Possible Correlation between Glucagon & Glucagon-Like Peptide 1 (GLP-1) with Type 2 Diabetic and Heart Failure

Michael Edwar[1]*, Mohamed Kamar[1], Hazem M. ELashmawy[1], Omar F. Tawfik[2], Azza M. Ahmed[3]

[1]Internal Medicine Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

[2]Cardiology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

[3]Clinical Pathology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

Corresponding author: Michael Edwar

E-mail: michael1991edwar@gmail.com, michaelfarag@medicine.zu.edu.eg

Conflict of interest: None declared

Funding: No funding sources

Abstract

Background: The history of glucagon started in 1920s when Kimball and Murlin stated that a circulating molecule with an impact on glucose homeostasis oppose the insulin effect is present. The glycogenolytic, ketogenic and gluconeogenic effects of glucagon were demonstrated in dogs at first. Shortly after glucagon was refined and sequenced at Eli Lilly (IN, USA), and constructed commercially by the company for treatment of insulin-induced hypoglycemia. Classically, the pathogenesis of T2DM is centralized on insulin resistance and β cell dysfunction; however the inappropriately raised α -cell function and resultant hyperglucagonemia have long been identified as a supporter of hyperglycemia in diabetic patients by promoting glucose production by the liver. Glucagon's positive inotropic and chronotropic impacts were first shown in the isolated heart of cats, guinea pigs, rats, and dogs and were thereafter proved in vivo in humans. Although several hormones might be involved in postprandial insulin secretion, most of the incretin effect can be explained by increases in glucose dependant insulinotropic peptide so-called gastric inhibitory polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). GLP-1 is secreted from the intestinal L cells that are located with increasing density from the duodenum to the colon. Agonists of the GLP-1 receptor improve glycemic control via both their acute insulinotropic action and, under certain circumstances, also by chronic action to preserve β-cell mass through stimulation of β-cell proliferation and inhibition of apoptosis. Endothelial dysfunction is a common co-morbidity associated with insulin resistance and T2DM. Treatment of type-2 diabetic patients that present coronary artery disease with GLP-1 improves endothelial function without affecting insulin resistance.

Keywords: Glucagon, Glucagon-like peptide 1 (GLP-1), Type 2 Diabetes, Heart Failure

Tob Regul Sci.™ 2023;9(1): 3000-3009
DOI: doi.org/10.18001/TRS.9.1.207

Introduction

The history of glucagon started in 1920s when Kimball and Murlin stated that a circulating molecule with an impact on glucose homeostasis oppose the insulin effect is present. The glycogenolytic, ketogenic and gluconeogenic effects of glucagon were demonstrated in dogs at first. Shortly after glucagon was refined and sequenced at Eli Lilly (IN, USA), and constructed commercially by the company for treatment of insulin-induced hypoglycemia **(1).**

Glucagon physiology

Bioactive glucagon is secreted after enzymatic cleavage of the proglucagon precursor by prohormone convertase 2 (PC2) to produce 29 amino acids glucagon molecule . Glucagon is produced from α cells of pancreas in response to falling glucose levels (hypoglycemia e.g., long-term fasting) or rising concentrations of amino acids **(2).** Its secretion is also regulated by the autonomic nervous system and the intestinal peptides (oxyntomodulin and glucose-dependent insulinotropic polypeptide (GIP) enhance whereas GLP-1 inhibits glucagon secretion) **(1).**

In addition to the complexity of stimulatory and inhibitory extrapancreatic factors, glucagon secretion is also regulated by intra-islet factors (paracrine regulation) **(3);** the secretion of which may, in turn, depend on stimulation by gut-derived hormones and/or neural signals; these signals include somatostatin (from δ cells) and possibly amylin, insulin, γ aminobutyric acid and zinc (from β cells) **(4).**

