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# Impaired glucose tolerance in low-carbohydrate diet: maybe only a physiological state

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TO THE EDITOR: in the recent work of Bielohuby et al. (1) published in this journal, the authors discussed the hypothesis that the restriction of carbohydrates, substituted by the high consumption of fats, induces a state of glucose intolerance and insulin resistance in rats, which was demonstrated through diverse methodologies, including the hyperinsulinemic euglycemic clamps. It was further shown that these effects are independent of the visceral adipose mass and caloric consumption.

Within this perspective, some considerations become interesting. The metabolic state induced by the restriction of carbohydrates in ketogenic diets is similar in many points to prolonged fasting, in which the metabolic flux is altered, favoring the fatty acids and ketone bodies as a source of energy and decreasing the need for glucose. This decreased need for glucose is especially useful since it preserves the muscle mass that could otherwise be "cannibalized" by proteolytic processes that would overcome to provide substrates for hepatic gluconeogenesis (2, 10). In this context, the intense oxidation of fatty acids decreases the glycolysis, glucose uptake, and oxidation, a process described previously by Randle et al. (6a). The final products of fatty acids and ketone body oxidation (NADH and acetyl-CoA) and the increase in intracellular cyclic AMP induced by hormones inhibit the pyruvate dehydrogenase complex, the main determinant of the rate of glucose utilization as an energy source (7, 8). For that reason, it should be common in clinical practice that patients submitted to oral glucose tolerance tests not be under severe carbohydrate restriction, since this could alter the response to the glucose overload. Thus, we suggest that the results from Bielohuby et al. (1) can be interpreted as a unique and not necessarily harmful metabolic condition, which is characteristic of this state, besides being transitory. As demonstrated by Kinzig et al. (4), the glucose intolerance and the peripheral insulin resistance are rapidly reversible with the reintroduction of carbohydrates in the diet.

Additionally, the condition of induced insulin resistance is different from that induced by mitochondrial dysfunction, caused by oxidative stress generated by the glucose overload (3), which evidently does not occur with the carbohydrate restriction. In that context, ketogenic diets have not yet demonstrated adverse effects in the mitochondrial function; on the other hand, in vivo and in vitro physiological concentrations of β-hydroxybutyrate, a ketone body, increased the resistance to oxidative stress, according to a recent publication (9). It has also been demonstrated that ketogenic diets have the capacity to increase the concentrations of adiponectin, which is an important anti-inflammatory agent (5), whereas β-hydroxybutyrate stimulates the secretion of adiponectin through the activation of the hydroxycarboxylic acid receptor 2 (6).

Therefore, we conclude that the work of Bielohuby et al. (1) is a good example of the malleability of the in vivo response to insulin, which can be modulated to benefit the current metabolic state, and that the results found are not necessarily equivalent to those found in pathological processes.

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## DISCLOSURES

The authors declare they have no conflicts of interest, financial or otherwise,to disclose.

## AUTHOR CONTRIBUTIONS

R.d.O.C. contributed to the conception and design of the research; R.d.O.C. and F.B.L. edited and revised the manuscript; R.d.O.C. and F.B.L. approved the final version of the manuscript.

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