Introduction

The global prevalence of type 2 diabetes is increasing rapidly and nowadays affects almost 250 million people. Cardiovascular disease is the most prevalent complication of type 2 diabetes, and primarily responsible for the increased morbidity and mortality rates in these patients. The present thesis focuses on the possible meal-induced metabolic mechanisms underlying the increased cardiovascular risk in type 2 diabetes.

In Western society, we are in the postprandial state for a large part of the day. Metabolic risk factors for cardiovascular disease are usually measured in the fasting state, which only represents a small part of the actual metabolic state. Furthermore, the fasting state does not always predict the metabolic processes in the postprandial phase. Disturbances in postprandial metabolic control may substantially contribute to development of cardiovascular disease.

The main aim of the studies presented in this thesis was to investigate associations of postprandial metabolism with cardiovascular disease risk. The contribution of fasting and post-load glucose, triglyceride and (pro)insulin levels and of fasting CETP concentration to cardiovascular disease risk is investigated. These questions were addressed in the Hoorn prandial study and in the Hoorn Study.

Study design

In postmenopausal women, diabetes confers a higher relative risk for cardiovascular disease than in men and fasting and postprandial triglyceride levels are increased. Therefore, most of the research questions were addressed in postmenopausal women with diabetes.

The Hoorn prandial study was designed to elucidate the relative contribution of postprandial hyperglycaemia and postprandial hypertriglyceridaemia to cardiovascular disease risk. Postmenopausal normoglycaemic women and women with type 2 diabetes participated in a postprandial study in order to determine postprandial glucose, insulin, triglyceride and CETP concentrations (Chapter 2, 3, 4 and 9).
Summary

The Hoorn Study is a population-based cohort study consisting of 2484 participants of which baseline measurements started in 1989. In 2000-2001, at the age of 60-85 years, participants with type 2 diabetes, impaired glucose metabolism and normal glucose metabolism were re-invited for follow-up examination. The Hoorn Study data were used for the analyses presented in Chapter 5, 6, 7, and 8.

Main findings and discussion

In Chapter 2, potential determinants of fasting and postprandial glucose and triglyceride excursions were assessed. Fasting and postprandial glucose levels were not associated with each other in women with normal glucose metabolism (NGM), but in patients with DM2 they did. The main associates of postprandial glucose in NGM women were age and fasting triglycerides. In contrast, fasting triglyceride levels were the strongest determinant of postprandial triglyceride levels in women with NGM and diabetes, which was in line with earlier studies.

In Chapter 3, we investigated the relative contribution of these postprandial glucose and triglyceride excursions to carotid intima media thickness (cIMT), as a marker for atherosclerosis. Postprandial glucose levels were associated with cIMT in women with NGM. Of interest, no such association was found with either fasting or 2-hour glucose levels after an oral glucose tolerance test (OGTT). Measuring glucose levels following a meal is probably more representative for daytime glucose levels. These findings require prospective studies to confirm that post-load glucose levels following a meal is a stronger predictor of future risk of macrovascular and microvascular complications than post-OGTT glucose levels. Nevertheless, this study suggests that the postprandial glucose concentrations and/or the mechanisms responsible for postprandial glucose regulation, play a role in atherosclerosis.

No an association between fasting or postprandial triglycerides and cIMT was found (Chapter 3). The composition of lipoproteins, which was not assessed in the postprandial state may be more strongly associated with atherosclerosis. Alternatively, given the changes in lipid metabolism that occur after the menopause, the postprandial triglyceride response in postmenopausal women might not be an appropriate reflection of triglyceride exposure in the past. Despite the increased cardiovascular risk due to diabetes in postmenopausal
women, until now, very few studies determined the relation between postprandial triglycerides and cardiovascular disease for men and women separately. Longitudinal studies, stratified for gender may probably elucidate whether postprandial triglycerides or lipoprotein composition are a risk factor for cardiovascular disease in postmenopausal women.

