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Commentary

Adipose tissue lipolysis, plasma fatty acids, and glucose homeostasis in people with obesity: New pieces that help solve the puzzle

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Insulin is the key regulator of plasma glucose concentration, because it potently suppresses hepatic glucose production and stimulates tissue glucose uptake. Obesity is often associated with both insulin resistance and hyperinsulinemia. The concurrence of the two is commonly thought to reflect a homeostatic feedback loop in which the insulin resistance-mediated increase in plasma glucose stimulates insulin secretion from β-cells to maintain euglycemia [1]. Continuous overstimulation of β-cells leads to β-cell dysfunction, i.e., an insufficient β-cell response to the rise in glucose, resulting in hyperglycemia despite hyperinsulinemia and ultimately type 2 diabetes (T2D) [1]. However, it has also been proposed that insulin hypersecretion is the initial defect that causes insulin resistance and the vicious cycle that eventually results in T2D [1]. Alternatively, it has been suggested that insulin resistance and insulin hypersecretion occur simultaneously because they have a common cause – adipose tissue dysfunction. According to this hypothesis, enlargement of adipocytes leads to a cascade of events that includes impaired adipose tissue perfusion, inflammation, reduced insulin action on triglyceride lipolysis, and increased fatty acid release into the circulation, which in turn causes both insulin resistance in the liver and muscles and increased insulin secretion from β-cells [1–4]. In this issue of EBioMedicine, Fryk and colleagues [5] describe the results from two studies that provide new insights into this complex relationship.

In one study, the authors measured basal plasma fatty acid and C-peptide (a marker of insulin secretion) concentrations in a subset (n = 242) of 50 year-old lean and obese (defined as BMI >28 kg/m^2) men and women who participated in a population study in the city of Gothenburg (Sweden). The participants were specifically selected, because their fasting plasma glucose concentration was <5.0 mM (90 mg/dl). This cut-off is significantly less than the cut-off used to define normal fasting plasma glucose (<100 mg/dl) and eliminates potential confounding by incipient abnormalities in glycemic control. A fasting plasma glucose value between 90 mg/dl and 99 mg/dl, although still within the normal range, is a strong independent predictor of future T2D [6]. Participants with obesity were separated into those with normal plasma insulin concentration and insulin sensitivity (assessed by using the HOMA insulin resistance index) and those with high plasma insulin concentration and insulin resistance. The authors found plasma glucose concentration was not different among the lean and two obese groups. However, plasma fatty acid and C-peptide concentrations progressively increased from the lean to the insulin-sensitive obese to the insulin-resistant obese groups. Although it is tempting to attribute the differences in insulin secretion among groups to the differences in plasma fatty acid concentration, it is impossible to infer causality. Nevertheless, the authors provide compelling arguments that suggest fatty acids could be mechanistically involved in causing insulin hypersecretion. In addition, increased β-cell mass may have also contributed to insulin hypersecretion in the obese [7].

In the second study, Fryk and colleagues [5] evaluated plasma glucose, insulin, and fatty acid concentrations before and for three hours after ingesting 75 g of glucose in three groups of men and women: i) healthy lean, ii) insulin-resistant, but normoglycemic obese, and iii) obese with T2D. In addition, the authors assessed the rate of release of glycerol from adipocytes by using microdialysis in conjunction with radiolabeled xenon injection, which enables a direct assessment of the rate of adipose tissue triglyceride lipolysis. An adipose tissue biopsy sample was obtained to assess adipocyte size and gene expression. As expected, T2D was associated with hyperglycemia whereas plasma glucose concentration was not different between the non-diabetic obese and the lean groups. However, fatty acid and glycerol concentrations were more than double in both the diabetic and non-diabetic obese compared with the lean group. In addition, adipocytes were larger and postprandial adipose tissue perfusion was about 70% less in both the diabetic and non-diabetic obese compared with the lean group, with no (adipocyte size, perfusion, plasma glycerol) or only small (plasma fatty acids) differences between the diabetic and non-diabetic obese groups. Gene expression markers of inflammation in adipose tissue were also markedly greater in the obese than lean participants with no

