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The Effect of GLP-1 and GIP on the Microvascular Blood Flow after Consuming a Mixed Nutrient Meal: A Research Protocol

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Abstract

Introduction: Nutrient and gas exchange via microvascular blood flow is a key process of circulatory function. There is a significant decrease in the microvascular blood flow to skeletal muscle after orally ingesting glucose. Incretins like glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP), are released in response to glucose in the gut, stimulating insulin release. Incretins roles in promoting glucose uptake is thought to impact vascular blood flow. Our protocol plans to investigate if incretins and the subsequent insulin release contribute to the decrease in microvascular blood flow.

Methods: 20 healthy young adults will consume a high glucose mixed nutrient meal. Using contrast-enhanced ultrasound (CEU) and a blood glucose meter, microvascular blood flow and blood glucose will be measured. Blood GLP-1 and GIP will be measured using a sandwich enzyme immunoassay, while an electrochemiluminescence technique using an autoanalyzer will measure insulin. Measurements will be recorded at 0, 1, and 2 hours post-prandial. In a randomized order, the protocol will be repeated with infusion of GIP and GLP-1 inhibitors, GIP(3-30)NH_2 and exendin(9-39)NH_2 or saline.

Results: With normal incretin secretion, we anticipate a significant decrease in microvascular blood flow, along with an increase in blood insulin, GIP/GLP-1 levels. We postulate that supressing incretins will increase the microvascular blood flow along with decreased plasma insulin and no change in GLP-1/GIP levels.

Discussion: Through our methods, we propose a study design which evaluates the relationship of incretins and insulin on post-prandial microvascular blood flow. Our expected results aim to provide data that can be applied to the progressive treatment of type II diabetes with incretins like GLP-1. Understanding the impact of incretin treatment on the microvascular blood flow could be beneficial to the discovery of an adverse effect or how glucose uptake in peripheral tissues is altered. These are vital aspects of developing a clinical treatment to diabetes and our results will provide a basis to work off.

Conclusion: The goal of this protocol was to investigate and provide insight to fully understand incretins and their effects. It will propel research on the biochemical pathways involving incretin and microvascular blood flow, which then helps progress treatment of complications like diabetes.

Keywords: microvascular blood flow; incretin; GIP; GLP-1; insulin; glucose; digestion

Introduction

A vital aspect of human circulatory function is the nutrient and gas exchange that occurs via microvascular blood flow in capillary beds [1]. There is a significant difference in skeletal muscle microvascular blood flow after the ingestion of a glucose-rich meal compared to the intravenous (IV) administration of glucose [2][3]. By orally ingesting glucose, microvascular blood flow decreases 780% in comparison to the microvascular perfusion after IV administered glucose [2][3].

Insulin is the most important hormone responsible for the uptake of glucose into myocytes from the blood [4]. During hyperglycemia, insulin will be released from the pancreas to promote the uptake and storage of glucose systemically (~85% in muscle) [4]. This insulin response commonly occurs after the digestion of a meal, as blood glucose levels tend to rise [4]. Insulin is also a vasoactive hormone, promoting vasodilation of blood vessels by stimulating production of nitric oxide (NO) from the vascular endothelium [5]. Vasodilation increases blood flow to the myocytes and therefore aids in delivery of glucose to the targeted tissues [5]. Given the known actions of insulin increasing bulk blood flow, an increase in microvascular blood flow would be expected. However, it has been shown that a decrease in the skeletal muscle microvascular blood flow arises after the ingestion of a glucose-rich meal despite increases in insulin [2].

Incretins are peptide hormones synthesized in the gut and aid the stimulation of insulin secretion during hyperglycemia [6]. Gastric inhibitory peptide (GIP) and

glucagon-like peptide-1 (GLP-1) are the two known incretins responsible for the incretin effect [6]. Both GIP and GLP-1 begin secreting within one minute of ingestion of nutrients and reach their peak after approximately one hour (h) [6]. The secretion of GLP-1 and GIP is mainly stimulated by glucose and other carbohydrates such as sucrose, starch, triglycerides and some amino acids [7]. This stimulation is dependent on the dosage of carbohydrates present in the GI (gastrointestinal) tract [7]. It has been found that the incretin effect can triple the insulin response [8]. Previous studies have shown that the compounds GIP(3-30)NH_2 and exendin(9-39)NH_2 are effective and safe receptor antagonists of GIP and GLP-1 in humans, respectively [9]. GIP(3-30)NH_2 is an antagonist that blocks binding of GIP to the GIP receptors, thus preventing all GIP mediated functions, such as increased insulin release [10]. Exendin(9-39)NH_2, is an efficacious GLP-1 receptor antagonist that binds to the orthosteric site and inhibits any GLP-1 induced functions [11]. GIP(3-30)NH_2 and exendin(9-39)NH_2 are valuable tools that can be utilized to examine incretin physiology, as they allow us to identify if physiological responses occur in the absence of incretin function [9][10][11].