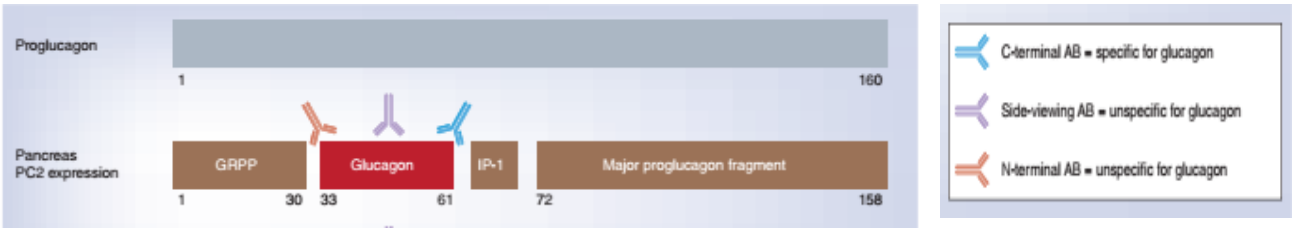

Figure (1): **Molecular processing of proglucagon to glucagon in humans and immuno-based methods for detection.**

NB: Glucagon (33–61) results from prohormone convertase 2-dependent processing of proglucagon (1–160).

Glucagon carries out the following functions:

- Glucagon boosts insulin secretion and may in this way; regulate its secretion via insulin receptors expressed on the α cells **(5).** However, insulin arriving via the arterial supply to the α cells may also directly inhibit glucagon secretion **(6).**
- On lipid metabolism:

  igapo-lipoproteins by liver. In addition, glucagon determines lipolysis in white adipose tissue.

  - Glucagon increments energy expenditure and thermogenesis by incrementing oxygen consumption, blood flow and heat production in brown fat
  - Glucagon increments fatty acid oxidation and ketone-body production **(7)**

Glucagon lowers food intake, increases satiation (possibly mediated through ghrelin), decrements gastric emptying, and inhibits motility of gastrointestinal tract **(8).**

- Glucagon has positive chronotropic and inotropic effects on the cardiac muscle **(1).**
- Glucagon regulates secretion of other hormones, such as growth hormone, ghrelin, insulin, somatostatin, and cortisol **(8).**

Glucagon's effects on T2DM development

Schematically, T2DM is discriminated by: β-cell failure, α-cells insulin resistance and decreased incretin effect.

- β-cell failure due to a partial loss of β-cell mass and β-cell dysfunction, affected by genetic background and by long term exposure to gluco- and lipotoxicity, amylin and advanced glycation end products (AGEs).
- α-cells insulin resistance the so called by Unger and Orci, "paracrinopathy" and T2DM "a bi-hormonal disorder". In T2DM, α-cells might be resistant to the inhibitory impact of insulin or to other β-cell secretory products such as zinc or γ-aminobutyric acid (**9).**

Classically, the pathogenesis of T2DM is centralized on insulin resistance and β cell dysfunction; however, the inappropriately raised α -cell function and resultant hyperglucagonemia have long been identified as a supporter of hyperglycemia in diabetic patients by promoting glucose production by the liver **(10).** Certainly, raised fasting levels of glucagon, inappropriate glucose-induced glucagon inhibition and disrupted insulin–glucagon interaction in the postprandial period were expressed in patients with T2DM, in contrast to healthy individuals who expressed plasma glucagon and insulin levels inversely correlated in the postprandial state. The flop of the inverse relationship between these two hormones in T2DM patients might be secondary to the diminished mass of insulin pulses and implies that alterations in the cross-talk between β - and α -cells may underlie hyperglucagonemia **(11).**

Glucagon's effects on the cardiovascular system

Farah and Tuttle were the first to document that glucagon operates on the heart to augment cardiac output by enhancing the potency and length of cardiac contractions. Glucagon's positive inotropic and chronotropic impacts were first shown in the isolated heart of cats, guinea pigs, rats, and dogs **(12)** and were thereafter proved in vivo in humans **(13).**

