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EDITORIAL

Macronutrient composition and metabolic regulation: Do our islets care what we eat?

The study by Klinsmann et al. in this issue investigated effects of macronutrients, particularly carbohydrates and fat, on the insulin-to-glucagon ratio in vitro and in vivo.[1] Furthermore, the authors tested whether this ratio is altered in individuals with type 2 diabetes. Insulin and glucagon are the main hormones regulating glucose homeostasis. Yet, over many years there has been an imbalance in the research on type 2 diabetes mellitus between insulin and glucagon favoring insulin. The anabolic hormone insulin increases cellular glucose uptake and promotes triacylglycerol storage. In contrast, glucagon elicits glucose and fatty acid release from their storage sites. Insulin administration improves hyperglycemia in patients with type 2 diabetes mellitus. However, high insulin levels attained during insulin treatment can also promote further weight gain.[2] Thus, insulin can have positive as well as negative metabolic actions in a person with type 2 diabetes considering that excess adiposity is a crucial underlying cause of the condition. The idea that insulin could contribute to the pathogenesis of diabetes mellitus is not new and was already entertained in the 1920s. Decades later in 1973 Unger and Orci proposed their bihormonal-abnormality hypothesis of type 2 diabetes mellitus, which also puts glucagon at the center of the disease.[3] Today, strategies to antagonize glucagon action and at the same time utilize glucagon's effects on increasing energy expenditure and decreasing food intake are of great interest, both, in mechanism-oriented studies and in clinical development of new antidiabetic drugs. Apparently, consideration of either insulin or glucagon in isolation is insufficient. Due to the interdependence of the cells within the pancreas,[4] the insulin-to-glucagon ratio may provide a more comprehensive insight into metabolic regulation. Mechanisms regulating their secretion within the pancreas are complex (Figure 1) and secretory function is further modified by metabolic diseases such as type 2 diabetes.[5] Particularly, effects of different macronutrients on insulin and glucagon secretion in mildly impaired glycemic control are not well studied.

Klinsmann et al. used a translational approach to assess influences of carbohydrates and fat on the insulin-to-glucagon ratio in vitro and in vivo.[1] First, they isolated pancreatic islets from 10- to 16-week-old female mice and maintained the islets in vitro. Afterward, they applied solutions with different fatty acid palmitate and glucose concentrations to the islets. Finally, they measured insulin and glucagon in supernatants. The authors observed that, both, glucose and palmitate stimulated insulin release. Moreover, palmitate stimulated and glucose-inhibited glucagon secretion. Of note, there was no interaction between macronutrients on hormone secretion. Thus, the insulin-to-glucagon ratio increased with glucose application and remained unchanged following palmitate application in isolated rodent islets.

Next, the authors conducted human investigations in individuals without or with type 2 diabetes mellitus. The group with type 2 diabetes mellitus was significantly older and more obese compared with the non-diabetic group. The majority of patients with type 2 diabetes mellitus were on antidiabetic drugs, however, insulin secretagogues were discontinued before testing. Study participants ingested one carbohydrate- and one fat-enriched meal in a cross-over fashion with a washout of at least 1 month in men and of at least 2 months in women between tests. The authors obtained venous blood samples before and in regular intervals following food ingestion for insulin and glucagon measurements. In light of their in vitro results, the authors hypothesized that carbohydrates would have a stronger impact on the insulin-to-glucagon ratio than fat. While glucose excursions were similar after carbohydrate and fat ingestion in individuals without diabetes mellitus, blood glucose elevation was more pronounced after carbohydrate compared to fat ingestion in individuals with type 2 diabetes. In line with fasting or postprandial hyperinsulinemia and hyperglucagonemia in patients with type 2 diabetes,[6] the authors observed that insulin and glucagon secretion depended on the glycemic status, with only the meal composition impacting the insulin-to-glucagon ratio. The fat-rich meal reduced the insulin-to-glucagon ratio more in obese individuals and less efficiently in those with poor glycemic control.

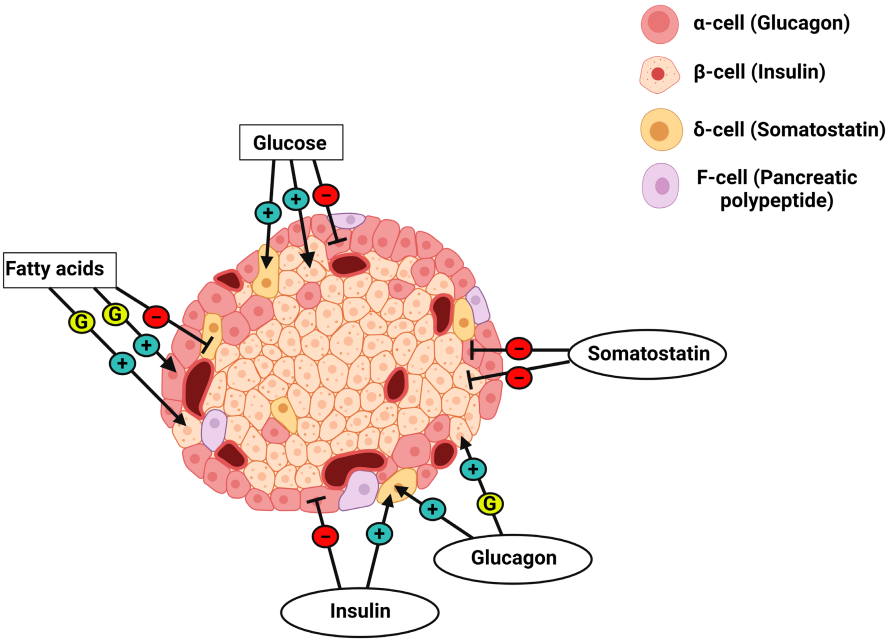

FIGURE 1 General concept of pancreatic hormones and macronutrients affecting secretion within the endocrine cells of the pancreas; + signs indicate a positive and − signs a negative effect on hormonal secretion, G indicates glucose-dependent effects. Created with BioRender.com.

