diet is still key to health effects. Overall, dietary interventions have strong implications for public health. These implications might be even bigger as dietary effects might be passed on to the next generation via epigenetic changes [16].

Economic relevance

The economic burden of the metabolic syndrome is in trillions, including health care costs and loss of potential economic activity [4]. The major components of costs are disease management and particularly the consequent cardiovascular events [17]. Costs increase when more conditions of the metabolic syndrome are met. In 2020, 210 billion euros were spent in Europe on cardiovascular disease [18], and in 2021, 173 billion euros on type 2 diabetes [19]. Since the prevalence of the metabolic syndrome increases with age [20], this economic burden will rise in the future because of the continuously ageing population. Therefore, it is of importance to implement treatment and management strategies, but also preventive strategies to lower the number of individuals with the metabolic syndrome. Cost-effective lifestyle interventions can be applied to attenuate or prevent disease development. Here we showed that dietary factors such as NWT-03

and dietary interventions with whole foods or polyphenols targeting BDNF improved metabolic risk markers and markers of cognitive health, thereby lowering the health and economic burden of the metabolic syndrome and its consequences.

Target population

All human intervention studies presented in this thesis were performed in (older) adults. While the first study with NWT-03 included men and women with the metabolic syndrome, the study with dietary macronutrients included healthy overweight and obese men, and the study with almonds both overweight and obese men and women with prediabetes, but not yet diabetes. These study populations all have an increased risk for developing cardiovascular disease and type 2 diabetes, but hypothetically can benefit most of the dietary interventions aimed to reverse disease development. The study with dietary macronutrients focused only on men in order to eliminate possible sex differences. Targeting men was applied to the initial design of the study to examine postprandial vascular function [21], but this selection was also favorable in the study presented here as sex hormones or steroids seemingly modulate BDNF regulation [22]. Moreover, discrepancies exist in BDNF concentrations between different populations, *i.e.*, BDNF concentrations are influenced by the diabetic state [23]. Future research on BDNF should take into account these differences between target populations. Another focus should be on healthy individuals to examine BDNF reference concentrations and whether they can benefit of such dietary interventions as presented in this thesis by boosting BDNF.

Translation into practice

The research findings presented in this thesis have been published or are in process of being published in peer-reviewed scientific journals, which makes the obtained knowledge openly accessible for scientists, health professionals, and the general public. One of the goals is to stimulate more research on the effects of dietary interventions on metabolic health, vascular function, and cognition. Furthermore, the obtained information might be relevant to authorities, policy makers, and health agencies to be implemented in the dietary guidelines supporting a healthy diet. For example, nut consumption is already part of the generally advised dietary guidelines. However, we found no beneficial effects of almonds when they are added to the diet. It could be that more supporting guidelines are needed on how to incorporate them into the diet to result in its proclaimed health benefits. Feasibility of diet changes is important for its

success. Findings have also been presented at scientific conferences to share knowledge and increase awareness of the important role of a healthy diet in the treatment, management, and prevention of cardiovascular disease and type 2 diabetes.