The glucagon cardiovascular influences start around 1–3 min after its administration into the circulation, with a peak after 5 min and a period of up to 20 min. Glucagon's positive chronotropic and inotropic impacts are less considerable but lengthier than those observed by the administration of catecholamines. However, in contrast to catecholamines, glucagon's cardiac impacts are not chaperoned by an augmented risk of cardiac arrhythmias. The chronotropic but not the inotropic impact of glucagon can be stopped by propranolol (β -adrenergic receptor blocker), implying that glucagon's impact on myocardial contraction is, against catecholamines, separated from β -adrenergic signaling **(13).**

Collectively, these data point to the therapeutic importance of glucagon in the management of acute heart failure and imply that glucagon has the potential as a life-saving first aid drug to

neutralize the acute cardiac depressant impact of β-blockers or Ca2+ channel inhibitors. In line with this concept, in patients with heart disease, the glucagon administration has been shown to raise heart rate, improve cardiac output, and enhance cardiac index, stroke power index, and left ventricular ejection and pressure **(14).**

Glucagon's cardiovascular impacts are executed by stimulation of adenyl cyclase and thereon increased production of cAMP in the cardiac muscle. In contrast to catecholamines, the increment in cAMP levels does not affect the activation of -adrenergic receptors, observable worth encouraging the usage of glucagon to enhance cardiac function following unexpected abuse of β-blockers **(13).**

Among HF patients, the more the severity of HF, the less the hemodynamic response to glucagon. In addition, glucagon shows a weaker response in chronic than in acute HF. The inotropic properties of glucagon are more powerful in the ventricle than in the atrium. It does not raise irritability of the myocardium and it is active in the existence of digitalis and propranolol. Thus, trials for the therapeutic benefits of glucagon have been made in situations of: myocardial infarction, resistant heart failure, intoxication with β-/calcium channel blockers, heart block, and hypotension following cardiac operations **(15).**

Glucagon also promotes the atrioventricular conductivity and its inotropic action is chaperoned by an antiarrhythmogenic effect (which might be due partially to raised insulin-mediated uptake of potassium by the cardiac muscle following glucagon administration) **(9).**

Furthermore, glucagon can reduce histamine-induced cardiac injury during reperfusion **(7)** and reforms the pressure of the coronary perfusion during ischemic vasodilation **(16).**

As an inotropic agent, glucagon improves heart function and, thus, it improves oxygen consumption, lipolysis, and beta-oxidation of lipids **(10).**

Glucagon-like peptide 1 (GLP-1)

The incretin effect is defined as the augmentation of insulin secretion after oral glucose intake compared with the insulin secretion after an isoglycemic intravenous glucose infusion. In healthy individuals, the incretin effect is responsible for up to 70% of insulin secretion after an oral glucose load and is thus essential for postprandial regulation of glucose levels. The incretin effect is mediated by gut-derived peptide hormones, so-called incretins, which are released in response to the oral intake of nutrients **(17).**

Although several hormones might be involved in postprandial insulin secretion, most of the incretin effect can be explained by increases in glucose dependant insulinotropic peptide so-called gastric inhibitory polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) **(18).**

GLP-1 physiology

GLP-1 is secreted from the intestinal L cells that are located with increasing density from the duodenum to the colon. GLP-1 is produced by post-translational processing of proglucagon by proprotein convertase subtilisin-kexin type 1 (PCSK1) or PCSK3 (also known as furin) and exists

in two equally bioactive forms, namely, glycine-extended GLP-1 (GLP-1 7–37) and amidated GLP-1 (GLP1 7–36) **(19).**

Following the ingestion of nutrients, a rise in the plasma concentration of GLP1 is observed within minutes **(20).** However, owing to local degradation of GLP1 by the enzyme Dipeptidyl-peptidase 4 (DPP 4) and further degradation by DPP4 in the liver, only 10–15% of endogenously released GLP1 reaches the systemic circulation **(21).**

