Letter to the Editor: "Serum Carnitine Metabolites and Incident Type 2 Diabetes Mellitus in Patients With Suspected Stable Angina Pectoris"

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The *Journal of Clinical Endocrinology & Metabolism* recently published an article by Strand *et al.* (1). The authors examined whether serum levels of long-chain palmitoylcarnitine predict long-term risk for type 2 diabetes (T2D) independently of traditional risk factors, possibly reflecting dysfunctional fatty acid (FA) metabolism in patients susceptible to T2D development. We are concerned about the common trend of using acylcarnitine measurements in fasted subjects and subsequent data interpretations that relate fasted-state acylcarnitine concentrations to insulin sensitivity.

In the past 10 years, long-chain acylcarnitine levels have emerged as markers of insulin resistance and diabetes; however, in most studies acylcarnitines have been measured in fasted subjects (1, 2), which is not an appropriate metabolic state for the characterization of insulin resistance. The fasted and postprandial states are characterized by different intensities of FA metabolism and different prevailing regulatory mechanisms. Therefore, measurements of acylcarnitine levels in both states would help us to better understand the importance of changes in acylcarnitine concentrations in the context of metabolic status and the concentrations of other diagnostic markers.

Carnitine palmitoyltransferase 1–mediated long-chain acylcarnitine synthesis is a step in mitochondrial FA oxidation, and various mitochondrial disorders that are characterized by incomplete FA oxidation cause the accumulation of long-chain acylcarnitines (3). In rare mitochondrial genetic disorders, ischemia, and the late stages of heart failure, acylcarnitines accumulate in mitochondria because of a transient or permanent inhibition of FA-dependent oxidative phosphorylation in the mitochondria (3, 4). Accordingly, any measured increase in acylcarnitine concentration has been associated with the incomplete mitochondrial metabolism of FA. This assumption is misleading because physiologically, the highest concentrations of long-chain acylcarnitines (up to five times higher than in the fed state) are present during the fasted and starvation states, when FA metabolism in the heart and other muscles is significantly increased and predominates over carbohydrate metabolism (5, 6). In addition, patients with diabetes but without mitochondrial dysfunction show elevated concentrations of long-chain acylcarnitines, accompanied by marked upregulation of FA oxidation (6). Overall, mitochondrial dysfunction might be diagnosed by comparing plasma levels of acylcarnitine in healthy subjects and patients in the fasted state but not in the fed state, when extramitochondrial regulatory mechanisms become more important. In contrast, in the fasted state the comparably low level of insulin is unable to inhibit long-chain acylcarnitine production by carnitine palmitoyltransferase 1, and measurements of acylcarnitines cannot be associated with insulin resistance.

An appropriate state for studies of insulin action, both physiologically and in various diseases, is after glucose intake. Because T2D is characterized by insulin resistance, which causes impaired insulin-mediated glucose uptake in the peripheral tissues, insulin sensitivity should be evaluated in the state during which the highest concentration of insulin is present in the circulation or, preferably, during the transition from the fasted to the fed state, based on measurements from both states. In healthy subjects in the fed state, to facilitate glucose metabolism, the increased concentration of insulin inhibits long-chain acylcarnitine

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Abbreviations: FA, fatty acid; T2D, type 2 diabetes.

production and subsequent FA metabolism. Disturbances in insulin signaling lead to the inability of insulin to inhibit long-chain acylcarnitine production in the postprandial state (5, 6). The limitation of acylcarnitine measurements after glucose load could be that hyperinsulinemia suppresses the synthesis of acylcarnitines, thereby masking insulin resistance. Therefore, the insulin clamp method may be preferable for evaluating changes in acylcarnitine concentrations in response to insulin (6). It must be noted that plasma long-chain acylcarnitine concentrations are not associated with whole-body insulin responses but represent primarily the acylcarnitine content of the heart (7, 8). Overall, acylcarnitine measurements in the fasted state are appropriate for the assessment of mitochondrial function, whereas insulin resistance can be detected only in the postprandial state after controlled glucose load.

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