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COMMENT ON NOLAN ET AL.

Insulin Resistance as a Physiological Defense Against Metabolic Stress: Implications for the Management of Subsets of Type 2 Diabetes. Diabetes 2015;64:673–686

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We read with great interest the recent article by Nolan et al. (1) in which the authors, summarizing previous basic and pathophysiological research, propose the concept of insulin resistance (IR) as a protective mechanism in overweight/obese subjects with type 2 diabetes. As a consequence of this premise, they argue against intensive insulin treatment as an approach to override IR with the final goal of satisfactory blood glucose control in obese subjects unlikely to correct positive energy balance through lifestyle interventions (1).

While congratulating them for this important point of view that further underlines the need for a "personalized" medical approach to type 2 diabetes phenotypes, we believe that an additional consequence could be derived from their considerations: is β-cell failure a defense mechanism in IR subjects, too?

It is well recognized and accepted that in type 2 diabetes hyperglycemia develops when β-cells cannot cope with the increasing insulin demand to maintain euglycemia because of IR (2). If the premise of harmful effects of hyperinsulinemia is correct, β-cell failure in overweight/obese subjects would be a mechanism to protect organs and tissues from overexposure to insulin and its potential negative long-term effects (1). At the same time, lack of insulin, the consequent glycosuria, and β-oxidation "shift" of metabolism would eventually result, at least theoretically, in restoring insulin sensitivity. While β-cell failure would preserve some tissue from being overexposed to insulin, it would also result in glucose-mediated damages to the nerves, eye, and kidney, leaving the clinician to face a trade-off (1).

Notwithstanding all these considerations, we certainly believe that the reflections of Nolan et al. (1) further emphasize that the simple, historical, and etymological "glucocentric" approach of diabetes should be reconsidered (3), particularly when it is viewed in light of its relationship with not only microvascular and macrovascular complications but also nonvascular complications (4,5).

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