

# Acetylcarnitine

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## VALORIZATION

### **Social relevance**

The number of people with overweight is increasing rapidly worldwide, reaching pandemic proportions. In 2014, 39% of the adults were overweight and 13% were obese worldwide. A combination of excessive food intake (high-caloric, high-fat) and low physical activity are the primary contributors to the development of overweight (1). Overweight is associated with the development of chronic metabolic disease such as type 2 diabetes mellitus (T2DM). An important characteristic of T2DM is that the metabolic effects of insulin on glucose metabolism are blunted (2). In the healthy state, the plasma concentration of glucose is tightly regulated within a narrow range. After food intake, the plasma concentration of the hormone insulin raises, causing the uptake of glucose into tissue, thereby regulating plasma glucose levels. In T2DM, this regulation is poor and hyperglycemia can develop. As the prevalence of T2DM is tightly linked to obesity, also T2DM, just like overweight, is increasing dramatically worldwide. Recent estimates reported 171 million people worldwide diagnosed with T2DM in the year 2000 and expected to increase towards 366 million in 2030 (5). Since T2DM is associated with reduced quality of life, decreased life expectancy, and increased risk of morbidities such as cardiovascular diseases, the diabetes-related costs are a major burden on our health care systems. Therefore, it is important to increase our understanding of this disease to improve prevention and cure. Nowadays treatment of T2DM consist of glucose lowering medication, diet, increasing physical activity or a combination of these. However, T2DM is a complex metabolic disease whereby underlying mechanism are yet not completely understood and not all patients respond well to the conventional treatment. Understanding the underlying mechanisms might result in new treatment strategies.

### **Activities and products**

The research performed in this thesis was executed as a tight collaboration of the department of radiology and the department of Nutrition and Movement Sciences at the Maastricht University Medical Center, within the Diabetes and Metabolism Research group ([www.dmrg.nl](http://www.dmrg.nl)). The Diabetes and Metabolism Research group focusses on unraveling the underlying mechanisms in the etiology of type 2 diabetes Mellitus (T2DM) by performing translation research. In the current thesis we applied *non-invasive* magnetic resonance spectroscopy (MRS) techniques to investigate acetylcarnitine metabolism in healthy and metabolically compromised individuals.

$^1\text{H}$ -MRS is an excellent tool to non-invasively and dynamically assess acetylcarnitine concentrations in contrast to muscle biopsies which are invasive and do not allow dynamic determination of metabolites in humans.

The results presented in the current thesis are or will be implemented in original scientific articles. These articles have been published or are submitted to international well-recognized peer-reviewed journals. The articles can be found online and can be assessed by scientist worldwide. In addition, results and knowledge obtained from the studies performed in this thesis have been presented and communicated to the scientific community on national and international conferences via oral presentations and posters. In this way, the international scientific community can take notice of the current results, thereby advancing the knowledge of the field.

### **Innovation**

Our knowledge about the role of carnitine metabolism and specifically, acetylcarnitine formation in metabolic flexibility and insulin sensitivity in humans is currently limited. One of the reasons is that, until recently, the only means to quantify acetylcarnitine was the determination by mass spectrometry in muscle biopsies (7). The invasiveness of the muscle biopsy is an evident limitation of this method and does not allow dynamic determination of acetylcarnitine concentrations in humans. The recently developed proton magnetic resonance spectroscopy ( $^1\text{H}$ -MRS) technique using long echo times to determine acetylcarnitine concentrations in humans *in vivo* (8) opens a broad window of opportunities to assess acetylcarnitine concentration in humans and gain understanding of the role of acetylcarnitine in glucose tolerance, metabolic flexibility and insulin sensitivity.  $^1\text{H}$ -MRS is an excellent tool to non-invasively and dynamically assess these acetylcarnitine concentrations.

In this thesis, we applied this novel  $^1\text{H}$ -MRS technique to determine acetylcarnitine concentrations in humans with different glucose homeostasis, normal glucose tolerant overweight (NGT) and impaired glucose tolerant (IGT) individuals. The possibility to perform dynamic acetylcarnitine measurements was instrumental in gaining more detailed knowledge concerning carnitine metabolism in these individuals prone to develop T2DM. This non-invasive MR approach enabled resting acetylcarnitine determination at different time points during the day (i.e. morning 7:00 AM and afternoon 5:00 PM) as well as before exercise and at near-maximal acetylcarnitine

abundance, immediately after exercise, showing striking differences between individuals with different glucose homeostasis.