When glucose is administered via an IV method, glucose bypasses absorption in the digestive tract [3]. This method prevents any glucose from triggering the release of GLP-1 and GIP. In comparison, glucose ingestion from a meal high in carbohydrates must travel throughout the digestive tract before absorption resulting in glucose mediated GLP-1 and GIP secretion [7]. The differences in glucose delivery method that occur prior to the peripheral uptake of glucose have been shown to potentiate differences in vascular function. One study discovered that in humans, acute hyperglycemia delivered via an IV resulted in enhanced skeletal muscle microvascular prefusion [3]. Notably, they pharmacologically suppressed insulin to obtain these results. Therefore, insulin and GLP-1/GIP cannot be associated with the increase in microvascular blood flow [3]. This is contradictory to another study that found a decrease in microvascular blood flow after orally ingesting glucose to become hyperglycemic [2]. As the hyperglycemia was orally induced, it allowed for the physiological effects of incretins and insulin [2]. These findings demonstrate a knowledge gap in the regulation of post-prandial muscle microvascular blood flow. This also draws the question if GLP-1 and GIP, along with insulin play a role in the contradictory findings on skeletal muscle microvascular blood flow.

GLP-1 and GIP mediated functions related to glucose uptake and microvascular blood flow are a very prevalent and novel topic in physiological research. Moreover, the role of insulin and GLP-1/GIP mediating the microvascular response after a meal has not been researched thoroughly, which provides an immediate basis for investigation. We aimed to explore how the release of incretins triggered by orally ingested glucose impacts skeletal muscle microvascular blood flow. To do this, we designed a research protocol to test whether supressing incretin function influences microvascular blood flow. We hypothesized that our study would show that the functions of incretins with digestion can decrease skeletal muscle microvascular blood flow via an insulin mediated mechanism.

Methods

Participant Selection and Methodology

10 young (< 40 years-old) healthy male and female adults will be selected for the study. Participants will be screened for normal blood pressure and body mass index prior to participation. Exclusion criteria will include any subject who has any present day or previous history of smoking or lung disease, any cardiometabolic disorders, and medication or vitamin use that could impact microvascular function or glycemic control. Notably, participants cannot have used or use the following common prescription drugs: aldosterone receptor blockers, angiotensin converting enzyme inhibitors, statins and pentoxifylline [12][13]. Additionally, any supplementation with vitamin C, commonly called ascorbic acid, or niacin (vitamin B-3) will prevent entry into the study [14][15]. This criterion was adapted from a related study [2]. Moderate to vigorous exercise, caffeine consumption and alcohol consumption will be restricted for 24 h prior to study visits. Additionally, the participants will be required to fast with only the ingestion of water for 8 h prior to study visits.

Treatment Protocol

Each participant (n=20) will be exposed to an active incretin trial and an incretin supressed trial, in a double-blind randomized cross-over study design. Data collection will occur over two days, in which day one the participants will be exposed to the active incretin trial and on day two they will undergo the incretin supressed trial.

Prior to experimentation on both days of data collection, the resting values of blood incretin: GLP-1 and GIP, insulin, glucose, and microvascular blood flow will be measured for each subject. The mean values of each variable will be referred to as the resting conditions. All data collection will be measured while the participants lay supine on a standard medical bed.

To analyze any incretin effect on microvascular blood flow properly, blood GLP-1, GIP, and insulin levels, along with microvascular blood flow will be measured at time points of 0, 1 and 2 h post-prandial. Blood glucose levels will be monitored to assess the successful digestion of the meal and entry into the blood stream mediating the incretin pathway.

