



**Karolinska  
Institutet**

**Institutionen för fysiologi och farmakologi**

**Regulators of Glucose and Lipid  
Metabolism in Skeletal Muscle and  
Serum  
Implications for obesity and type 2  
diabetes**

**AKADEMISK AVHANDLING**

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## ABSTRACT

**Type 2 diabetes mellitus (T2DM) has become a growing worldwide problem of public health importance. Insulin resistance is commonly associated with obesity and a key factor mediating the progression to T2DM. The failure of insulin sensitive peripheral tissues to respond to insulin results in an increase in serum glucose levels that leads to an impaired homeostatic state. Skeletal muscle plays a crucial role in maintaining glucose metabolism. Impairments in both glucose and lipid metabolism arising from a dysregulation of hormones, free fatty acids, or other factors contribute significantly to the pathogenesis of T2DM.**

**The roles of several circulating metabolites in the development of insulin resistance have been described. However the molecular mechanisms involved in skeletal muscle insulin resistance remain poorly defined. Furthermore, the biological interactions between skeletal muscle, novel circulating factors, and lifestyle factors such as exercise in the regulation of glucose and lipid metabolism need to be investigated. This thesis aims at examining the role of novel regulators of glucose and lipid metabolism, uncovering the molecular targets involved in the development of skeletal muscle insulin resistance, and describing their clinical implications in obesity and T2DM.**

**Physical exercise has beneficial effects on glucose and lipid metabolism and hence improves cardiovascular risk factors. In Study I, we report differential effects of Nordic walking (low-moderate intensity exercise) on cardiovascular risk factors in normal and impaired glucose tolerant individuals. We provide evidence to support the recommendation of a more intense and supervised exercise modality for significant improvements in cardiovascular risk factors.**

**Fibroblast growth factor (FGF)-21 is a member of the FGF family that plays a role in a variety of endocrine functions, including the regulation of glucose and lipid metabolism. Observations from animal models have suggested a potential therapeutic role of this growth factor in T2DM. In Study II, we provide evidence for direct effects of FGF-21 in skeletal muscle glucose uptake. Using cell-surface photolabeling of human myotubes, we report enhanced glucose transporter-1 abundance at the cell membrane, coincident with increased basal and insulin-stimulated glucose uptake. We further confirm a paradoxical increase in serum FGF-21 in T2DM in humans, and identify BMI as the strongest independent predictor of FGF-21 serum levels. The mechanisms controlling the metabolic actions of FGF-21 are currently being resolved.**

**Signal transducer and activator of transcription factor 3 (STAT3) is involved in cytokine- and nutrient-induced insulin resistance. The role of STAT3 in the development of skeletal muscle insulin resistance and T2DM pathogenesis is incompletely defined. In Study III, we report an increased STAT3 phosphorylation in T2DM. Using palmitate and STAT3 specific siRNA treatment of myotubes in vitro, we provide evidence for the role of STAT3 in the development of lipid-induced skeletal muscle insulin resistance.**

**Collectively, the work presented in this thesis contributes to the understanding of various regulators of glucose and lipid metabolism from the whole body physiology context to molecular mechanisms in skeletal muscle. Metabolic alterations result from the interplay between biological processes within the cells, tissues and organs. These alterations may translate into ill health such as T2DM. Information from Translational studies like the ones presented in this thesis will help to identify molecules with both clinical significance and therapeutic potential**