However, in overweight individuals we noticed that lipid resonances are present in some individuals around the same frequency as the acetylcarnitine peak (2.13Hz), a problem not present in young healthy lean individuals. This makes the determination of the isolated acetylcarnitine resonance difficult and lipid contamination of the results is very likely. One way to circumvent this and applied in the current thesis, is to prolong the echo time even further, in order to relatively suppress the lipid resonances even more. However, these long echo times have a large impact on the MR acquisition time, making the measurements lengthy and strongly T2-dependant. Therefore, we developed an editing sequence to determine acetylcarnitine concentrations with additional lipid suppression. This new alternative sequence makes use of the difference in T1 between acetylcarnitine- and lipid resonances and allows better differentiation between lipids and acetylcarnitine (10). This allows more accurate quantification of acetylcarnitine concentrations at TE=350ms in overweight population, thereby opening a broad window of opportunity for researchers worldwide to investigate the metabolite acetylcarnitine non-invasively and over time in humans.

### **Target groups**

In this thesis we reported that supplementation with carnitine positively affects the formation of acetylcarnitine and improved metabolic flexibility in individuals at risk to develop type 2 diabetes. Therefore, carnitine supplementation might be an interesting aid to postpone or even prevent the development of T2DM in these individuals at risk. This strikes out the great importance of carnitine in this pre-diabetic population. Since carnitine is a free available food supplement, carnitine intake is a feasible and directly applicable strategy to postpone the development of diabetes. The latter could be of importance to pharmaceutical industry to improve the use of the food supplement carnitine.

Although further research is needed to investigate the effect of carnitine in T2 diabetic patients, animal research indicates very promising results already. The current thesis might be a good rationale for further investigations on the potential of carnitine as important add-on therapy to the usual anti-diabetic treatment which might be very important for patients suffering from type 2 diabetes.

Therefore, the role of carnitine in individuals at risk to develop diabetes and type 2 diabetic patients is of great importance to general practitioners, endocrinologist, dieticians and life style coaches. These professions are in direct contact with the patients and individuals at risk and can directly indicate the advantage of carnitine supplementation on glucose metabolism. Personalized treatment to combat diabetes, e.g. different treatment based on high or low carnitine status, might be an important role for these professions to treat type 2 diabetic patients and individuals at risk. A possible personalization of carnitine supplementation based on the novel acetylcarnitine measurements by proton magnetic resonance spectroscopy (with the long TE protocol) would provide an easy, robust tool that can be applied on any clinical MRI scanner.

### **Planning and realization**

Supplementation with carnitine in IGT individuals increased plasma and skeletal muscle acetylcarnitine concentrations and concomitantly improved metabolic flexibility. In T2DM, acetylcarnitine concentrations are likely to be even more reduced than in IGT individuals. Therefore, an interesting next step would be to investigate whether supplementation with carnitine in T2DM patients could elevate the capacity to form acetylcarnitine in the skeletal muscle and subsequently improve metabolic flexibility and insulin sensitivity. Carnitine might be a useful add-on therapy to improve glucose tolerance and metabolic health in this patient group. Furthermore, understanding whether the acetylcarnitine concentration in muscle (as determined by MRS) is a valid predictor of the success of carnitine supplementation in type 2 diabetic patients might be very important in personalized treatment. If this is indeed a valid predictor, tailored supplementation in type 2 diabetes patients to restore insulin sensitivity and metabolic flexibility might be possible. This may open a window of opportunity to screen patients with type 2 diabetes and subject at risk of developing type 2 diabetes (such as impaired glucose tolerant individuals) for skeletal muscle carnitine status. Based on the skeletal muscle carnitine status it could be decided whether carnitine supplementation is beneficial. Just as carnitine may be an interesting add-on therapy in type 2 diabetic patients with low carnitine status, carnitine could also be an important food supplement in populations at risk of developing diabetes. Currently, it is unclear which subgroups of diabetic patients would benefit the most from carnitine supplementation, as the carnitine concentration in plasma (which can be determined easily) is very different from carnitine status in skeletal muscle (which up to now required muscle biopsies). I will continue to perform human studies to investigate the possible opportunity of carnitine as a tailored add on therapy in T2DM patients.

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