Active Incretin Trial

Participants in this treatment will receive a high glucose mixed-nutrient meal of 300 grams (g) (45% carbohydrate, 35% fat, 20% protein). This will consist of eggs, cheese, and a carbohydrate solution of 135 g dextrose powder (Sigma-Aldrich, St. Louis, MO, USA) dissolved in 200 millilitres

(mL) of water. The meal and drink are to be consumed within 5 minutes. To blind the participants, they will receive an IV infusion of saline (0.9% NaCl) (Sigma-Aldrich, St. Louis, MO, USA). 800 mL of saline is to be administered through a slow infusion period over 2.5 h prior to ingestion of the meal and the 2 h measurement period.

Incretin Supressed Trial

The same participants will receive the same meal and dextrose solution as the incretin active trial. They will also have an IV infusion of both GIP(3-30)NH_2 and exendin(9-39)NH_2, (Phoenix Pharmaceuticals, Burlingame, CA, USA) and (Sigma-Aldrich, St. Louis, MO, USA) respectively. In order to suppress incretin effects, both GIP(3-30)NH_2 and exendin(9-39)NH_2 are to be diluted in saline (Sigma-Aldrich, St. Louis, MO, USA) where both are soluble. An initial high dose of exendin(9-39)NH_2 is delivered 2.5 h prior to the meal, this initial dose is 20 nmol/Kg for 10 minutes (mins), after which a continuous infusion of 400 pmol/kg/min is maintained for the remaining 2 h measurement period [11]. The GIP(3-30)NH_2 is administered 20 mins prior to the meal, and infused at a constant rate of 1000 pmol/kg/min for the remaining 2 h [10]. The concentrations and administration processes follow the recommendation of the Copenhagen center for clinical metabolic research and previous human trials using exendin (9-39)NH_2 and GIP(3-30)NH_2 [9][10][11]. The concentrations and administration processes follow the recommendations of the Copenhagen center for clinical metabolic research and protocols from previous human trials using exendin (9-39)NH_2 and GIP(3-30)NH_2 [9][10][11].

Microvascular Blood Flow

Contrast-enhanced ultrasound (CEU) will be utilized to measure muscle microvascular perfusion in the vastus lateralis. A 9L-D H40442LM transducer (bandwidth 3–8 MHz, field of view (FOV) 43 mm) and LOGIQ E9 ultrasound machine (GE Healthcare, Wauwatosa, WI, USA) are to be used to perform the CEU [16]. Lipid-shelled octafluoropropane microbubbles (Definity, Bristol-Myers Squibb Medical Imaging) will be injected intravenously [17]. The infusion rate for the microbubbles will be 2.25 ml/min [2]. Imaging is to be first performed immediately prior to the meal for baseline microvascular blood flow, at 60 minutes post-prandial and at 120 minutes postprandial. Imaging is to start after 4 minutes of microbubble infusion to allow for whole-body equilibrium, after which four 45-s videos will be captured [2]. The imaging will be performed through increasing pulsing ultrasound signal intervals (0.05 s – 15 s), which destroys the microbubbles [17]. The function $y=A(1-e^{-\beta t})$ will be used to graph the replenishment of microbubbles, with y representing the video intensity (VI) at time t; A is the plateau VI, which represents microvascular blood volume at the area of interest, and β is the microvascular blood velocity [18]. The microvascular blood flow will be determined using the product of A and β [19].

Measurement of Biochemical Markers

Blood samples for the measurement of biochemical markers will be taken at 0, 60 and 120 min timepoints. A COUNTOUR©NEXT blood glucose meter will be utilized to measure blood glucose (Ascensia Diabetes Care, Mississauga, ON, CAN). GLP-1 and GIP level will be measured with a commercially available sandwich enzyme immunoassay kits (Code No. 27784 and 27201 respectively, Immuno-Biological Laboratories Co. Ltd., Gunma, Japan). Insulin will be measured using an electrochemiluminescence technique using an autoanalyzer (Cobas E-411, Japan).

