COMMENT ON ADAM ET AL.

Metformin Effect on Nontargeted Metabolite Profiles in Patients With Type 2 Diabetes and in Multiple Murine Tissues. Diabetes 2016;65:3776–3785

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We read with interest the recent article by Adam et al. (1) suggesting an action of metformin on citrulline metabolism in patients with type 2 diabetes. This study provides compelling evidence that metformin treatment is associated with a decrease in plasma citrulline in these patients and also in multiple tissues in diabetic mice. The authors speculate that high citrulline may be associated with insulin resistance, and the accompanying commentary (2) questioned whether a metformin-mediated decrease in citrullinemia may be involved in metformin's mechanism of action. We would like to draw attention on some aspects of citrulline's properties.

First, in terms of citrulline concentration, the study by Adam et al. (1) raises several questions because the authors did not specify whether the decrease is to a level below normal or just a normalization of citrullinemia. Citrullinemia has been repeatedly shown to be increased and arginine availability to be decreased with insulin resistance, e.g., in experimental models of high-fat feeding (3) as well as in humans (4). Citrullinemia is determined by citrulline's intestinal production from glutamine and arginine and its renal utilization for arginine synthesis (5). The liver does not play any significant role in these interorgan exchanges because liver citrulline is almost exclusively synthesized locally and channeled into the urea cycle. Intestinal citrulline synthesis is preserved in metabolic syndrome (3). Current data thus point to possible modifications in renal citrulline utilization. Indeed, we recently showed in healthy elderly volunteers that citrullinemia was associated positively with waist circumference and negatively with creatinine clearance (6). The modification of kidney citrulline metabolism under metformin treatment thus deserves to be studied.

Second, recent works, including ours, demonstrate that citrulline supplementation may be beneficial in situations of insulin resistance. On the one hand, citrulline improves insulin sensitivity at least in part through its effect on the liver and the visceral adipose tissue (7). In our recent studies (reviewed in [7]), we showed that citrulline-induced improvement in insulin sensitivity in nonalcoholic fatty liver disease was associated with *1*) decreased hepatic lipid synthesis, *2*) decreased visceral fat mass, *3*) preserved fat free mass, and *4*) decreased inflammatory processes. Among the possible underlying mechanisms, citrulline prevents the alterations in arginine metabolism as shown by normalized plasma arginine-to-(ornithine+citrulline) ratio and arginine-to-lysine ratio, and some of the peripheral effects of citrulline may stem from an improvement in nitric oxide synthesis (7). On the other hand, citrulline improves vascular function also through the arginine/nitric oxide pathway, and citrulline supplementation is associated with a reduction in resting blood pressure (8).

Last, metformin and citrulline are both potent antioxidants and their interactions deserve to be studied.

The question arises, therefore, whether all these results are two sides of the same coin: citrulline as an insulin-sensitizing amino acid and a marker of insulin resistance. It would thus be interesting to evaluate whether this citrulline increase is a compensatory mechanism for insulin resistance or just a consequence of type 2 diabetes–induced alterations in renal metabolism.

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