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LETTER

On the causal relationships between hyperinsulinaemia, insulin resistance, obesity and dysglycaemia in type 2 diabetes: Reply to Johnson JD [letter]

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Abbreviations

iAUC	Incremental AUC
IGT	Impaired glucose tolerance
NGT	Normal glucose tolerance

To the Editor: We appreciate the thoughtful comments by Johnson [1] on our review [2] and agree that in general we have overlapping views that identify beta cell dysfunction as playing the central role in the pathogenesis of type 2 diabetes. What distinguishes us is we believe beta cell dysfunction with impaired insulin release usually occurs early, whereas he feels primary hyperinsulinaemia is frequently present initially [1]. As insulin resistance and hyperinsulinaemia are likely bidirectional, with obesity as a cause and potential consequence of both, determining cause/effect for each element in humans is extremely difficult. Based on rodent insulin gene knockout studies, Johnson suggests hyperinsulinaemia contributes to the development of obesity and insulin resistance. In contrast, we maintain that the development of obesity and insulin resistance unmasks the beta cell defect by asking it to work harder than it can. To enhance the debate, we respond with a few additional comments.

First, it is well recognised that the physiology of insulin production and release by the beta cell is complex, with insulin secretion tightly regulated and dependent on several factors including, but not limited to, the nature, quantity and route of administration of the stimulus as well as tissue sensitivity to insulin. Glucose is a critical modulator of the insulin response, both as a stimulus and a potentiator. In Fig. 2 in his commentary [1], Johnson redrew data from Mitrakou et al. [3] and suggests that while impaired glucose tolerance (IGT) is characterised by diminished early insulin release during an OGTT, it is also associated with fasting and fed hyperinsulinaemia. This interpretation fails to account for the difference in glucose concentrations in those with dysglycaemia and its impact on insulin responses. In the example cited, both the fasting and post-load glucose concentrations are elevated in those with IGT [3]. While the commensurate insulin concentrations are elevated in the fasting state, they only exceed those observed in the normal glucose tolerance (NGT) group beyond the first hour post-glucose ingestion when the glucose stimulus remains elevated as a result of a delayed/reduced early insulin response. Thus, our interpretation differs from his in that we believe that the insulin profile later in the test demonstrates higher concentrations because the glucose stimulus differs and therefore does not represent primary hyperinsulinaemia but rather impaired beta cell function.

To highlight the importance of considering the stimulus (here oral glucose), we further examined the OGTT data from the 613 Japanese Americans we reported in our original publication [2]. Individuals were categorised based on the 2 h plasma glucose as NGT, IGT or type 2 diabetes (Fig. 1). Given the dysglycaemia, glucose concentrations were elevated in individuals with IGT or type 2 diabetes (Fig. 1a) so that the incremental AUC (iAUC) above fasting determined over the whole duration of the test increased progressively with deteriorating glucose tolerance (Fig. 1c). Like Mitrakou et al's observations [3], individuals with IGT or type 2 diabetes displayed increased basal insulin levels and a reduced early insulin

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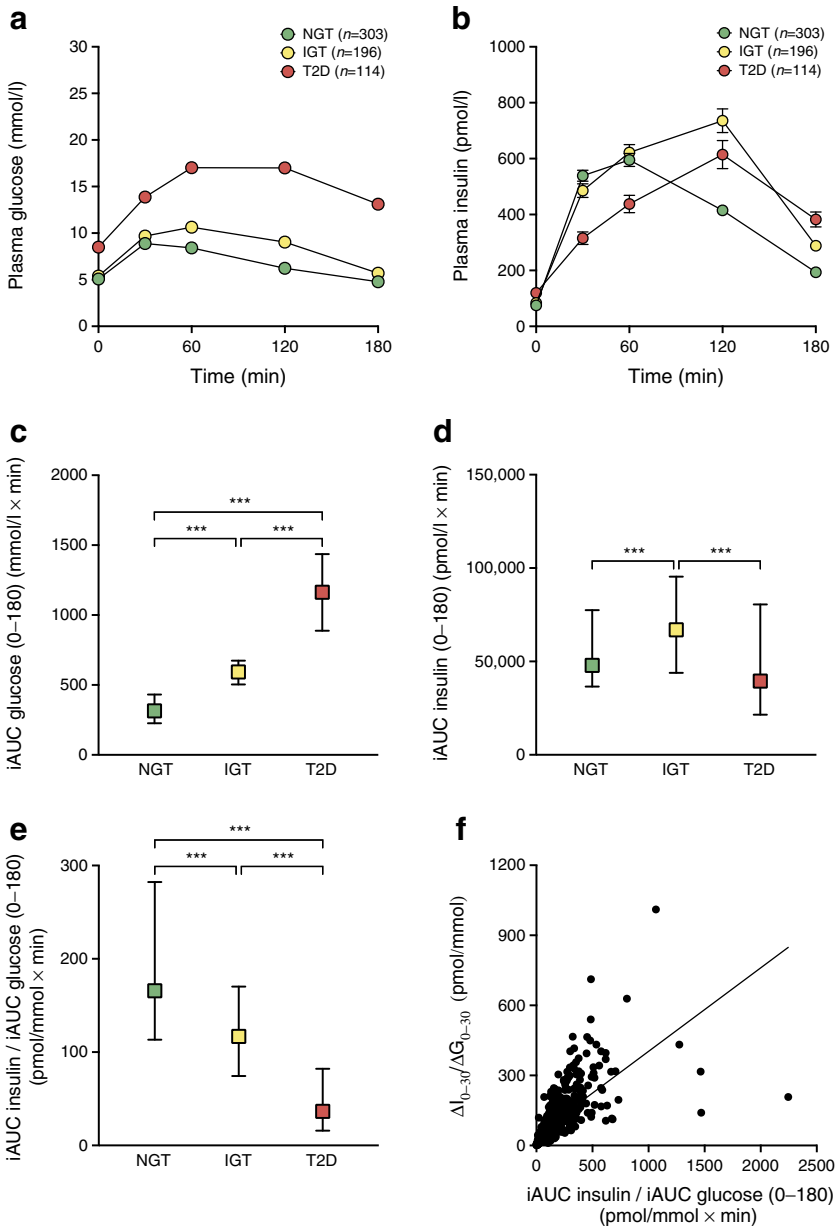