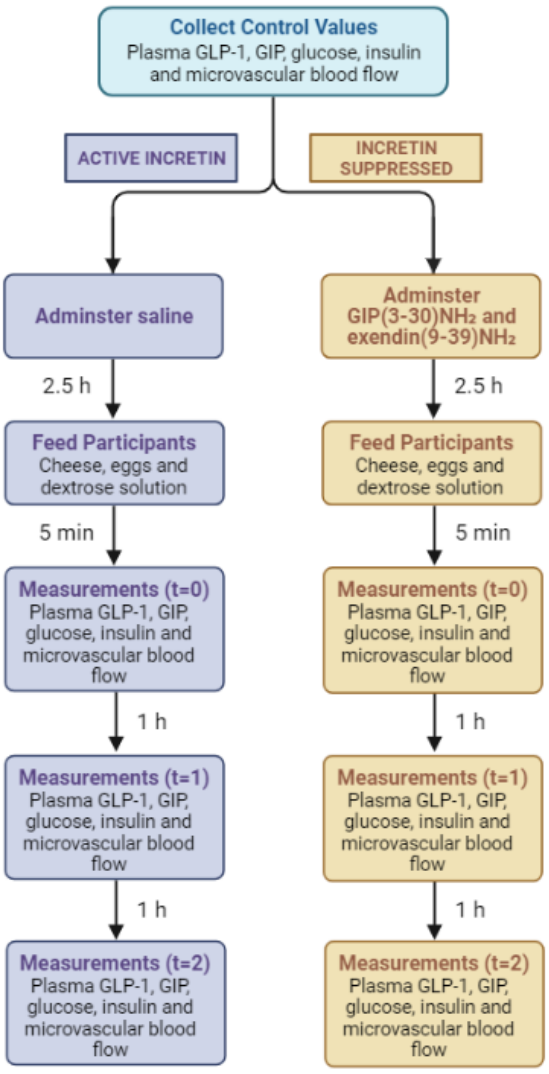

Figure 1. Experimental design of the active incretin and incretin suppressed trials. Flowchart detailing the timeline of the experimental design. Each arrow represents progression to the next step of the methodological design. Time between measurements, feeding and interventions is displayed above each arrow when necessary. Same patients are used in both trials (n=20). t = time post-prandial. Graphic was created using BioRender (Toronto, ON, Canada).

Analysis

We anticipate using repeated measures analysis of variance (ANOVA) to determine any significant differences in each variable measured at the baseline, 0 h, 1 h and 2 h post prandial timepoints. We will also run post hoc tests to uncover which exact variables are different and at which timepoints. This will be completed for both the active incretin and supressed incretin trials, for the purpose of comparison with each other.

Results

We predict that the participants in the incretin active trial will experience a decrease in skeletal muscle microvascular blood flow compared to baseline measures. Previous studies demonstrated that skeletal muscle microvascular blood flow was hindered after a high glucose mixed meal [2]. With GLP-1 and GIP free to activate their respective receptors, we expect subjects in this trial to exhibit increased GLP-1, GIP, and insulin levels in comparison to control values [6].

There is currently no empirical data on skeletal muscle microvascular blood flow following the inhibition of incretins and a high glucose mixed meal. However, we believe that there will be improvements in microvascular blood flow in comparison to the baseline values. We came to this conclusion after assessing previous studies where skeletal muscle microvascular blood flow was increased following IV induced hyperglycemia, where incretin pathways were bypassed, and insulin was inhibited [3]. The incretin supressed trial will administer GIP(3-30)NH_2 and exendin(9-39)NH_2, and thus we expect a lack of GLP-1 and GIP effect through little to no increase in insulin [8]. However, blood GLP-1 and GIP levels should increase as they are still being released [7].

We expect that in both trials blood glucose levels are to rise above baseline and indicate that the meal has been properly digested and passed through the GI tract. In the incretin suppressed trial, we expect an exaggerated and prolonged hyperglycemic state, which will return to baseline approximately 180 minutes post-prandial [9][4]. Besides the intensified hyperglycemia we expect no other side effects from the use of the incretin inhibitors [9]. We use the incretin suppressed trial as a control to confirm that incretin inhibition has indeed suppressed insulin release. It is expected that blood glucose levels will return to baseline after 180 minutes with no side affects

Discussion

The proposition of this method was brought about by the importance of understanding the roles of incretins GLP-1 as well as GIP and their effects on skeletal microvascular blood flow. By understanding the mechanisms of GLP-1 and GIP, we can build upon our knowledge of how these incretins, insulin, and other mediating factors work together to maintain a proper homeostatic environment in the body.

