Diabetes & Metabolism 45 (2019) 197–200

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

Short report

Effect of short-term intensive insulin therapy on the incretin response in early type 2 diabetes

H. Choi [a], C.K. Kramer [a,b], B. Zinman [a,b,c], P.W. Connelly [b,d,e], R. Retnakaran [a,b,c,*]

[a] Leadership Sinai center for diabetes, Mount Sinai hospital, Toronto, Canada
[b] Division of endocrinology, university of Toronto, Toronto, Canada
[c] Lunenfeld-Tanenbaum research institute, Mount Sinai hospital, Toronto, Canada
[d] Keenan research center for biomedical science of St. Michael's hospital, Toronto, Canada
[e] Department of laboratory medicine and pathobiology, university of Toronto, Toronto, Canada

ARTICLE INFO

Article history:
Received 10 October 2017
Accepted 3 January 2018
Available online 11 January 2018

Keywords:
GIP
GLP-1
Glucagon-like peptide-1
Glucose-dependent insulinotropic polypeptide
Intensive insulin therapy

ABSTRACT

Aims. – Short-term intensive insulin therapy (IIT) and gastric bypass surgery are both interventions that can improve beta-cell function, reduce insulin resistance and induce remission of type 2 diabetes. Whereas gastric bypass yields an enhanced glucagon-like peptide-1 (GLP-1) response that may contribute to its metabolic benefits, the effect of short-term IIT on the incretin response is unclear. Thus, we sought to evaluate the impact of IIT on GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) secretion in early type 2 diabetes.

Methods. – In this study, 63 patients (age 59 ± 8.3 years, baseline A1c 6.8 ± 0.7%, diabetes duration 3.0 ± 2.1 years) underwent 4 weeks of IIT (basal insulin detemir and pre-meal insulin aspart). GLP-1, GIP and glucagon responses were assessed by the area-under-the-curve (AUC) of these hormones on oral glucose tolerance tests at baseline and 1-day after the completion of therapy. Beta-cell function was assessed by Insulin Secretion-Sensitivity Index-2 (ISSI-2), with insulin resistance measured by Homeostasis Model Assessment (HOMA-IR).

Results. – As expected, comparing the post-therapy oral glucose tolerance test to that at baseline, IIT increased ISSI-2 ($P = 0.02$), decreased HOMA-IR ($P < 0.001$), and reduced $AUC_{glucagon}$ ($P < 0.001$). Of note, however, IIT had no significant impact on $AUC_{GLP\text{-}1}$ ($P = 0.24$) and reduced AUC_{GIP} ($P = 0.02$).

Conclusion. – Despite improving beta-cell function, insulin resistance and glucagonemia, short-term IIT does not change GLP-1 secretion and decreases the GIP response to an oral glucose challenge in early type 2 diabetes. Thus, the beneficial impact of this therapy on glucose homeostasis is not attributable to its effects on incretin secretion.

1. Abbreviations

AUC	area-under-the-curve
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
HOMA-IR	Homeostasis Model Assessment of insulin resistance
IIT	intensive insulin therapy
ISSI-2	Insulin Secretion-Sensitivity Index-2
OGTT	oral glucose tolerance test
T2DM	type 2 diabetes

2. Introduction

In patients with type 2 diabetes (T2DM), gastric bypass surgery can improve beta-cell function, reduce insulin resistance and induce remission of diabetes [1–3]. One notable feature of the altered metabolic physiology following gastric bypass is a marked enhancement of the secretion of glucagon-like peptide-1 (GLP-1) in response to a nutrient challenge [2–5]. It has been suggested that the enhanced GLP-1 response may contribute to the sustained metabolic benefits achieved with gastric bypass [2,3], although its potential causal role in this regard remains under debate [4,5].

When administered early in the course of T2DM, short-term intensive insulin therapy (IIT) for 2-4 weeks is a non-surgical intervention that can also improve beta-cell function, reduce insulin resistance and induce subsequent remission of diabetes

* Corresponding author at: Leadership Sinai center for diabetes, Professor of medicine, university of Toronto, Mount Sinai hospital, 60, Murray Street, Suite L5-025, Mailbox-21, Toronto, Ontario, Canada M5T 3L9.
E-mail address: ravi.retnakaran@sinaihealthsystem.ca (R. Retnakaran).

https://doi.org/10.1016/j.diabet.2018.01.003
1262-3636/

[6–8]. However, the mechanistic basis of these effects (whether alleviation of glucotoxicity or the anti-lipolytic, anti-inflammatory, anti-apoptotic or other effects of insulin) remains unclear [7]. Similarly, the effect of short-term IIT on the incretin response is unclear [9,10]. In this context, we sought to evaluate the impact of IIT on GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) secretion in early T2DM.

