

# Acylcarnitines in health and disease: biomarkers and drug targets

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## Introduction

Acylcarnitines are fatty acid metabolism intermediates that emerge from the cellular energy metabolism pathways in mitochondria and peroxisomes. An acylcarnitine molecule contains mostly diet-derived biofactor L-carnitine coupled to a fatty acid moiety which can be classified as long-chain, medium-chain, short-chain, branched, hydroxylated, saturated or unsaturated. There are more than 1000 various acylcarnitines now analyzed and included in the Human Metabolome Database (Dambrova et al., 2022). The proportionally largest part of the body acylcarnitine pool consists of short-chain acylcarnitines, containing acetyl-, propionyl-moiety of fatty acids. Metabolomic profiling assays by tandem mass spectrometry frequently include acylcarnitine profile measurements in blood plasma and urine samples and identify metabolic phenotypes, which are associated with certain disease risks.

## Acylcarnitines as biomarkers

Historically acylcarnitines are recognized and used as biomarkers for inborn or acquired fatty acid oxidation defects (McCann et al., 2021; Wanders et al., 2020), also as a part of newborn screening programs (Martín-Rivada et al., 2022). Accumulation of a specific acylcarnitine, especially long-chain and very-long-chain acylcarnitine, can signal about defective mitochondrial  $\beta$ -oxidation enzymes and mitochondrial trifunctional protein in the fatty acid metabolism pathways. The changes in acylcarnitine concentrations have been linked also to the risks of non-communicable diseases, such as diabetes

mellitus, cardiovascular and neurological diseases and also some cancers (Dambrova et al., 2022). The plasma concentrations of acylcarnitines change along with the fed-and-fasted state cycles and availability of energy substrates, fatty acids and glucose. In healthy subjects, fatty acid metabolism and acylcarnitine production dominate during the fasted state, and this has to be taken into account when collecting samples for analysis. In turn, altered changes in plasma concentrations of long-chain acylcarnitines in fasted and fed states can serve as a valuable marker of tissue-specific insulin sensitivity (Makarova et al., 2019). More research is needed to establish reference levels for various acylcarnitines under different physiological states of energy metabolism in health and disease.

## Acylcarnitines as food supplements

Short-chain acylcarnitines, acetylcarnitine and propionylcarnitine, are proposed as useful food supplements. Some studies have shown positive effects of acetylcarnitine intake in dementia, cognitive dysfunction, neurodegenerative disease, pain, Alzheimer's disease, depressive disorder, neuralgia, type 2 diabetes and diabetic neuropathy, hyperammonemia, fatigue and dystrophy (Dambrova et al., 2022). Propionylcarnitine supplementation has been found useful in the case of some vascular diseases, including intermittent claudication, colitis, ischemia and also male sexual dysfunction (Dambrova et al., 2022). However, it has to be noted that more data are needed to study metabolic and biochemical cascade of events leading to altered levels of

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acylcarnitines, bioavailability of supplements and concentration changes after the supplementation.

### Acylcarnitine accumulation-induced disease states

At altered concentrations long-chain acylcarnitines are known to affect the activity of enzymes and ion channels, mitochondrial functionality, increase free radical production, as well as impact signaling pathways leading to various cardiovascular diseases (Dambrova et al., 2021, Dambrova et al., 2022). Since long-chain acylcarnitines induce harmful effects on mitochondria and energy metabolism pathways, their accumulation is suggested as an actor in the induction of an energetic crisis in inflammation (McCoin et al., 2015). It has been shown recently that a long-chain acylcarnitine, palmitoylcarnitine, stimulates insulin release and induces dephosphorylation of the insulin receptor (Vilks et al., 2021). This finding provides additional molecular details to previous preclinical studies pointing at altered changes in long-chain acylcarnitine levels in case of insulin resistance (Aguer et al., 2015; Liepinsh et al., 2016). The increased levels of long-chain acylcarnitines can be proposed as a target for the treatment of inherited diseases of fatty acid oxidation, diabetes/insulin resistance, and cardiovascular diseases.

### Future perspectives

In order for acylcarnitines to gain wider recognition as biomarkers and new drug target resource, bioanalytical technologies and big data analysis should be used to advance understanding of the physiological roles of acylcarnitines and their involvement in the pathogenesis of various disease states.

### Conclusion

The metabolomic profiling data point to acylcarnitines as important fatty acid intermediates that signal about disturbances in the cellular energy metabolism pathways and present early signs of certain disease pathogenesis. Dietary and pharmacological means of acylcarnitine level regulation can be used to counteract pathological changes in acylcarnitine concentrations.

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