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(majority of genes assessed) or only small differences between the non-diabetic and diabetic obese. Glycerol release from adipose tissue, expressed per kg tissue, was not different among the lean and obese groups. Accordingly, the greater plasma fatty acid concentrations in the obese groups compared with the lean group were due to the greater fat mass – not increased adipose tissue triglyceride lipolysis, presumably because hyperinsulinemia can compensate for insulin resistance at the cellular/tissue level but not for the increase in adipose tissue mass. It is unlikely that this conclusion was affected by lack of statistical power because there was no trend for differences in adipose tissue glycerol release among the groups.

In summary, these data provide new insights that help disentangle the complex interrelationship between excess body fat and metabolic function. First, the data suggest basal insulin hypersecretion in people with obesity occurs even in the absence of insulin resistance and is associated with an increase in plasma fatty acid concentration, presumably because of the increased fat mass. Secondly, obesity is associated with marked alterations in adipose tissue biology (adipocyte size, perfusion, inflammation), but they do not affect the lipolytic rate; they also do not predict plasma fatty acid concentration and appear to be unrelated to, or only make a minor contribution to the heterogeneity in glucose homeostasis among people with obesity. These results challenge some conventional wisdom, but are in line with the findings from other studies [8,9], and underscore the need for more mechanistic studies to understand the pathogenesis of metabolic dysfunction in people with obesity. These findings also have important clinical implications, because insulin hypersecretion is an independent risk factor for T2D [10], and suggest metabolically healthy obesity - commonly thought of as obesity without insulin resistance [4] – may not exist.

Contributors

HCEK and BM performed the literature search and wrote the manuscript.

Declaration of Competing Interest

The authors have nothing to disclose.

References

[1] Czech MP. Insulin action and resistance in obesity and type 2 diabetes. Nat Med 2017;23(7):804–14.
[2] Ghaben AL, Scherer PE. Adipogenesis and metabolic health. Nat Rev Mol Cell Biol 2019;20(4):242–58.
[3] Broussard JL, Kolka CM, Castro AV, et al. Elevated nocturnal NEFA are an early signal for hyperinsulinaemic compensation during diet-induced insulin resistance in dogs. Diabetologia 2015;58(11):2663–70.
[4] Smith GI, Mittendorfer B, Klein S. Metabolically healthy obesity: facts and fantasies. J Clin Investig 2019;129(10):3978–89.
[5] Fryk E, Olausson J, Mossberg K, et al. Hyperinsulinemia and insulin resistance in the obese may develop as part of a homeostatic response to elevated free fatty acids: a mechanistic case-control and a population-based cohort study. EBioMedicine (thelancet.com). EBioMedicine 2020. doi: 10.1016/j.ebiom.2021.103264.
[6] Brambilla P, La Valle E, Falbo R, et al. Normal fasting plasma glucose and risk of type 2 diabetes. Diabetes Care 2011;34(6):1372–4.
[7] Saisho Y, Butler AE, Manesso E, Elashoff D, Rizza RA, Butler PC. Beta-cell mass and turnover in humans: effects of obesity and aging. Diabetes Care 2013;36(1):111–7.
[8] Karpe F, Dickmann JR, Frayn KN. Fatty acids, obesity, and insulin resistance: time for a reevaluation. Diabetes 2011;60(10):2441–9.
[9] van Vliet S, Koh HE, Patterson BW, et al. Obesity Is Associated With Increased Basal and Postprandial beta-Cell Insulin Secretion Even in the Absence of Insulin Resistance. Diabetes 2020;69(10):2112–9.
[10] Trico D, Natali A, Arslanian S, Mari A, Ferrannini E. Identification, pathophysiology, and clinical implications of primary insulin hypersecretion in nondiabetic adults and adolescents. JCI Insight 2018;3(24):e124912.