This rapid degradation of GLP-1 by DPP-4 is responsible for the short half-life of exogenously administered GLP-1, which amounts to 1–2 minutes. GLP-1 exerts its actions through the GLP-1 receptors (GLP-1R), which is expressed in numerous tissues, including the pancreas, kidney, heart, lung, adipose and smooth muscle, as well as in specific nuclei in the central nervous system. The widespread distribution of the GLP-1R suggests that GLP-1 has several additional effects other than regulating glucose metabolism **(17).**

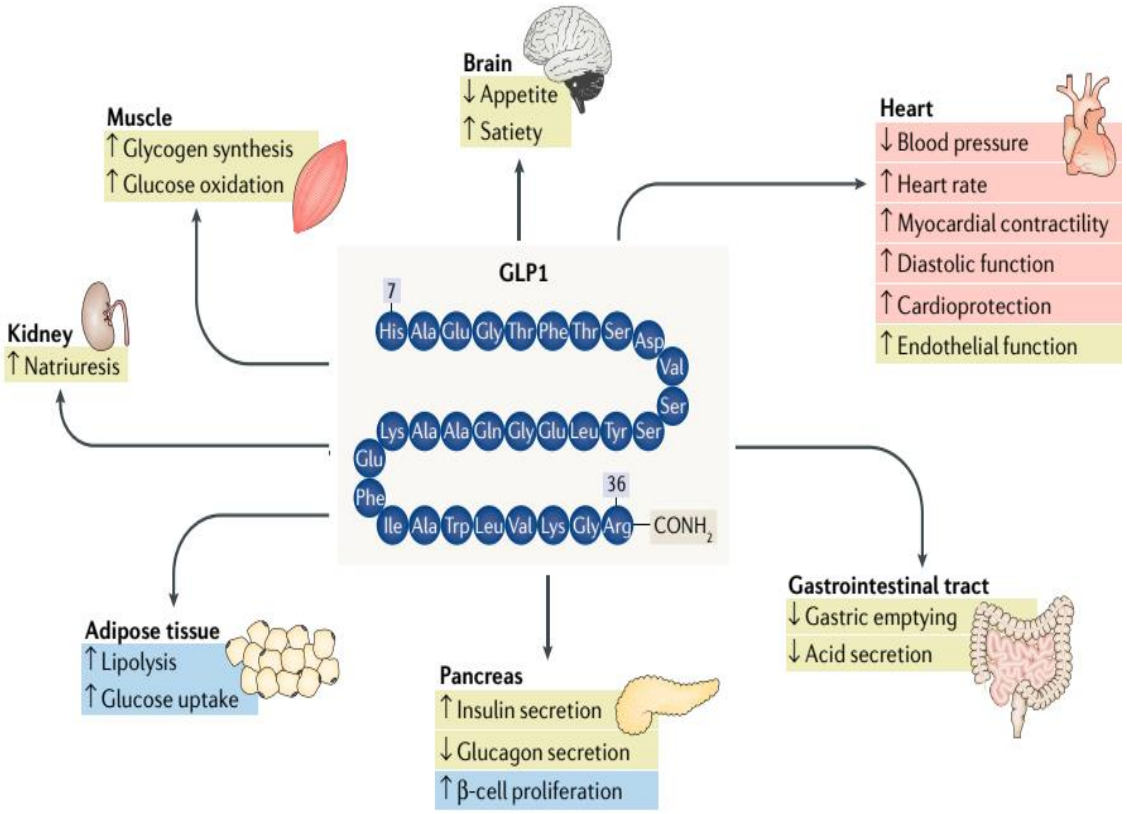

Figure (2): **Effects of GLP-1and GLP-1R on various tissues (17).**

Effects on the β-cell

GLP-1 effects on insulin secretion

In the pancreatic β-cells, stimulation of the GLP-1R results in glucose-dependent insulin secretion, meaning that the insulinotropic effects of GLP-1 are present only when plasma levels of glucose are above normal fasting plasma levels. Additionally, GLP-1 is a strong inhibitor of glucagon secretion (which is also strictly glucose dependent), which is possibly mediated by a direct effect on the pancreatic α-cells. However, this inhibitory effect is more likely to occur via the paracrine

effects of increased levels of somatostatin and insulin from neighboring δ-cells and β-cells, respectively **(19).**