3. Methods

The study population consisted of adults with T2DM who underwent a short course of IIT to determine eligibility for a clinical trial (NCT01270789). The protocol for this IIT phase has been previously described in detail [8,11]. In brief, inclusion criteria were age 30–75 years; T2DM of $\leq$7-year duration; treatment with 0–2 oral anti-diabetic medications and serum negativity for anti-glutamic acid decarboxylase antibodies. Exclusion criteria included current insulin or GLP-1 agonist therapy, renal/hepatic dysfunction, malignancy, and chronic infection. The protocol was approved by the Mount Sinai Hospital Research Ethics Board and all participants provided written informed consent.

3.1. Study design

At the start, participants stopped anti-diabetic medications (metformin or sulfonylurea) the day before and fasted overnight prior to undergoing a baseline 2-hour, 75 g oral glucose tolerance test (OGTT) the next morning. After this OGTT, they began a 4-week course of multiple daily insulin injection therapy (basal insulin detemir and pre-meal insulin aspart). The initial total daily dose of insulin was 0.2–0.4 U/kg, consisting of 40% basal insulin and 60% bolus insulin. While receiving IIT, participants were asked to perform self-monitoring of capillary blood glucose at least 4 times/day (at fasting, before meals, 2-hours after meals, and at bedtime). These measurements enabled insulin dose titration to target fasting glucose between 4.0–6.0 mmol/L and 2-hr postprandial glucose $<$ 8 mmol/L. On the final day of IIT, the last insulin dose was the pre-dinner aspart, with no bedtime basal detemir. An OGTT was performed the day after cessation of IIT, using the same protocol as at baseline.

3.2. Laboratory measurements

On each OGTT, venous blood samples were drawn for the measurement of glucose, insulin, glucagon, GLP-1, and GIP at fasting and at 30,60,90 and 120 minutes following ingestion of the 75 g glucose load. Specific insulin was measured with the Roche-Elecsys-1010 immunoassay analyzer and electrochemiluminescence immunoassay kit (Roche Diagnostics, Laval, QC). Samples for glucagon/incretin measurement were collected in chilled tubes with aprotinin and kept on ice before immediate storage at −80 C. Glucagon was measured by ELISA assay 10-1271-01 from Mercodia (Uppsala, Sweden). Total GLP-1 was measured using ELISA assay EZGLP1T-36K (EMD Millipore, St. Charles, MO). The assay has a detection limit of 1.5 pM. Total GIP was measured with ELISA assay EZHGIP-54K (EMD Millipore, St. Charles, MO). The assay has a detection limit of 4.2 pg/mL.

GLP-1, GIP and glucagon responses were assessed by the respective area-under-the-curve (AUC), calculated by trapezoidal rule. Beta-cell function was assessed with the Insulin Secretion-Sensitivity Index-2 (ISSI-2) and insulin resistance was assessed by Homeostatic Model Assessment (HOMA-IR), as previously described [8,11].

