

# Improvement of muscle lipid-turnover in insulin resistance and type 2 diabetes

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## IMPACT PARAGRAPH

### **What is the main purpose of the research described in this thesis and what are the main results and conclusions?**

Prevalence of type 2 diabetes is increasing rapidly not only in the Netherlands but worldwide. Obesity is an important underlying factor in the development of type 2 diabetes. Especially the storage of lipids in tissues other than fat tissue, for example muscle, liver, heart and pancreas is crucial. This increased prevalence is accompanied with co-morbidities in type 2 diabetes patients, reducing the life expectancy but also the quality of life. Furthermore, health care costs related to this are immensely high causing a severe economic-burden. This highlights the importance of understanding the aetiology of type 2 diabetes and developing effective treatment strategies to lower this economic but also social burden caused by this disease.

In **chapter 2**, a literature study was performed investigating the effect of supplementation and pharmacological agents on whole body lipid metabolism, and the effect on lipid storage and insulin sensitivity in muscle tissue. Current pharmacological treatments are focussed on lowering of glucose levels. However, it is necessary to reduce or prevent the storage of ectopic fat, which is one of the underlying problems that cause the development of type 2 diabetes. We conclude from this review that especially supplements and pharmacological agents that reduce the uptake of fat into muscle tissue, resulting in less fat in muscle tissue, are effective in increasing insulin sensitivity in muscle tissue. In addition, some pharmacological agents increase insulin sensitivity as a result of higher fat oxidation, without lowering the amount of fat in muscle tissue, which stresses that perhaps not the ectopic fat storage per se but the turnover of fat in muscle tissue is more important.

In **chapter 3** we further investigated the relation between fat storage in skeletal muscle and insulin sensitivity. To this end, we investigated a) trained, b) insulin resistant untrained, and c) insulin sensitive untrained individuals. Interestingly, a paradox was present with athletes and insulin resistance individuals both having high lipid storage in muscle with athletes having a high fat turnover and insulin resistant individuals a low fat turnover. Interestingly, the location of the lipids stored is different and apparently crucial in developing insulin resistance and type 2 diabetes. Athletes have a pronounced storage of fat connected to the mitochondria, where insulin resistant individuals store fat away from mitochondria, possibly underneath the skeletal muscle cell membrane, hampering

insulin signalling.

This challenged us to improve lipid oxidation/turnover by the use of supplements. In specify, we first investigated the potential effects of carnitine supplementation. Carnitine is well now for its role in lipid oxidation, but is more recently also pointed out as important player in maintaining proper glucose homeostasis. In **chapter 4** and **chapter 5**, we investigated the potential effect of carnitine to rescue lipid-induced insulin resistance. Since carnitine supplementation showed beneficial and promising effects in pre-diabetics, we here investigated the therapeutic potential in type 2 diabetes patients. We revealed that insulin resistance reduced, less lipids were stored in the liver and glucose levels tended to reduced. Therefore, we concluded that carnitine supplementation might be a strategy to treat type 2 diabetes and lower insulin resistance.

Next, in **chapter 6** and **chapter 7**, we investigated the potential of the pharmacological component SGLT2 inhibitors, a relatively new drug for patients with type 2 diabetes. SGLT2 inhibitors have been shown to improve glucose control and reduce body weight, as a result of glucose loss in urine. Other studies have shown that treatment with SGLT2 inhibitors show effects that are similar to the effects of exercise and following a diet. We investigated if SGLT2 inhibitor treatment results in less fat storage in liver and muscle and reduce insulin resistance. We showed that SGLT2 inhibitor treatment increases whole-body fat oxidation, decreases fat storage in liver and improves muscle metabolic health. Therefore, we concluded that SGLT2 inhibitor treatment can be used to lower whole-body storage of fat and to improve the health of muscle tissue.