In our protocol, we began with the ingestion of a mixed nutrient meal and no inhibition of incretins through GIP(3-30)NH_2 and exendin(9-39)NH_2. From this treatment, we expect an increase in insulin production and a significant decrease in microvascular blood flow as well as high incretin levels in the bloodstream. This would allow us to confirm that incretin does indeed have an exponential effect on insulin as well as the expected decrease in microvascular blood flow. Additionally, it would allow for a comparative analysis between incretin activation brought upon by glucose of the mixed nutrient meal and the baseline results. In turn, we could then place the results against that of the results obtained from the inhibition of incretin receptors.

Through the IV administration of GIP(3-30)NH_2 and exendin(9-39)NH_2 the function of incretin peptides GIP and GLP-1 will be inhibited during the digestion of the mixed nutrient meal. From this treatment we would still expect increased GLP-1 and GIP, but minimal changes in blood insulin when compared to resting values. We also anticipate that the microvascular blood flow will increase compared to controls. This would indicate that GIP(3-30)NH_2 and exendin(9-39)NH_2 successfully blocked the GIP and GLP-1 receptors from eliciting any incretin mediated insulin release. From this, we can gather that the decreased GIP and GLP-1 are potentially responsible for the decrease in blood insulin levels. Subsequently, it poses a potential relationship between both incretins GIP and GLP-1 with insulin and its ability to affect microvascular blood flow. In this case we expect to find a substantial positive effect when the incretins are inhibited. Moreover, when this is placed against the active trial, we expect to provide evidence that when insulin, GLP-1 and GIP levels are low, microvascular perfusion is high. These revelations can then be applied to external uses in better understanding nutrient exchange in humans. For instance, patients with type II diabetes become unable to uptake glucose properly due insulin resistance [20]. By better understanding how the blood delivery of insulin occurs via hormones like GLP-1 and GIP, we can potentially help improve glucose uptake in type II diabetes patients.

Lastly, as there is very little data explaining as to why this correlation would occur, many theories and ideas have evolved. One of which is the theory of nutritive vs. non-nutritive pathways wherein blood flow is redirected through capillaries based on metabolic need [21]. This is a highly controversial theory that there are two vascular routes closely aligned within skeletal muscles [21]. One of which directly lays on the muscle and supplies it with nutrients, while the other lays slightly further and acts as a blood shunt [21]. This theory suggests that when hyperglycemia is induced, the non-nutritive pathway is recruited, which would lead to lower myocyte glucose transport, potentially contributing to acute hyperglycemia-induced insulin resistance [21]. Additionally, other biochemical mechanisms that have not been examined in the context of incretins and its effects on microvascular blood flow could

be at play. There is the possibility that glucose under hyperglycemic conditions is redistributed to other areas of the body instead of skeletal muscle. Specifically, under hyperglycemic conditions the body may employ a mechanism to distribute glucose to areas of the body such as white adipose tissue instead of skeletal muscle [22]. In our protocol, we only observe microvascular blood flow within skeletal muscle. Therefore, this redistribution could be the cause of the decreased microvascular blood flow that is expected to be observed.

Conclusions

Through this protocol, we expect to provide valuable data linking a decrease in microvascular blood flow with elevated plasma GLP-1, GIP and insulin levels post-prandially. As we only expect to find a relationship between GLP-1, GIP and microvascular blood flow, we will not determine incretins as the cause behind the decreased microvascular perfusion. However, our expected findings will provide a clear relationship between the decrease in microvascular blood flow after orally ingesting glucose and the glucose mediated release of GLP-1 and GIP. Therefore, further work into the underlying biochemical pathways of incretins and their effects on microvascular blood flow must be done to attribute a cause. We recommend future studies to investigate insulin-specific receptors in the microvasculature of skeletal muscle to detect any functional anomalies in comparison to previously studied insulin receptors. We expect studies such as this to enhance research on microvascular blood flow function with potential beneficial impacts for nutrient exchange in humans and its applications. This could involve future finding that possibly improve insulin delivery and glucose uptake in type II diabetes patients.

