Short and medium chain acylcarnitines as markers of outcome in diabetic and non-diabetic subjects with acute coronary syndromes

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Funding Acknowledgement: Type of funding source: Foundation. Main funding source(s): Zurich Heart House - Foundation for Cardiovascular Research

Background: Dietary carnitine that is not absorbed can serve as a precursor for gut microbiota-dependent generation of trimethylamine N-oxide (TMAO), a pro-atherogenic and pro-thrombosis promoting metabolite. Gut microbiome-derived metabolites of dietary carnitine, including TMAO and g-butyrobetaine, may accelerate atherosclerosis, increase platelet reactivity and in vivo thrombosis. Carnitine metabolism also produces numerous molecular species of short, medium and long chain acylcarnitines, which play important roles in energy metabolism and intracellular fatty acid transport.

Purpose: We sought to evaluate the differences between diabetics and non-diabetics presenting with ACS with respect to acylcarnitines, and to explore their relationship with incident cardiovascular outcomes.

Methods: Using a large, prospectively recruited cohort of patients presenting to the cardiac cath lab with suspected acute coronary syndromes, we measured levels of plasma acylcarnitines, carnitine and its gut microbial-derived metabolites to assess their relationship with independently adjudicated major adverse cardiac events (MACE = myocardial infarction, stroke or TIA, need for revascularization or all-cause mortality) amongst diabetics and non-diabetics.

Results: We analysed 1683 patients who presented with ACS, were treated according to current guidelines and had undergone acylcarnitine analysis. There were 294 diabetics and 1389 non-diabetics. Diabetics had significantly higher plasma levels of all acyl carnitine metabolites than non-diabetics ($P<0.001$), but not of carnitine itself. Baseline plasma levels of all gut microbiome derived carnitine metabolites (TMAO, g-butyrobetaine and crotonobetaine) were also significantly higher in those who subsequently experienced a MACE. All carnitine metabolites, apart from octenoylcarnitine, were significantly associated with MACE on univariate analysis, while acetylcarnitine and crotonobetaine were independently associated with MACE after multivariate adjustment.

Conclusion: Serum short- and medium- chain acylcarnitine levels are significantly higher in diabetic patients presenting with ACS and predict MACE. After multivariate adjustment, acetylcarnitine and crotonobetaine remained an independent predictor of MACE.