REFERENCES

1. Wang Y, Landheer S, van Gilst WH, van Amerongen A, Hammes HP, Henning RH, et al. Attenuation of Renovascular Damage in Zucker Diabetic Fatty Rat by NWT-03, An Egg Protein Hydrolysate with ACE- and DPP4-Inhibitory Activity. PLoS One. 2012;7(10):e46781.
2. Plat J, Severins N, Morrison S, Mensink RP. Effects of NWT-03, an Egg-Protein Hydrolysate, on Blood Pressure in Normotensive, High-Normotensive and Mild-Hypertensive Men and Women: A Dose-Finding Study. Br J Nutr. 2017;117(7):942-50.
3. Plat J, Severins N, Mensink RP. Improvement of Pulse Wave Velocity and Metabolic Cardiovascular Risk Parameters Through Egg Protein Hydrolysate Intake: A Randomized Trial in Overweight or Obese Subjects with Impaired Glucose Tolerance or Type 2 Diabetes. Journal of Functional Foods. 2019;52:418-23.
4. Saklayen MG. The Global Epidemic of the Metabolic Syndrome. Curr Hypertens Rep. 2018;20(2):12.
5. Birdsill AC, Carlsson CM, Willette AA, Okonkwo OC, Johnson SC, Xu G, et al. Low Cerebral Blood Flow is Associated with Lower Memory Function in Metabolic Syndrome. Obesity (Silver Spring). 2013;21(7):1313-20.
6. World Health Organization. Cardiovascular diseases (CVDs) fact sheet. June 2021. [Internet]. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). [Accessed on 04/04/2022].
7. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and Regional Diabetes Prevalence Estimates for 2019 and Projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th Edition. Diabetes Res Clin Pract. 2019;157.
8. Stern MP, Williams K, Gonzalez-Villalpando C, Hunt KJ, Haffner SM. Does the Metabolic Syndrome Improve Identification of Individuals at Risk of Type 2 Diabetes andor Cardiovascular Disease. Diabetes Care. 2004;27:2676-81.
9. Alvarez S, Coffey R, Algotar AM. Prediabetes. StatPearls Publishing; 2021.
10. Ferrannini E, Gastaldelli A, Iozzo P. Pathophysiology of Prediabetes. Med Clin North Am. 2011;95(2):327-39, vii-viii.
11. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and Management of the Metabolic Syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112(17):2735-52.
12. Kowianski P, Lietzau G, Czuba E, Waskow M, Steliga A, Morys J. BDNF: A Key Factor with Multipotent Impact on Brain Signaling and Synaptic Plasticity. Cell Mol Neurobiol. 2018;38(3):579-93.
13. Marosi K, Mattson MP. BDNF Mediates Adaptive Brain and Body Responses to Energetic Challenges. Trends Endocrinol Metab. 2014;25(2):89-98.
14. Brandhorst S, Longo VD. Dietary Restrictions and Nutrition in the Prevention and Treatment of Cardiovascular Disease. Circ Res. 2019;124(6):952-65.
15. Musa-Veloso K, Paulionis L, Poon T, Lee HY. The Effects of Almond Consumption on Fasting Blood Lipid Levels: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. J Nutr Sci. 2016;5:e34.
16. Gómez-Pinilla F. Brain Foods: The Effects of Nutrients on Brain Function. Nat Rev Neurosci. 2008;9(7):568-78.
17. Scholze J, Alegria E, Ferri C, Langham S, Stevens W, Jeffries D, et al. Epidemiological and Economic Burden of Metabolic Syndrome and Its Consequences in Patients with Hypertension in Germany, Spain and Italy; A Prevelance-Based Model. BMC Public Health. 2010;10(529).

18. European Society of Cardiology. Fighting cardiovascular disease – a blueprint for EU action. June 2020. [Internet]. Available from: https://www.mepheartgroup.eu/wp-content/uploads/05748-CVD-plan_FINAL.pdf. [Accessed on 06/04/2022].
19. International Diabetes Federation. IDF Diabetes Atlas, 10th edition. Diabetes around the world in 2021. [Internet]. Available from: https://diabetesatlas.org/. [Accessed on 06/04/2022].
20. Hildrum B, Mykletun A, Hole T, Midthjell K, Dahl AA. Age-Specific Prevalence of the Metabolic Syndrome Defined by the International Diabetes Federation and the National Cholesterol Education Program: The Norwegian HUNT 2 Study. BMC Public Health. 2007;7:220.
21. Smeets E, Mensink RP, Joris PJ. Dietary Macronutrients Do Not Differently Affect Postprandial Vascular Endothelial Function in Apparently Healthy Overweight and Slightly Obese Men. Eur J Nutr. 2021;60(3):1443-51.
22. Chan CB, Ye K. Sex Differences in Brain-Derived Neurotrophic Factor Signaling and Functions. J Neurosci Res. 2017;95(1-2):328-35.
23. Rozanska O, Uruska A, Zozulinska-Ziolkiewicz D. Brain-Derived Neurotrophic Factor and Diabetes. Int J Mol Sci. 2020;21(3).