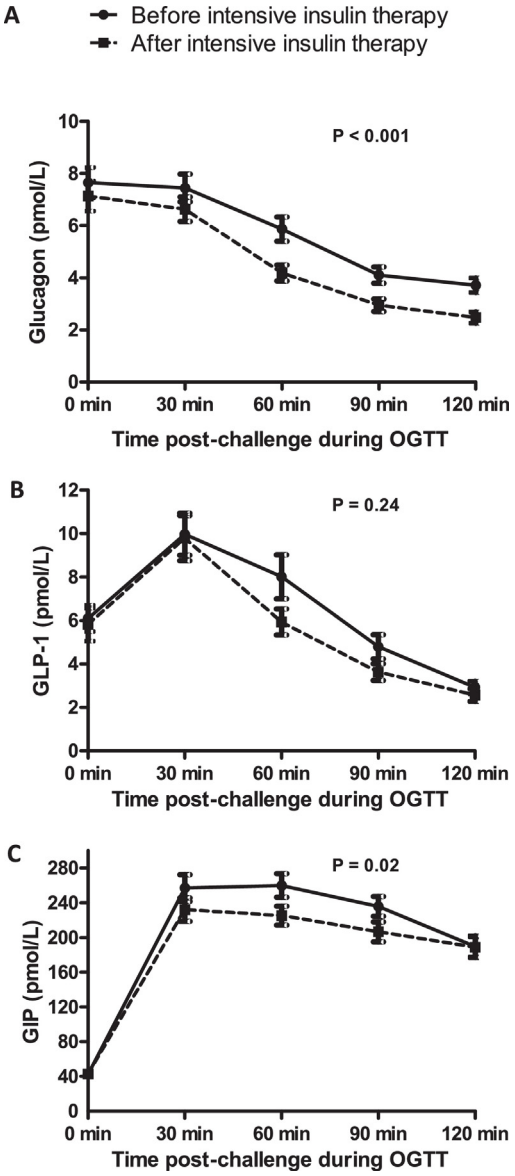

Fig. 1. Glucagon and incretin responses to 75 g oral glucose tolerance test before (solid line) and after (dashed line) short-term intensive insulin therapy: A. Glucagon. B. GLP-1. C. GIP. *P* value is the comparison of area-under-the-curve before and after IIT.

3.3. Statistical analysis

All analyses were conducted using SPSS 18.0 (Chicago, IL). Metabolic characteristics of participants before and after IIT were compared using Student t-test for paired-samples. Normally-distributed continuous variables were presented as mean $\pm$ SD and skewed variables were presented as median and interquartile range. The glucagon and incretin response profiles on the OGTT before and after IIT were plotted, with the respective AUC compared between the tests (Fig. 1). Spearman correlation analysis was performed to assess the univariate correlations of metabolic measures before and after IIT with the change in AUC_{GIP} and change in $AUC_{GLP\text{-}1}$ (Table S1; see supplementary materials associated with this article on line).

4. Results

The study population consisted of 63 adults (40 male) with (mean $\pm$ SD) age 59 $\pm$ 8.3 years and T2DM of mean 3.0 $\pm$ 2.1years

duration. As compared to that at baseline, the post-therapy OGTT confirmed that IIT improved glycaemic control (fasting glucose (6.7 ± 1.3 vs 6.2 ± 1.1 mmol/L, $P = 0.002$) and A1c ($6.8 \pm 0.7\%$ vs $6.3 \pm 0.5\%$, $P < 0.001$)), reduced body mass index (29.9 ± 6.2 vs 29.5 ± 6.1 kg/m^2, $P < 0.001$) and improved beta-cell function (ISSI-2: median [interquartile range] 179 [120–225] vs 189 [141–290], $P = 0.02$) and insulin resistance (HOMA-IR: 4.0 [2.5–5.7] vs 2.9 [1.7–4.8], $P < 0.001$). Fig. 1 shows the glucagon, GLP-1 and GIP responses to the OGTT before and after therapy. Of note, IIT reduced $AUC_{glucagon}$ (mean 24.0 ± 12.6 vs 18.7 ± 9.6, $P < 0.001$). However, the therapy had no impact on $AUC_{GLP\text{-}1}$ (median [interquartile range]: 22 [12–37] vs 18 [12–37], $P = 0.24$) and reduced AUC_{GIP} (859 [631–1039] vs 718 [632–1037], $P = 0.02$), with no change in fasting GIP. Sensitivity analyses excluding (i) participants who had been on metformin or (ii) those who had been on any oral anti-diabetic medication prior to the study showed no significant differences in $AUC_{GLP\text{-}1}$ and AUC_{GIP} between the baseline and post-IIT OGTTs, although it should be noted that these restrictions yielded very modest sample sizes (data not shown).

On Spearman correlation analysis, baseline BMI ($r = -0{,}34$, $P = 0.007$) and AUCglucagon ($r = -0.31$, $P = 0.02$) were inversely associated with the change in $AUC_{GLP\text{-}1}$, while the changes in fasting glucose ($r = 0.27$, $P = 0.03$) and $AUC_{glucagon}$ ($r = 0.39$, $P = 0.004$) were positively associated (Table S1; see supplementary materials associated with this article on line). The change in AUC_{GIP} was inversely associated with the change in ISSI-2 ($r = -0.29$, $P = 0.03$) and positively correlated with the change in HOMA-IR ($r = 0.31$, $P = 0.02$).