List of Abbreviations Used

IV: intravenous
GIP: gastric inhibitory peptide
GLP-1: glucagon-like peptide-1
CEU: contrast-enhanced ultrasound
NO: nitric oxide
FOV: field of view
VI: video intensity
GI: gastrointestinal
h: hours
mins: minutes
g: grams
mL: millilitres
ANOVA: analysis of variance
Kg: kilogram
nmol: nanomole
pmol: picomole

Conflicts of Interest

The authors declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent

Written and informed consent will be provided by 20 (total) healthy male and female young adults. To ensure the subjects had a high standard of health, several forms regarding their physical attributes such as weight, height, age, etc. will be provided to the participants before they are granted access to participating in the study. The subjects will be screened for their blood pressure prior to participation. After an overview of their written consent and health screening, the subjects will participate in the study. This study will be sent to be approved by the McMaster research ethics board. In accordance to the tri-council policy statement from the government of Canada, the McMaster research ethics board is responsible for approving the use of saline as a placebo as well as exendin $(9\text{-}39)NH_2$ and $GIP(3\text{-}30)NH_2$ as compounds to be administered via IV.

Authors' Contributions

LTM: made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, drafted the manuscript, and gave final approval of the version to be published.
RTB: made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, designed all graphic artwork, drafted the manuscript, and gave final approval of the version to be published.
AHHGI: made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, drafted the manuscript, and gave final approval of the version to be published.

Acknowledgements

We would like to thank Jeremy Cohen for guiding us through the URNCST Journal Mentored Paper, which lead us to be able to submit our manuscript for publication.

Funding

This study was not funded.

References

[1] Lévy BI. The importance of microcirculation and tissue perfusion in hypertension. Current Medical Research and Opinion. 2005 Aug 12;21(5):S1-S6. https://doi.org/10.1185/030079905X56411
[2] Parker L, Morrison DJ, Betik AC, Roberts-Thomson K, Kaur G, Wadley GD, Shaw CS, Keske MA. High-glucose mixed-nutrient meal ingestion impairs skeletal muscle microvascular blood flow in healthy young men. American Journal of Physiology-Endocrinology and Metabolism. 2020 Jun 5;318(6):E1014–E1021. https://doi.org/10.1152/ajpendo.00540.2019

[3] Horton WB, Jahn LA, Hartline LM, Aylor KW, Patrie JT, Barrett EJ. Acute hyperglycaemia enhances both vascular endothelial function and cardiac and skeletal muscle microvascular function in healthy humans. The Journal of Physiology. 2021 Jan 22. https://doi.org/10.1113/jp281286

[4] Baron AD, Brechtel G, Wallace P, Edelman SV. Rates and tissue sites of non-insulin- and insulin-mediated glucose uptake in humans. American Journal of Physiology-Endocrinology and Metabolism. 1988 Dec 1;255(6):E769–E774. https://doi.org/10.1152/ajpendo.1988.255.6.E769

[5] Chen YL, Messina EJ. Dilation of isolated skeletal muscle arterioles by insulin is endothelium dependent and nitric oxide mediated. American Journal of Physiology - Heart and Circulatory Physiology. 1996 Jun 1;270(6):H2120-H2128. https://doi.org/10.1152/ajpheart.1996.270.6.H2120

[6] Vollmer K, Holst JJ, Baller B, Ellrichmann M, Nauck MA, Schmidt WE, Meier JJ. Predictors of incretin concentrations in subjects with normal, impaired, and diabetic glucose tolerance. Diabetes. 2007 Dec 5;57(3):678–87. https://doi.org/10.2337/db07-1124

[7] Kim W, Egan JM. The role of incretins in glucose homeostasis and diabetes treatment. Pharmacological Reviews. 2008 Dec 12;60(4):470–512. https://doi.org/10.1124/pr.108.000604

[8] Nauck MA, Meier JJ. Incretin hormones: Their role in health and disease. Diabetes, Obesity and Metabolism. 2018 Feb 24;20(1):5–21. https://doi.org/10.1111/dom.13129

[9] Gasbjerg LS, Helsted MM, Hartmann B, Sparre-Ulrich AH, Veedfald S, Stensen S, et al. GIP and GLP-1 receptor antagonism during a meal in healthy individuals. Journal of Clinical Endocrinology and Metabolism. 2020 Feb 20;105(3):e725–38. https://doi.org/10.1210/clinem/dgz175

[10] Lynggaard MB, Gasbjerg LS, Christensen MB, Knop FK. GIP(3-30)NH2 – a tool for the study of GIP Physiology. Current Opinion in Pharmacology. 2020 Dec;55:31–40. https://doi.org/10.1016/j.coph.2020.08.011