In addition to its ability to stimulate insulin secretion, GLP-1 promotes insulin synthesis via stimulation of insulin gene expression **(13).**

Moreover, its effect on the endocrine pancreas, GLP-1 has a pronounced effect on gastrointestinal motility. The presence of nutrients in the small intestinal lumen, particularly in the ileum, which is rich in L cells, induces the release of GLP-1, which delays gastric emptying and thereby postpones nutrient uptake from the gut to result in reduced postprandial plasma glucose excursions **(17).** This physiological phenomenon is known as 'the ileal brake'. Importantly, the delay in gastric emptying seems to be dependent on the intermittent activation of the GLP-1R, as this effect is lost when GLP-1Rs are continuously activated **(22).**

GLP-1 effects on β-cell proliferation and apoptosis

The progression to T2DM is invariably associated with a decline in functional β-cell mass. The replication rate of human β-cells is greatest in young childhood and puberty but declines with increasing age **(23).**

Collectively, these observations suggest that age related changes in β-cell neogenesis and replication might be causally linked to the development of T2DM diabetes **(24).**

Agonists of the GLP-1 receptor improve glycemic control via both their acute insulinotropic action and, under certain circumstances, also by chronic action to preserve β-cell mass through stimulation of β-cell proliferation and inhibition of apoptosis **(6).**

Cardiovascular effects of GLP-1

GLP-1R mRNA was discovered to be in the heart of rats and humans. Expression was subsequently confirmed at the protein level and histologically. In the mice scattered GLP-1R expression was detected in cardiomyocytes of the atrium but not in the ventricles, and widespread expression was detected in smooth muscle cells of coronary vessels **(13).**

In humans, the presence of GLP-1R has primarily been demonstrated in the endothelium, the coronary arteries and the smooth muscle cells **(25).**

Although best known for its insulinotropic and weight lowering action, GLP-1R agonism also confers a series of beneficial effects on the cardiovascular system in rodents. These include an increase of cardiomyocyte survival via inhibition of apoptosis, improvement of regional, global cardiac output following injury and heart failure **(26)** and amelioration of endothelial dysfunction **(9).**

Effects of GLP-1 on cardiac performance after cardiac Injury

Endothelial dysfunction is a common co-morbidity associated with insulin resistance and T2DM. Treatment of type-2 diabetic patients that present coronary artery disease with GLP-1 improves endothelial function without affecting insulin resistance **(25).**

Similar findings have been reported for GLP-1 treatment of T1DM but GLP-1 improvement of endothelial function seems to be related to native GLP-1 and is not observed when GLP-1R agonists are compared head-to-head with equally glucose lowering medications. GLP-1

improvement of endothelial function, assessed by flow-mediated vasodilatation, was also demonstrated during a hyperglycemic clamp in patients with T2DM and normoglycemic controls **(9).**

In dogs with acute myocardial infarction, infusion of GLP-1 improves cardiac performance by increasing myocardial glucose uptake and by enhancing left ventricular function. In the same animal model, infusion of GLP-1 limited myocardial stunning (ventricular dysfunction without myocardial necrosis) following reperfusion. These data are in agreement with non-controlled clinical studies reporting that 72 h of native GLP-1 infusion improved regional and global left ventricular performance in patients with acute myocardial infarction and severe systolic dysfunction **(27).**

Generally, these data indicate that GLP-1 improves cardiac performance and output in the post-ischemic heart but otherwise may decrease cardiac output under non-pathological conditions. These data suggest that cardiomyocyte GLP-1R signaling is required for regulation of HR but is unrelated to the cardioprotective effects of GLP-1R agonism following cardiac injury **(13).**