An index for early insulin secretion was used in Chapter 4 to describe meal-induced early insulin secretion. In women with type 2 diabetes, early insulin secretion following the fat-rich meal was higher than following the carbohydrate-rich meal. In type 2 diabetes and in NGM, the early insulin secretion index was associated with lower postprandial (2 and 4 hour) glucose levels. The hypothesis that modification of diet composition might improve blood glucose levels without weight loss in patients with type 2 diabetes, is supported by these data. Managing hyperglycaemia by changing meal-composition rather than using pharmaceutical drugs might be attractive. The longer term efficacy of this approach and the longer term effects on lipid metabolism should be considered before further recommendations can be made.

The relationship of fasting and post-load levels of insulin and proinsulin with 11-year risk on cardiovascular disease mortality and all-cause mortality was studied in Chapter 5. A 13 pmol/l higher fasting proinsulin level independently predicted a 33% higher risk for cardiovascular mortality and a 21% higher risk for all-cause mortality. This association was independent of glucose tolerance status and insulin resistance. These findings suggest atherogenic properties for proinsulin as a molecule. Two-hour post-load insulin and proinsulin concentrations were not significantly associated with mortality. This might be due to higher biological variability in post-load as compared to fasting proinsulin concentrations.

In Chapters 6 and 7, we assessed genetic, metabolic and dietary factors that were associated with fasting CETP concentration. CETP plays a key role in lipid metabolism and in reverse cholesterol transport by transferring triglycerides and cholesterol between lipoproteins. Variation in the -629C/A polymorphism of the CETP gene was an important determinant of CETP concentration. Independent of this polymorphism, women had higher CETP concentration as compared to men and total cholesterol levels were associated with higher CETP concentration, whereas alcohol intake was associated with lower CETP concentration (Chapter 6). The independent association between plasma total cholesterol and plasma CETP concentration (Chapter 6) can be explained by
cholesterol-mediated stimulation of CETP synthesis. The postprandial data from Chapter 9 also demonstrate that CETP-synthesis may in part be enhanced by dietary cholesterol. The female sex hormone estradiol is also known to stimulate CETP gene expression. Despite the resulting lower CETP concentrations in postmenopausal women as compared to premenopausal women, postmenopausal women still have higher CETP concentrations as compared to men (Chapter 6). From previous studies, some information is available about factors that potentially affect cellular secretion of CETP, which may underlie the inverse association between alcohol intake and CETP concentration (Chapter 6).

Furthermore, we found that a dietary pattern, which was rich in fat, was associated with lower CETP concentrations but with a higher prevalence of type 2 diabetes (Chapter 7). Given the high correlation between cholesterol intake and this dietary pattern, we would have expected this pattern to increase CETP concentration. On the other hand, the dietary pattern correlated with high amounts of saturated and mono-unsaturated fat intake, which are known to have opposite effects on CETP concentration. The mechanism of these diet-induced changes in CETP concentration is not clearly established.

Whether CETP concentration was associated with prevalent cardiovascular disease or cIMT was assessed in Chapter 8. We found that the associations differed between men and women and between glucose tolerance status groups. In women with diabetes, a 1 mg/l higher CETP concentration was associated with a 3.3-fold increased prevalence of cardiovascular disease. The combination of elevated levels of CETP as compared to men, an increase in cholesterol and triglycerides after the menopause and the insulin resistant state are likely contributors to the elevated cardiovascular disease risk in postmenopausal women with type 2 diabetes. We would suggest that the individual metabolic setting in postmenopausal women with diabetes provides a setting in which CETP is potentially atherogenic. The postprandial increase in CETP concentration as described in Chapter 9 together with a postprandial increase in triglyceride-rich particles may lead to an even more adverse lipid distribution in the postprandial phase.

To conclude,

Disturbances in postprandial glucose and lipoprotein profile might both
contribute to cardiovascular risk. Regulation of postprandial glucose might be important even in healthy persons. We speculate that other lipoprotein particles than triglyceride-rich lipoproteins in the postprandial state may be involved in atherogenesis. The increased cardiovascular risk due to diabetes in postmenopausal women might in part be the result of an atherogenic lipid profile, of which the concentration and/or composition is mediated by CETP.