Cholesterol efflux as a measure of HDL functionality in humans

Valorisation

Social and economic relevance

Despite considerable progress in tackling the development of cardiovascular disease (CVD), it remains one of the leading causes of death. On a yearly basis, CVD is responsible for 3.9 million of death in Europe and account for 31% of all global death worldwide. In 2015, more than 85 million people were living with CVD in Europe. In this context, CVD represents also a major economic burden. Overall, in Europe, it is estimated that CVD cost 210 billion euros yearly, including cost due to health care, loss of productivity and to informal care of people with CVD [1, 2]. Therefore, it is essential to better understand the underlying mechanism leading to CVD, in order to develop effective strategies to prevent or delay CVD development.

Atherosclerosis is the main underlying pathology in CVD development and dyslipidemia is an important risk factor for atherosclerosis. Interventions targeting low-density lipoprotein cholesterol (LDL-C) have been successfully developed [3, 4]. However, subjects using therapies to reduce their LDL-C concentrations often fail to reach the desired LDL-C concentrations, leading to a remaining risk for CVD. It is therefore essential to discover other approaches to further reduce CVD risk. Increasing high-density lipoprotein cholesterol (HDL-C) concentrations is also an attractive target, as many epidemiological studies have found an inverse association between HDL-C concentrations and CVD risk [5, 6]. However, raising HDL-C levels failed to reduce CVD risk [7], while recent evidences suggest that increasing the cholesterol efflux capacity of HDL particles protects against the development and the recurrence of CVD [8-10]. It is therefore time to switch the research focus from HDL-C to HDL functionality, i.e. HDL-mediated cholesterol efflux capacity.

The most important behavioral risk factors for CVD are unhealthy diets, lack of physical activity, smoking and an excessive use of alcohol [2]. Foods containing bioactive components, so-called functional foods, can be used for the prevention of CVD, and beneficial effects on lipid metabolism have already been shown [11]. However, functional foods aiming at increasing HDL cholesterol efflux capacity are not yet available, and development of such food items is therefore needed. In this thesis, we aimed to identify potential ingredients that might improve HDL-mediated cholesterol efflux. We first hypothesized that theobromine could be one of the potentially healthy components in cocoa. Indeed, dark chocolate consumption is a highly consumed food and has been associated with a reduction in the risk to develop cardiovascular disease (CVD) [12]. It is therefore of interest to identify which compound(s) in cocoa is/are responsible for the beneficial effects, as the identified compound(s) could subsequently be used as functional ingredients.

Unfortunately, we did not find that theobromine had any beneficial effects on HDL cholesterol efflux capacity. Secondly, nowadays many functional food products enriched in plant sterol and plant stanol, such as margarines, have been developed and were shown to reduce cholesterol concentrations [13]. However, in line with theobromine, plant sterol and stanol enriched products did also not improve HDL cholesterol efflux capacity.

Relevance of measurements

The research described in this dissertation helps to better understand how HDL cholesterol efflux capacity can be modulated and improved in humans, in order to reduce CVD risk. In 2016, over 1.9 billion of the global adult population was overweight; of these more than 650 million were obese. Because people with overweight and obesity are at high risk to develop CVD [14], the effect of weight loss on HDL efflux capacity is therefore of clinical importance when studying CVD risk. In addition, the majority of the population spends a large part of the day in the postprandial state, and disturbances in postprandial lipoproteins metabolism are important risk markers for CVD [15, 16]. In this context, measuring not only fasting but also postprandial cholesterol efflux capacity is of importance. Furthermore, the microRNAs (miRNAs) signature has been demonstrated to be altered in diseased subjects [17]. A better understanding of the involvement of specific miRNAs in the modulation of HDL-mediated cholesterol efflux is of interest, and could help for the development of strategies using miRNA-based therapies. MiRNAs therapies are currently being developed, and Miravirsen, a miR-122 antagonist, is currently in phase II clinical trials and may be the first miRNA-targeted drug receiving FDA (Food and Drug Administration) approval for the treatment of hepatitis C [18, 19]. Ultimately, the discovery of new therapies targeting the increase of HDL functionality, either via miRNAs or not, would help to reduce the costs generated by the treatment of CVD.

Translation into practice

With the present thesis, we expect to increase the awareness of the medical, societal and economic consequences of CVD, and to highlight the potential impact of genetic background, miRNAs and nutrition on HDL functionality as related to CVD risk. The results presented in this thesis have been presented at several national and international conferences. Furthermore, the research findings have been or will be submitted to international peer-reviewed scientific journals.

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