5. Discussion

In this study, we demonstrate that, when administered in early T2DM, short-term IIT does not change GLP-1 secretion and decreases the GIP response to an oral glucose challenge. At the same time, this therapy improved beta-cell function, reduced glucagonemia and lowered insulin resistance. It thus, emerges that the impact of short-term IIT on incretin secretion does not contribute to the beneficial metabolic effects of this therapy in early T2DM.

Amongst non-surgical therapeutic options early in the course of T2DM, an intriguing feature of short-term IIT is its capacity to induce a subsequent sustained remission of diabetes [6,7]. Indeed, a meta-analysis has shown that, after IIT for 2–5 weeks, 59% of patients can maintain drug-free normo-glycaemia for 6 months, with remission persisting for 1 year in 46% of patients [7]. Although this effect is not permanent and ultimately wanes over time, there is interest in its presumed underlying mechanism of initial amelioration of the reversible beta-cell dysfunction that may predominate in early T2DM [11]. In this context, there exist parallels to gastric bypass, which yields many of the same metabolic benefits and can also induce long-term remission, the likelihood of which is greater with shorter duration of diabetes [12]. Notably, gastric bypass induces a marked enhancement of GLP-1 secretion, which has been implicated as a key determinant of its metabolic benefits, although its centrality in this regard is under debate [2–5]. Taken together, these data raise the question of whether effects on GLP-1 secretion could be relevant to the metabolic benefits of short-term IIT.

The few previous studies relevant to this question have been limited by very modest sample sizes and have yielded conflicting findings. In 9 Caucasian patients with T2DM, 4 weeks of IIT had no effect on postprandial GLP-1 and GIP secretion [9]. Conversely, in a study of 26 hospitalized Japanese patients with longstanding T2DM of mean 13.5-year duration, treatment with IIT for 10–14 days increased GLP-1 secretion but did not improve beta-cell function or insulin resistance [10]. The applicability of the latter study to the current research question (i.e. the relevance of GLP-1 to the established metabolic benefits of IIT in early T2DM) is limited by the long duration of diabetes in its study population, in whom the anticipated beneficial metabolic impact of IIT was not achieved. In contrast, in 63 ambulatory patients with T2DM of mean 3.0-year duration, we show that IIT clearly did not increase the GLP-1 response to oral glucose, despite improving beta-cell function, glucagonemia and insulin resistance.

In contrast to its effect on GLP-1, the impact of gastric bypass surgery on GIP secretion is unclear, with previous studies reporting both increased and decreased responses [13,14]. While we demonstrate a reduction in the GIP response to an oral glucose challenge following IIT (possibly reflecting its insulinotropic activity), the physiologic implications of this finding are unclear. At present, the most prudent interpretation of these data is that its effect on GIP is not a key determinant of the metabolic benefits of IIT.

A limitation of this study is that these data show the incretin response to an oral glucose challenge, rather than to mixed meals across the day, as would happen in daily living. Previous studies have shown varying levels of incretin responses to the OGTT that are likely partly attributable to differences in assays. However, this caveat regarding assays notwithstanding, the incretin responses observed in the current report are comparable to those seen in other studies in the literature. Another limitation is that diet while on IIT was not measured. We also cannot exclude the possibility that IIT may affect beta-cell responsiveness to GLP-1, as has been suggested in the earlier study of 9 patients who received this therapy [15]. In addition, the sample size is relatively modest and participants had good metabolic control at baseline (mean A1c 6.8%) such that the benefits of IIT on incretin secretion could have been muted. However, the study population is more than 2 times larger than that of previous studies [9,10] and was sufficient to demonstrate the beneficial effects of IIT on beta-cell function, insulin resistance and glucagonemia.

6. Conclusion

In summary, despite improving beta-cell function, insulin resistance and glucagonemia, 4-weeks of IIT does not change GLP-1 secretion and decreases the GIP response to an oral glucose challenge in early T2DM. We thus, conclude that when implemented early in the course of T2DM, the beneficial impact of short-term IIT on glucose homeostasis is not attributable to its effects on incretin secretion.

Contributions

RR and BZ designed the study and protocol. HC, CK, BZ and RR implemented the study and acquired the data. CK performed the statistical analyses. HC and RR wrote the manuscript. PWC supervised the biochemical analyses. All authors contributed to interpretation of the data and critical revision of the manuscript. All authors approved the manuscript.

Funding

This study was funded by an investigator-initiated research grant from Novo Nordisk. The funding source had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript and decision to submit the manuscript for publication.

Disclosure of interest

BZ and RR have received research funding and consulting honoraria from Novo Nordisk. HC, CK and PWC have nothing to disclose.

