

Summary

The natural history of type 2 diabetes (T2DM) is characterized by glucometabolic abnormalities that may develop during 5-10 years prior to the diagnosis of the disease. In susceptible individuals, mostly in the setting of overweight or obesity, blood glucose levels may rise into the pre-diabetic range over time, resulting in either impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or both, as defined by a standardized 75-g oral glucose tolerance test (OGTT). In general, the annual risk of individuals with impaired glucose metabolism (IGM) to progress to T2DM ranges from 5-10%. It has been established that individuals with IGM already manifest the characteristic defects of T2DM, i.e. reduced insulin sensitivity and impaired islet-cell function. However, the pathophysiological features of individuals with IFG, IGT or both, show distinct differences and only partly overlap. **Part 1** of this thesis provides more insight into the underlying pathophysiology of IGM, specifically focusing on mechanisms related to insulin resistance and beta-cell dysfunction and the contribution of alterations in lipid handling in these two key defects leading to T2DM.

Part 2 The role of the renin-angiotensin system in metabolism

In addition to impairments in glucose metabolism, individuals with IGM often display several concurrent cardiometabolic abnormalities, including hyperinsulinemia, dyslipidemia and hypertension. Consequently, obese insulin-resistant individuals are often treated with lipid lowering and antihypertensive medication. With respect to the latter, retrospective analyses of clinical trials showed that diuretics and beta-blockers increased the risk of new onset T2DM in individuals with IGM. In contrast, blood pressure lowering medication that block the renin-angiotensin system (RAS), i.e. angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) have been related to delayed onset of T2DM in non-diabetic subjects with or without hypertension. In **Part 2** of this thesis we investigated whether the diabetes-preventing effects of RAS blockade may be related to improved insulin sensitivity and/or beta cell function and investigated several of the underlying mechanisms.

In summary, we confirm the mechanisms possibly accounting for the protective effect of RAS blockade with an ARB in the onset of T2DM in individuals with IGM, since 26-weeks treatment improved both insulin sensitivity as well as beta-cell function. The underlying mechanisms addressed in this thesis include improvement in beta-cell function and adipose tissue function. Based on rodent data, RAS blockade may additionally improve insulin sensitivity via direct effects on skeletal muscle insulin signaling or mitochondrial function.

The clinical translation of these findings could be that physicians, when prescribing blood-pressure lowering therapy in individuals with hypertension and concurrent glucometabolic derangements, may consider ARB or ACEi as first-choice therapy, provided that there are no specific indications to use beta-blockers or diuretics. Given their beneficial metabolic actions, on top of the anti-hypertensive effects, agents that interfere with the RAS may help to prevent or delay the onset of T2DM in these high-risk individuals.