[11] Gasbjerg LS, Bari EJ, Christensen M, Knop FK. Exendin(9-39)NH2: Recommendations for clinical use based on a systematic literature review. Diabetes, Obesity and Metabolism. 2021 Aug 5;23(11):2419–36. https://doi.org/10.1111/dom.14507

[12] Yong J, Tian J, Yang X, Xing H, He Y, Song X. Effects of oral drugs on coronary microvascular function in patients without significant stenosis of epicardial coronary arteries: A systematic review and meta-analysis of coronary flow reserve. Frontiers in Cardiovascular Medicine. 2020 Oct 30;7:580419. https://doi.org/10.3389/fcvm.2020.580419

[13] Ohshima N, Sato M. Effect of pentoxifylline on microvascular blood flow velocity. Angiology. 1981 Nov;32(11):752–63. https://doi.org/10.1177/000331978103201103

[14] Lavillegrand J-R, Raia L, Urbina T, Hariri G, Gabarre P, Bonny V, et al. Vitamin C improves microvascular reactivity and peripheral tissue perfusion in septic shock patients. Critical Care. 2022 Jan 21;26(1):25. https://doi.org/10.1186/s13054-022-03891-8

[15] Gasperi V, Sibilano M, Savini I, Catani MV. Niacin in the central nervous system: An update of biological aspects and clinical applications. International Journal of Molecular Sciences. 2019 Feb;20(4):974. https://doi.org/10.3390/ijms20040974

[16] Qureshi AI, Saleem MA, Aytac E, Wallery SS. Assessment of Skeletal Muscle Perfusion using Contrast-Enhanced Ultrasonography: Technical Note. Journal of Vascular and Interventional Neurology. 2017 Jan; 9(3):41–44. PMID: 28243350

[17] Lindner JR, Womack L, Barrett EJ, Weltman J, Price W, Harthun NL, Kaul S, Patrie JT. Limb stress-rest perfusion imaging with contrast ultrasound for the assessment of Peripheral Arterial Disease severity. JACC: Cardiovascular Imaging. 2008 May; 1(3):343–50. https://doi.org/10.1016/j.jcmg.2008.04.001

[18] Dawson D, Vincent MA, Barrett EJ, Kaul S, Clark A, Leong-Poi H, Lindner JR. Vascular recruitment in skeletal muscle during exercise and hyperinsulinemia assessed by contrast ultrasound. American Journal of Physiology - Endocrinology and Metabolism. 2002 Mar; 282(3):E714–E720. https://doi.org/10.1152/ajpendo.00373.2001

[19] Wei K, Jayaweera AR, Firoozan S, Linka A, Skyba DM, Kaul S. Quantification of myocardial blood flow with ultrasound-induced destruction of microbubbles administered as a constant venous infusion. Circulation. 1998 Feb 10;97(5):473–83. https://doi.org/10.1161/01.cir.97.5.473

[20] Kahn BB. Type 2 diabetes: When insulin secretion fails to compensate for insulin resistance. Cell. 1998 Mar 6;92(5):593–6. https://doi.org/10.1016/S0092-8674(00)81125-3

[21] Clark MG, Rattigan S, Clerk LH, Vincent MA, Clark AD, Youd JM, Newman JM. Nutritive and non-nutritive blood flow: Rest and exercise. Acta Physiologica Scandinavica. 2000 Apr; 168(4):519–30. https://doi.org/10.1046/j.1365-201x.2000.00704.x

[22] Cettour-Rose P, Samec S, Russell AP, Summermatter S, Mainieri D, Carrillo-Theander C, Montani JP, Seydoux J, Rohner-Jeanrenaud F, Dulloo AG. Redistribution of glucose from skeletal muscle to adipose tissue during catch-up fat: A link between catch-up growth and later metabolic syndrome. Diabetes. 2005Mar25;54(3):751–6. https://doi.org/10.2337/diabetes.54.3.751

Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Jeremy Cohen, Sera Whitelaw, Sonya Kouthouridis
Article Dates: Received Dec 03 21; Accepted Apr 13 22; Published May 13 22

Citation
Please cite this article as follows:
MacLean LT, Bevington RT, Ibrahim AHHG. The effect of GLP-1 and GIP on the microvascular blood flow after consuming a mixed nutrient meal: A research protocol. URNCST Journal. 2022 May 13: 5(6).
https://urncst.com/index.php/urncst/article/view/335
DOI Link: https://doi.org/10.26685/urncst.335

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