Which conclusions can we draw from these interesting findings? Although influences of meal macronutrient composition on weight loss remain a matter of debate,[7] the study by Klinsmann et al. indicates that macronutrient composition could be adjusted to tune the insulin-to-glucagon ratio in individuals with type 2 diabetes mellitus. Only interventions of this kind over longer time periods will establish a causal relationship and prove benefits in terms of long-term weight loss. At least in overweight-to-obese persons without type 2 diabetes mellitus, we did not observe a major difference in metabolic or cardiovascular benefits between fat-reduced or carbohydrate-reduced hypocaloric diets.[8,9] An interesting finding along these lines is that individuals with a higher body mass index showed a more pronounced response to a high-fat meal. This finding seemed independent of the disease status. As the authors only used the body mass index as a proxy for obesity, future studies should incorporate more detailed body composition analyses to further scrutinize the effect of body fat on the responsiveness to macronutrient composition. On the other hand, the reduced insulin-to-glucagon ratio after the high-fat meal was only seen in individuals with an HbA1c below 59.3 mmol/mol, indicating decreased effectiveness of fat-rich diets in those with poor glycemic control. As the authors point out, only by also incorporating amino acids, future research can complete the picture of macronutrient impact on metabolic regulation. We suggest that fatty acid composition should also be considered.

Increased knowledge regarding individual insulin and glucagon responses coupled with a more refined view on the physiology of both hormonal systems could pave the way to "personalized" or "precision" nutrition. The approach could prove useful as preventive measure in persons at risk of type 2 diabetes and as adjunctive therapy in patients with established disease. Perhaps, specific diets could be recommended to maximize successful weight loss and metabolic benefits based on hormonal secretory patterns. Another exciting research area with potential clinical implications is the interaction between nutrition and antidiabetic treatment strategies. The finding that the small subgroup of individuals using glucagon-like peptide-1 receptor agonists or dipeptidyl-peptidase 4 inhibitors, which augments endogenous glucagon-like peptide-1, exhibited alterations in the insulin-to-glucagon ratio while requiring confirmation in larger samples suggests that the idea is not completely off the mark. Indeed, insulin and glucagon secretion are, both, regulated by incretins such as glucagon-like peptide 1.[10] Meanwhile, more powerful drugs such as dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonists are in the clinic[11] and glucagon receptor agonists are being tested.[12] We propose that the interactions between insulin and glucagon secretion and gastrointestinal hormones, changes after incretin mimetic therapy, and how these interactions affect reward systems, food intake, and body weight regulation deserve attention. Finally, we should not forget the delta-cells in this context, with somatostatin being an equally important paracrine regulator in the pancreas. In addition to providing new insight into human physiology, such studies may address an important healthcare issue given the increasing number of people affected by obesity and type 2 diabetes.

CONFLICT OF INTEREST

DP has nothing to disclose. JJ served as advisor for Novo-Nordisk and Bayer, received research support from Boehringer-Ingelheim and Novo-Nordisk, and is co-founder of Eternygen GmbH.

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REFERENCES

1. Carolo dos Santos K, Olofsson C, Cunha JPMCM, et al. The impact of macronutrient composition on metabolic regulation: an islet-centric view. *Acta Physiol*. 2022:e13884.
2. Balkau B, Home PD, Vincent M, Marre M, Freemantle N. Factors associated with weight gain in people with type 2 diabetes starting on insulin. *Diabetes Care*. 2014;37(8):2108-2113.
3. Unger RH, Orci L. The essential role of glucagon in the pathogenesis of diabetes mellitus. *Lancet*. 1975;1(7897):14-16.
4. Zhu L, Dattaroy D, Pham J, et al. Intra-islet glucagon signaling is critical for maintaining glucose homeostasis. *JCI Insight*. 2019;5(10):e127994.
5. Omar-Hmeadi M, Lund PE, Gandasi NR, Tengholm A, Barg S. Paracrine control of α-cell glucagon exocytosis is compromised in human type-2 diabetes. *Nat Commun*. 2020;11(1):1896.
6. Lund A, Bagger JI, Christensen M, Knop FK, Vilsbøll T. Glucagon and type 2 diabetes: the return of the alpha cell. *Curr Diab Rep*. 2014;14(12):555.
7. Ge L, Sadeghirad B, Ball GDC, et al. Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: systematic review and network meta-analysis of randomised trials. *BMJ*. 2020;369:m696.
8. Haufe S, Engeli S, Kast P, et al. Randomized comparison of reduced fat and reduced carbohydrate hypocaloric diets on intrahepatic fat in overweight and obese human subjects. *Hepatology*. 2011;53(5):1504-1514.
9. Haufe S, Utz W, Engeli S, et al. Left ventricular mass and function with reduced-fat or reduced-carbohydrate hypocaloric diets in overweight and obese subjects. *Hypertension*. 2012;59(1):70-75.
10. Drucker DJ. The biology of incretin hormones. *Cell Metab*. 2006;3(3):153-165.
11. Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med*. 2021;385(6):503-515.
12. Pettus JH, D'Alessio D, Frias JP, et al. Efficacy and safety of the glucagon receptor antagonist RVT-1502 in type 2 diabetes uncontrolled on metformin monotherapy: a 12-week dose-ranging study. *Diabetes Care*. 2020;43(1):161-168.