SUMMARY

Chapter 1 starts with a brief outline about diabetes and the metabolic syndrome in relation to cardiovascular disease (CVD) risk in patients with type 2 diabetes mellitus (DM2) and introduces some new putative CVD risk determinants that may explain the excess CVD risk in patients with DM2.

In Chapter 2, we describe the determinants of postprandial triglyceride and glucose concentrations following two consecutive (breakfast and lunch) fat-rich and carbohydrate-rich meals in post-menopausal women with normal glucose metabolism (NGM) and in women with DM2 who were part of the Hoorn Prandial Study. The postprandial increment in triglycerides did not differ between women with NGM and DM2, whereas fasting triglycerides and the total triglyceride response was higher in DM2. Fasting triglyceride concentration, HbA1c, total cholesterol, and, inversely, high density lipoprotein (HDL) cholesterol were independently associated with the postprandial increment in triglycerides in women with NGM. In women with DM2, the fasting triglyceride concentration was the only determinant of the postprandial increment in triglycerides. In women with NGM, age and fasting triglycerides were independently associated with postprandial increment in glucose. In women with DM2, HbA1c was independently associated with the postprandial increment in glucose, and in women on statin therapy physical activity was an additional determinant. We concluded that the postprandial increment in triglycerides did not differ between post-menopausal women with NGM and well-controlled DM2. Furthermore, fasting triglyceride levels were a strong predictor of the postprandial increment in triglycerides, whereas the postprandial increment in glucose was especially determined by variables other than fasting glucose.

The study in Chapter 3 compared the associations of postprandial glucose and postprandial triglycerides with carotid intima media thickness (cIMT) after two consecutive fat-rich or carbohydrate rich meals in women with NGM and DM2. In women with NGM, an increase of 1.0 mmol/l in plasma glucose following the fat-rich meals and an increase of 1.8 mmol/l in plasma glucose concentration following the carbohydrate meals were associated with a 50 µm larger cIMT. No association between postprandial glucose and cIMT was found in women with DM2. Postprandial triglycerides were not associated with cIMT. The association between postprandial glucose and cIMT in women with NGM suggests that postprandial glucose in the normal range is a marker or a risk factor for atherosclerosis.
In the next chapter (Chapter 4), we addressed possible mechanisms that link postprandial dysmetabolism to CVD risk. The influence of two consecutive meals (breakfast and lunch) with different composition (both fat-rich or carbohydrate-rich) on acute changes in various markers of glycoxidative and lipoxidative stress, including oxidized low-density-lipoprotein (oxLDL), Nε-(carboxyethyl)-lysine (CEL), Nε-(carboxymethyl)-lysine (CML) and 3-deoxyglucosone (3DG) were studied in a sub-sample of the Hoorn Prandial Study (27 with NGM and 26 with DM2). We found significant elevations of oxLDL, 3DG and CML during the postprandial period in post-menopausal women with DM2 and NGM. The fasting values of oxLDL, 3DG and CML in women with DM2 were of similar magnitude as the postprandial values in women with NGM. The elevations of oxLDL were closely correlated with changes in postprandial triglycerides, whereas 3DG alterations were correlated with changes in postprandial glucose following the fat-rich meals. CML and CEL correlated to with neither postprandial glucose nor triglyceride changes. These results suggest that exaggerated glycoxidative and lipoxidative stress, due to postprandial dysmetabolism, may contribute to the increased CVD risk in DM2.

In Chapter 5 we studied the 8-hour time course of myeloperoxidase (MPO) following two consecutive (breakfast and lunch) fat-rich and carbohydrate rich-meals in postmenopausal women with NGM and in women with DM2. MPO is abundantly expressed in leukocytes, and released upon activation in the extracellular space. MPO has been associated with CVD and endothelial dysfunction. Postprandial leukocyte recruitment and activation with subsequent MPO release may contribute to atherosclerosis and CVD. We hypothesized that plasma MPO would increase in the postprandial state, due to leukocyte recruitment and/or activation, especially in individuals with DM2. Baseline MPO was not significantly different between NGM and DM2. Baseline MPO was weakly associated with leukocytes and inversely associated with HDL-cholesterol. In the postprandial phase, in contrast to our hypothesized increase, MPO decreased in NGM (both meal types) and in DM2 (fat-rich meals). Based on these results we concluded that our findings provide no support to our initial hypothesis that meal induced release of MPO might be a mechanism that contributes to CVD risk in DM2.

Chapter 6 reviews the applicability of alanine aminotransferase (ALT) as a marker of non-alcoholic fatty liver disease (NAFLD) and provides an overview of the epidemiological studies that assessed the associations between ALT and the metabolic syndrome, DM2 and CVD. We concluded that in epidemiological studies, ALT is an adequate marker of NAFLD, provided that alcohol-intake as a
confounding or effect-modifying variable is considered, and provided that other more rare causes of ALT elevation are excluded.

In a cross-sectional study in 64 normotriglyceridemic patients with DM2, we studied the relation of ALT with endothelial function, measured as flow-mediated vasodilatation (FMD), and with insulin sensitivity (M/I-value) (Chapter 7). We found that ALT was significantly, albeit weakly, associated with FMD and M/I-value, independent of obesity. Moreover, the relation of ALT with FMD was independent of insulin sensitivity. These findings suggest that in DM2, elevated ALT is associated with a more unfavorable CVD risk profile.

In the study described in Chapter 8 we used data from the Hoorn Study to assess the prospective relation of ALT with all-cause mortality, CVD and coronary heart disease (CHD) events in a population-based cohort of elderly Caucasian men and women. We demonstrated that individuals with ALT levels in the upper tertile, had a significantly higher risk for CHD events that those in the lower tertile, after adjustment for components of the metabolic syndrome and traditional risk factors. No significant associations were found between ALT and all-cause mortality and CVD events, after applying the same adjustment. This study shows that individuals with even slightly elevated ALT levels are at an increased risk for CHD events. The pathogenic mechanisms underlying this association are not incompletely understood and require further study.

In Chapter 9, we studied the prospective relation of ALT with incident metabolic syndrome and DM2. We found that higher ALT levels were related to conversion to the metabolic syndrome, after adjustment for confounding factors including alcohol-intake, age and the individual components of the metabolic syndrome. However, in contrast to previous reports, we could not demonstrate an independent prospective relation between ALT and the risk of DM2. These results suggest that the increased CVD risk might be mediated by metabolic derangements that differ from those that result in hyperglycemia (Chapter 9).

The last chapter (Chapter 10) discusses the methodological and pathophysiological aspects of the studies presented in this thesis.