Fig. 1 Decreased glucose-stimulated insulin release in individuals with IGT and type 2 diabetes. (**a**) Glucose and (**b**) insulin concentrations during an OGTT in 613 Japanese Americans. Participants were categorised based on ADA criteria as having NGT (green; n=303), IGT (yellow; n=196) or type 2 diabetes (T2D, red; n=114). iAUC for (**c**) glucose, (**d**) insulin, and (**e**) insulin over glucose (iAUC insulin/iAUC glucose) were calculated from 0 to 180 min. Data are reported as mean ± SEM (**a**, **b**), or median and IQR (**c**, **d**, **e**). ***p<0.001 based on Kruskal–Wallis with Dunn's multiple comparisons tests. (**f**) The relationship between the early insulin response to glucose, calculated as Δ insulin$_{0–30}$ /Δ glucose$_{0–30}$ ($\Delta I_{0–30}/\Delta G_{0–30}$), and incremental insulin over glucose (iAUC insulin /iAUC glucose) in the whole cohort was linear in nature (r^2= 0.43, p<0.001). Figure based on data in [15]

response. However, beyond 60 min, insulin levels were elevated (Fig. 1b) with the iAUC insulin higher in individuals with IGT vs those with NGT (Fig. 1d). When the prevailing glucose was accounted for, in the fasting state there was no longer evidence of basal insulin hyperresponsiveness and, post-load, the magnitude of the iAUC insulin was reduced by 38% in individuals with IGT and 75% in individuals with type 2 diabetes (Fig. 1e). Further, in the whole cohort regression analysis of the early insulin response ($\Delta I_{0–30}/\Delta G_{0–30}$; also known as the insulinogenic index) and iAUC insulin/iAUC glucose over the 180 min demonstrated the two measures to be strongly related ($r^2 = 0.43$, $p < 0.001$, Fig. 1f). We observed similar results in a subgroup of 430 individuals in whom we used C-peptide (data not shown), highlighting deficient beta cell responses in individuals with IGT or type 2 diabetes using either peptide. Our findings are also in accordance with Mitrakou et al. [3], who found insulin and glucose concentrations at 2 h were positively correlated. Thus, we would suggest one cannot simply assume that primary hyperinsulinaemia is present when insulin levels are elevated. Uncoupling insulin release from the stimulus can lead to erroneous conclusions about the functional status of the beta cell.

Second, we fully agree that type 2 diabetes is a heterogeneous disease [4] and this heterogeneity in some individuals may manifest as insulin hypersecretion independent of insulin sensitivity [5, 6]. In fact, as discussed in our review [2], data from the Restoring Insulin Secretion (RISE) Study highlight this

heterogeneity showing it exists within and between youth and adults. As a component of these observations, youth had greater insulin responses than adults even after adjusting for differences in insulin sensitivity [7, 8]. These observations could indicate primary hyperinsulinaemia; however, since it was not associated with hypoglycaemia and overall blood glucose levels did not differ, we suggest that the increased insulin responses may represent a compensatory mechanism for decreased insulin-independent glucose uptake (glucose effectiveness). Indeed, it is well established that glucose effectiveness is important for glucose disposal in humans [9] and studies have reported that it is reduced in individuals with obesity, the metabolic syndrome and/or IGT [10–13] and can itself predict the development of dysglycaemia [11, 14]. This consideration raises the question whether hyperinsulinaemia may be a biomarker of reduced glucose effectiveness? However, even if that was the case, we do not believe dysglycaemia should develop unless there is an underlying beta cell defect.