Acknowledgements

CK holds the Banting and Best Diabetes Centre New Investigator award and the Canadian Diabetes Association Clinician-Scientist award. BZ holds the Sam and Judy Pencer Family Chair in Diabetes Research at Mount Sinai Hospital and University of Toronto. RR is supported by a Heart and Stroke Foundation of Ontario Mid-Career Investigator Award. RR holds the Boehringer Ingelheim Chair in Beta-cell Preservation, Function and Regeneration at Mount Sinai Hospital. RR is guarantor, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2018.01.003.

References

[1] Isaman DJ, Rothberg AE, Herman WH. Reconciliation of type 2 diabetes remission rates in studies of Roux-en-Y gastric bypass. Diabetes Care 2016;39:2247–53.
[2] Kashyap SR, Daud S, Kelly KR, Gastaldelli A, Win H, Brethauer S, et al. Acute effects of gastric bypass versus gastric restrictive surgery on beta-cell function and insulinotropic hormones in severely obese patients with type 2 diabetes. Int J Obes 2010;34:462–71.
[3] Jørgensen NB, Dirksen C, Bojsen-Møller KN, Jacobsen SH, Worm D, Hansen DL, et al. Exaggerated glucagon-like peptide 1 response is important for improved β-cell function and glucose tolerance after Roux-en-Y gastric bypass in patients with type 2 diabetes. Diabetes 2013;62:3044–52.
[4] Jiménez A, Casamitjana R, Viaplana-Masclans J, Lacy A, Vidal J. GLP-1 action and glucose tolerance in subjects with remission of type 2 diabetes after gastric bypass surgery. Diabetes Care 2013;36:2062–9.
[5] Vetter ML, Wadden TA, Teff KL, Khan ZF, Carvajal R, Ritter S, et al. GLP-1 plays a limited role in improved glycemia shortly after Roux-en-Y gastric bypass: a comparison with intensive lifestyle modification. Diabetes 2015;64:434–46.
[6] Weng J, Li Y, Xu W, Shi L, Zhang Q, Zhu D, et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. Lancet 2008;371:1753–60.
[7] Kramer CK, Zinman B, Retnakaran R. Short-term intensive insulin therapy in type 2 diabetes mellitus: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2013;1:28–34.
[8] Kramer CK, Zinman B, Choi H, Retnakaran R. Effect of short-term intensive insulin therapy on post-challenge hyperglucagonemia in early type 2 diabetes. J Clin Endocrinol Metab 2015;100:2987–95.
[9] Højberg PV, Vilsbøll T, Zander M, Knop FK, Krarup T, Vølund A, et al. Four weeks of near-normalization of blood glucose has no effect on postprandial GLP-1 and GIP secretion, but augments pancreatic B-cell responsiveness to a meal in patients with Type 2 diabetes. Diabet Med 2008;25:1268–75.
[10] Shimodaira M, Muroya Y, Kumagai N, Tsuzawa K, Honda K. Effects of short-term intensive glycemic control on insulin, glucagon, and glucagon-like peptide-1 secretion in patients with Type 2 diabetes. J Endocrinol Invest 2013;36:734–8.
[11] Kramer CK, Zinman B, Choi H, Retnakaran R. Predictors of sustained drug-free diabetes remission over 48 weeks following short-term intensive insulin therapy in early type 2 diabetes. BMJ Open Diabetes Res Care 2016;4:e000270.
[12] Panunzi S, Carlsson L, De Gaetano A, Peltonen M, Rice T, Sjöström L, et al. Determinants of diabetes remission and glycemic control after bariatric surgery. Diabetes Care 2016;39:166–74.
[13] Laferrère B, Heshka S, Wang K, Khan Y, McGinty J, Teixeira J, et al. Incretin levels and effect are markedly enhanced 1 month after Roux-en-Y gastric bypass surgery in obese patients with type 2 diabetes. Diabetes Care 2007;30:1709–16.
[14] Rodieux F, Giusti V, D'Alessio DA, Suter M, Tappy L. Effects of gastric bypass and gastric banding on glucose kinetics and gut hormone release. Obesity 2008;16:298–305.
[15] Højberg PV, Zander M, Vilsbøll T, Knop FK, Krarup T, Vølund A, et al. Near normalisation of blood glucose improves the potentiating effect of GLP-1 on glucose-induced insulin secretion in patients with type 2 diabetes. Diabetologia 2008;51:632–40.