### **What is the contribution of the results in this research to the scientific community and societal challenges?**

The results of the studies described in this thesis contribute to the existing knowledge about the pathology and treatment of type 2 diabetes. With the knowledge obtained in this thesis, the understanding of the pathology and treatment of type 2 diabetes has increased. This provides opportunities for other researchers to develop new study ideas to further unravel the pathology of type 2 diabetes and improve the available treatment strategies.

With the rising prevalence of type 2 diabetes, effective treatment strategies for type 2

diabetes patients are increasingly important. Type 2 diabetes is associated with multiple comorbidities such as cardiovascular disease, liver disease and neuropathy. This has a major negative influence on the life expectancy but also reduces the quality of life of the patient. Therefore, the social impact of type 2 diabetes is high and highlights the importance of good treatment strategies. The results obtained in this thesis could contribute to this development of new treatment options and treatment strategies. In addition, the economic impact of type 2 diabetes is enormous due to very high healthcare costs to treat type 2 diabetes and occurring comorbidities. The results in this thesis can improve treatment and prevent/delay the onset of comorbidities and thereby reduce health care costs.

### **For whom are the research results interesting and relevant?**

The results in the theses are interesting for different groups of people like researchers, medical professionals, pharmacological and insurance companies, as well as to the general society.

In the current thesis, more knowledge has been acquired on the role of muscle lipid accumulation and lipid turnover in insulin resistance and type 2 diabetes. Furthermore, supplementation and pharmacological treatment strategies focusing on improving muscle lipid storage and insulin resistance in type 2 diabetes revealed very promising effects to combat and treat type 2 diabetes. This knowledge is of great importance to researchers because it contributes to better understanding of the etiology of type 2 diabetes as well as the development of better treatment strategies for this chronic disease. Future studies can be developed based on this knowledge as discussed in the general discussion (**chapter 8**).

Furthermore, general practitioners, endocrinologist, dieticians and other health care professionals involved in treating type 2 diabetes patients could use the findings in this thesis to treat type 2 diabetes patients. SGLT2 inhibitors are new pharmacological compounds for the treatment of diabetes and the results of this thesis support the advantages to prescribe this compound in treating type 2 diabetes. Health care professionals are in direct contact with the patients and can highlight the advantage of using SGLT2 inhibitors. Furthermore, health care professionals can inform patients on the advantage of using carnitine supplementation on improving type 2 diabetes. Since carnitine supplements are available without prescription of physicians, this is a feasibly

strategy to treat diabetes.

Next, the results of this thesis are of interest to all individuals in our society especially individuals at risk or diagnosed with type 2 diabetes. The results of these studies can help individuals understand the consequences of obesity and whole-body fat storage on metabolic health and stimulate patients with type 2 diabetes to improve their lifestyle, either with or without the use of medication.

**How can these target groups be involved in and informed about the research results, so that the acquired knowledge can be used in the future?**

The results presented in this thesis are or will be published as original scientific articles in international well-recognized peer-reviewed journals. Hereby, the scientific articles will be available online and become assessable worldwide for scientist, medical doctors and other people interested. Additionally, the conducted research and obtained results in this thesis have been communicated to the scientific and medical community worldwide. Results were presented on multiple national (Annual Dutch Diabetes Research Meeting and the International Society for Magnetic Resonance in Medicine division Benelux) and international conferences (International Society for Magnetic Resonance in Medicine, European Association for the Study of Diabetes, Cell Symposium: Exercise Metabolism and on the Keystone Symposia) through oral presentations and posters. In this way, the obtained knowledge in this thesis was dissimulated, thereby contributing to new research ideas for future research as well as treatment therapies for type 2 diabetes.

In addition to presenting these results at (inter)national conferences, all study participants received an information brochure illustrating the study results in non-professionals language. These results were also communicated on websites and social media like twitter and Facebook. Furthermore, meetings were organized to inform the society about the obtained research results on improving muscle lipid-turnover and insulin resistance in type 2 diabetes patients by using supplements and pharmacological compounds. Study participants were invited to these meeting as well as other people interested in research and or type 2 diabetes treatment.