Human cholesterol metabolism

Summary

For decades, cardiovascular disease (CVD) has been the major cause of morbidities and mortalities worldwide. It is known that atherosclerosis is the process underlying the development of CVD. Elevated blood cholesterol concentrations, especially low-density lipoprotein cholesterol (LDL-C), is a well-defined causal risk factor for the atherogenic process. Therefore, investigating processes regulating cholesterol homeostasis will provide important information to further improve our understanding of cholesterol metabolism and consequently cardiovascular health. Cholesterol homeostasis is maintained by the interplay between intestinal cholesterol absorption, endogenous cholesterol synthesis, and bile acid synthesis and excretion. A high intestinal cholesterol absorption is associated with a higher risk for CVD. Furthermore, inflammation plays an important role in almost all stages of atherosclerosis. Lifestyles and dietary changes have been recommended for CVD prevention i.e. increasing physical activity and promotion of weight loss. However, effects of physical activity, diet-induced weight loss and inflammation on cholesterol metabolism characteristics are largely unknown.

The aim of the studies described in this thesis was to investigate the effects of aerobic exercise and diet-induced weight loss as well as of a pro-inflammatory trigger (lipopolysaccharides [LPS]) on cholesterol metabolism characteristics. In addition, effects of plant sterol content in three different lipid emulsions used for home parenteral nutrition (HPN) on liver function and inflammatory markers were studied.

In **chapter 2**, characteristics of cholesterol metabolism i.e., intestinal cholesterol absorption and endogenous cholesterol synthesis in various metabolic disturbances were systematically reviewed. This chapter also described the validity of non-cholesterol sterol concentrations as markers for intestinal cholesterol absorption and endogenous cholesterol synthesis. Overall, there was an indication of distinctive patters for cholesterol absorption and cholesterol synthesis, suggesting that individuals with very different metabolic conditions can be classified as cholesterol absorber or cholesterol synthesizers. **Chapter 3** describes the effects of an 8-week aerobic exercise program training on markers of cholesterol absorption and cholesterol synthesis. In this study, 17 apparently healthy overweight and obese older men participated in a randomized, cross-over study. Compared with the control period, total cholesterol (TC)-standardized level of the cholesterol absorption marker campesterol tended to decrease with no change in the cholesterol synthesis marker lathosterol after 8 weeks. In **chapter 4**, we investigated the effects of diet-induced weigh loss on markers for cholesterol absorption and synthesis in abdominally obese men. In this chapter, we also examined cross-sectionally baseline differences between abdominally obese and normal weight men. For this, 54 apparently healthy abdominally obese and 26 normal weight men were recruited. Abdominal obese men were randomized either into a weight loss group or a non-weight loss control group. Subjects in the weight loss group consumed a caloric restricted diet for 6 weeks

followed immediately by a 2-week weight maintenance period to reach a waist circumference below 102 cm. In non-weight loss control group, subjects were instructed to maintain their habitual dietary intakes and physical activity levels. After weight loss, the TC-standardized levels of the cholesterol absorption marker cholestanol increased and the cholesterol synthesis marker lathosterol decreased. Cholesterol metabolism characteristics between previously abdominal obese and normal weight men became comparable. Changes in TC-standardized levels of cholestanol were not only negatively related to weight loss, but also negatively to changes in visceral fat volume. Cross-sectionally, mediation analyses revealed roles of visceral fat and intrahepatic fat in mediating the relationships between body mass index and markers for cholesterol absorption and synthesis. **Chapter 5** describes the effects of the acute proinflammatory trigger LPS on lipid and lipoprotein concentrations, high-density lipoprotein (HDL) functionality as well as markers of cholesterol metabolism. From a randomized study including 32 healthy young male subjects, we selected the eight subjects from the placebo arm which means they were infused with LPS only. LPS infusion decreased LDL-C concentrations, HDL functionality, markers of endogenous cholesterol synthesis as well as bile acid formation, but increased triglycerides concentrations. No effect on cholesterol absorption markers was observed. This study also demonstrated that desmosterol (endogenous cholesterol synthesis marker) and 7α-hydroxycholesterol (bile acid formation marker) were positively correlated with various markers for inflammatory responses, while there were negative correlations between changes in desmosterol and 7α-hydroxycholesterol and inflammatory response markers. The aim of a pilot study with 58 stable adult patients with intestinal failure receiving HPN was to investigate the effect of the plant sterol content in three different lipid emulsions on markers of inflammation and liver function (**Chapter 6**). It was concluded that patients receiving Intralipid had higher plasma plant sterol concentrations compared to those receiving ClinOleic or SMOFLipid emulsions. There were significant positive correlations between plasma plant sterol sterols and markers of liver function. Furthermore, patients receiving SMOFLipid had concentration of triglycerides and liver function markers apparently within normal values compared to those receiving ClinOleic or Intralipid emulsions.

Overall, in this thesis we focused on human cholesterol metabolism; more specifically the effects of aerobic exercise training, nutrition and inflammation on markers for intestinal cholesterol absorption and endogenous cholesterol synthesis. it was demonstrated that increased aerobic exercise, diet-induced weight loss and infusion of proinflammatory trigger (LPS) are related to changes in cholesterol metabolism characteristics. Future studies are needed to assess whether these changes have beneficial effects on the risk of CVD.