

SUMMARY
& SAMENVATTING

INTRODUCTION

Diabetes mellitus, a disease known from ancient times, has reached epidemic proportions in the previous decade, with more than 194 million affected people worldwide. Global estimations predict a further increase of almost 50% for the year 2010, with the greatest increase in the developing countries of Africa, Asia and South America. Type 2 diabetes mellitus (T2DM) accounts for some 90% of the adult onset diabetes. A large part of the medical and socio-economic burden of the disease is caused by the diabetes associated complications. Cardiovascular morbidity is 2 to 4 fold greater in type 2 diabetic patients, compared to non-diabetic persons. Micro-vascular complications include renal disease, retinopathy and neuropathy.

Both genetic predisposition and environmental factors are involved in the pathogenesis of T2DM. A positive family history confers a 2 to 4 fold risk for type 2 diabetes and 15-25% of first degree relatives of patients with type 2 diabetes develop impaired glucose tolerance or diabetes. Besides the general ageing of the population in many societies, which is strongly associated with the increase in T2DM, there are other factors which contribute to the development of T2DM.

An abundance of food, an increased energy density of the food and a more sedentary lifestyle have led to an increased prevalence of obesity, which is a strong risk factor for the development of T2DM. In particular upper body fat distribution is associated with an unfavourable metabolic and cardiovascular disease risk profile in both men and women. In addition to high fasting and post load glucose levels, which are used for the diagnosis, T2DM and precursor conditions are more or less characterised by a cluster of impaired insulin release, insulin resistance, an altered lipid profile, abdominal obesity and consequently a high risk for cardiovascular disease. This cluster of characteristics is also known as the Metabolic Syndrome. Although it is generally accepted that all these components aggregate in insulin resistant persons and all contribute to the pathogenesis of T2DM and the cardiovascular risk, for many of these components it is not clear what the independent contributions are. It is also not clear if these associations already exist in a population with a low cardiovascular disease (CVD) risk and to what degree they are dependent on insulin resistance. Our main research questions were;

- Is insulin secretion a better predictor for conversion to type 2 diabetes than insulin sensitivity?
- What happens to the insulin secretion in relation to the insulin sensitivity during 3 years of follow up?
- What determines the change of insulin secretion and insulin sensitivity in subjects with impaired glucose tolerance (IGT)?
- Can insulin sensitivity explain the relationships between body fat distribution and cardiovascular disease risk?
- Is insulin sensitivity associated with ECG abnormalities, independent of other CVD risk factors?
- Is insulin resistance independently associated with microalbuminuria?



STUDY DESIGN

The Hoorn IGT-Study was a prospective cohort study in which we investigated the role of insulin secretion and insulin sensitivity in the onset of type 2 diabetes in persons with IGT during a mean of 4 years of follow up. We also investigated putative determinants of change in insulin secretion (chapter 2 and 3).

The RISC Study is an ongoing prospective cohort study of 1500 persons, in 14 European

countries, with a low CVD risk. It is designed to investigate the role of insulin sensitivity in the pathogenesis of cardiovascular disease. In chapter 4, 5 and 6 three baseline studies (cross-sectional) are presented.

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MAIN FINDINGS AND DISCUSSION

In chapter 2 we presented the results of a prospective study of Caucasian, confirmed IGT persons and we found that insulin sensitivity, second phase insulin secretion and the disposition index were no independent predictors of T2DM conversion. The strongest predictor was the absence of a first insulin peak (the first and fast insulin release in response to a glucose load), when measured by hyperglycemic clamp.

In chapter 3 we investigated the 3-year changes in insulin sensitivity and insulin secretion in a subgroup of the same IGT persons. Seven persons developed T2DM, thirty-six remained IGT and seven converted to normal glucose tolerance (NGT). All categories were subject to a decrease in insulin sensitivity, although the T2DM group experienced the largest decrease (> 60%). The main difference between the categories was the difference in the change in insulin secretion. The persons who became NGT or remained IGT, both had an increase in insulin secretion of 140-160%. The increase in the T2DM category was next to nil. This was expressed in a decreasing disposition index (an integrated measure of glucose tolerance). The only determinant we found that was associated with a decrease in the disposition index was gamma-glutamyl-transferase (GGT), which is known to be a marker of intra-hepatic fat accumulation. This finding supports a present pathophysiological hypothesis, which suggests a direct link between ectopic fat accumulation and impaired insulin release.

In chapter 4 we found associations of leg and trunk fat mass with CVD risk markers, which have previously been found in less healthy or more elderly populations. After adjustment for overall body fat, larger leg fat mass was associated with a more favorable CVD risk profile. In men it was associated with lower triglycerides (TG's). Larger trunk fat mass was associated with a less favourable CVD risk profile. In men and women it was associated with a lower HDL-cholesterol (HDL) and higher TG's and in women only it was associated with higher fasting insulin, higher fasting glucose and higher blood pressure. However, we could not find a mediating or confounding role of whole body insulin sensitivity in these associations. This suggests a more direct influence of body fat on CVD risk profile. Furthermore, whole body insulin sensitivity was associated with ECG abnormalities independent of demographic factors, but not independently of estimates of body fat (chapter 5).

In chapter 6, we present the results of analyses on the association between insulin resistance and microalbuminuria. Insulin resistance was strongly associated with the prevalence of microalbuminuria, independently of heart rate, glomerular filtration rate (GFR), blood pressure, overweight and fasting insulin and TG's. High TG's were also associated with microalbuminuria, although not independent of insulin sensitivity. The existence of this association in a non-hypertensive, low CVD risk population; suggests a direct mechanistic link between insulin sensitivity and microalbuminuria.

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IN CONCLUSION

Although insulin resistance is regarded as an important determinant of conversion to T2DM and the most important clustering factor for the cardiovascular risk factors present in the metabolic syndrome, our data suggest other factors are also important. First of all,

in Caucasian IGT persons, impaired fast insulin release seemed to be a better predictor for T2DM conversion than insulin resistance. Secondly, from our studies in the “healthy” Europeans, we found that in all associations between different types of body fat and indicators of CVD, there was no, or very little, mediating or confounding role of insulin sensitivity. This was true for HDL-cholesterol, Triglycerides, blood pressure and even ECG abnormalities. However, we did find a strong association between insulin resistance and microalbuminuria and this has to be investigated further. Since the study was cross-sectional, conclusions on cause and consequence can’t be drawn. Therefore, much can be expected from the results of the follow up study of this population. What became clear in this study, is that even in a low risk population the detrimental influence of abdominal fat on the metabolic and CVD profile is already present. This underscores the idea that overweight is an important target in the prevention of CVD and should always be addressed, even in a young and healthy population. Thus, insulin resistance surely is an important factor in the pathogenesis of both type 2 diabetes and CVD. However, it is one among others.