Third, Johnson highlights the value of studies of genetically modified animals. We agree, but it is important to be careful when extrapolating from animal models to humans, particularly when considering type 2 diabetes. Type 2 diabetes is not a monogenic disease but is rather polygenic, highlighted in part by the increasing risk with increasing genetic risk scores.

In conclusion, we and Johnson certainly agree that an underlying beta cell defect characterised by reduced insulin secretion is required for dysglycaemia to develop. We hope further work will help elucidate whether in fact hyperinsulinaemia precedes insulin resistance or is a marker of some other abnormality, and whether the genetic basis for human type 2 diabetes includes genes that increase insulin secretion per se when accounting for known physiologic regulators of the beta cell's response.

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References

1. Johnson JD (2021) On the causal relationships between hyperinsulinaemia, insulin resistance, obesity and dysglycaemia in type 2 diabetes. Diabetologia https://doi.org/10.1007/s00125-021-05505-4
2. Esser N, Utzschneider KM, Kahn SE (2020) Early beta cell dysfunction vs insulin hypersecretion as the primary event in the pathogenesis of dysglycaemia. Diabetologia 63(10):2007–2021. https://doi.org/10.1007/s00125-020-05245-x
3. Mitrakou A, Kelley D, Mokan M et al (1992) Role of reduced suppression of glucose production and diminished early insulin release in impaired glucose tolerance. N Engl J Med 326(1):22–29. https://doi.org/10.1056/nejm199201023260104
4. Wagner R, Heni M, Tabák AG et al (2021) Pathophysiology-based subphenotyping of individuals at elevated risk for type 2 diabetes. Nat Med. https://doi.org/10.1038/s41591-020-1116-9
5. Trico D, Natali A, Arslanian S, Mari A, Ferrannini E (2018) Identification, pathophysiology, and clinical implications of primary insulin hypersecretion in nondiabetic adults and adolescents. JCI Insight 3(24):e124912. https://doi.org/10.1172/jci.insight.124912
6. van Vliet S, Koh HE, Patterson BW et al (2020) Obesity Is Associated With Increased Basal and Postprandial β-Cell Insulin Secretion Even in the Absence of Insulin Resistance. Diabetes 69(10):2112–2119. https://doi.org/10.2337/db20-0377
7. RISE Consortium (2018) Metabolic contrasts between youth and adults with impaired glucose tolerance or recently diagnosed type 2 diabetes: II. Observations using the oral glucose tolerance test. Diabetes Care 41(8):1707–1716. https://doi.org/10.2337/dc18-0243
8. RISE Consortium (2018) Metabolic contrasts between youth and adults with impaired glucose tolerance or recently diagnosed type 2 diabetes: I. Observations using the hyperglycemic clamp. Diabetes Care 41(8):1696–1706. https://doi.org/10.2337/dc18-0244
9. Best JD, Kahn SE, Ader M, Watanabe RM, Ni TC, Bergman RN (1996) Role of glucose effectiveness in the determination of glucose tolerance. Diabetes Care 19(9):1018–1030. https://doi.org/10.2337/diacare.19.9.1018
10. Araújo-Vilar D, García-Estévez DA, Cabezas-Cerrato J (1999) Insulin sensitivity, glucose effectiveness, and insulin secretion in nondiabetic offspring of patients with non-insulin-dependent diabetes mellitus: a cross-sectional study. Metabolism 48(8):978–983. https://doi.org/10.1016/s0026-0495(99)90193-2
11. Weiss R, Magge SN, Santoro N et al (2015) Glucose effectiveness in obese children: relation to degree of obesity and dysglycemia. Diabetes Care 38(4):689–695. https://doi.org/10.2337/dc14-2183
12. Spreghini N, Cianfarani S, Spreghini MR et al (2019) Oral glucose effectiveness and metabolic risk in obese children and adolescents. Acta Diabetol 56(8):955–962. https://doi.org/10.1007/s00592-019-01303-y
13. Hu S, Lu Y, Tura A, Pacini G, D'Argenio DZ (2021) An analysis of glucose effectiveness in subjects with or without type 2 diabetes via hierarchical modeling. Front Endocrinol (Lausanne) 12:641713. https://doi.org/10.3389/fendo.2021.641713
14. Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, Kahn CR (1992) Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25-year follow-up study. Lancet 340(8825):925–929. https://doi.org/10.1016/0140-6736(92)92814-v
15. Fujimoto WY, Leonetti DL, Kinyoun JL et al (1987) Prevalence of diabetes mellitus and impaired glucose tolerance among second-generation Japanese-American men. Diabetes 36(6):721–729. https://doi.org/10.2337/diab.36.6.721