Cardio metabolic effects of GLP-1(9-36amide)

Accumulating evidence indicates that some cardiac effects of GLP-1(7-36amide) are actually mediated via the DPP-4-generated GLP-1(9-36amide) and its smaller degradation products and, thus, are independent of GLP-1R signaling. At a dose of 0.3 nmol/L, pretreatment with GLP-1(7-36amide) improves recovery mice. Collectively, these data indicate that pharmacologic administration of GLP-1(9-36amide) may have a functional role to improve recovery from injury via GLP-1R-independent mechanisms, whereas GLP-1(7-36amide) but not GLP-1(9-36amide) affects cardiac contractility via GLP-1R signaling **(28).**

Effect of GLP-1 on heart rate (HR) and blood pressure (BP)

Most human researches found a stimulatory effect of GLP-1 on heart rate (HR) with unchanged or lowered BP only in hypertensive patients **(13).** Acute infusion of GLP-1 raises HR and cardiac output in healthy individuals, via GLP-1-induced vasodilation in skeletal muscle and adipose tissue. As displayed in health human volunteers, GLP-1 infusion acutely increments blood flow in the subcutaneous abdominal fat and skeletal muscle without changes in splanchnic blood flow. Notably, opposite to GIP, the GLP-1 induced increment in adipose tissue blood flow is not dependent on postprandial hyperglycemia and hyperinsulinemia

GLP-1R agonists **(29).** lead to reduce BP in people with T2DM. Also, in healthy individuals, acute administration of GLP-1, GLP-1(9-36amide), or exenatide did not influence renal blood flow or mesenteric blood flow, excluding splanchnic vasodilatation as a potential mechanism underlying the chronic hypotensive influence of GLP-1**(30).**

In a recent meta-analysis of 60 clinical studies, GLP-1R agonists were found to reduce diastolic BP with a range of - 1.84 to - 4.60 mmHg and to slightly raise HR by 2 to 3.35 beats/min. Relative to placebo, the decline of diastolic BP only achieved significance for the treatment of exenatide 10μg/twice daily (-1.08 mmHg) **(31).**

Potential mechanisms underlying GLP-1 improvement of BP may include GLP-1-induced vasodilatation and activation of nitric-oxide-dependent mechanisms. GLP-1R agonists could also enhance BP via its capacity to promote sodium excretion (natriuresis) through the kidneys **(29).** The chronic steady-state BP is affected by the intravascular volume, which is affected by the vascular tone and the extracellular fluid volume (ECFV); the ECFV is in turn defined by the sodium balance. Accordingly, when BP increments, the kidneys respond by enhancing natriuresis to reduce BP via lowering the ECFV. GLP-1R agonists acutely facilitate natriuresis in rodents and may also do so in humans, reducing BP, potentially also via lowering the ECFV **(32).**

GLP-1 and heart failure

Short-term infusion of recombinant GLP-1 over 48 h has been revealed a great enhancement in LV systolic and diastolic function, and boost insulin sensitivity and glucose uptake in cardiac muscle in the canine model of rapid pacing-induced dilated cardiomyopathy. Interestingly, GLP-1(9–36) exerts similar valuable consequences to native GLP-1 in this model, supporting the growing evidence that the metabolically inactive format of GLP-1 may recreate an active function in the cardiovascular system. Moreover, spontaneously hypertensive HF-prone rats (featured with hypertension, obesity, insulin resistance, and dilated cardiomyopathy), treated with long term GLP-1 from nine months of age (when they started to develop advanced HF and death) exhibited preserved contractile function of the myocardium, incremented myocardial glucose uptake, enhanced survival and a significant decline in myocyte apoptosis **(33).**

Importantly, these experimental data are supported by preliminary clinical trials demonstrating that GLP-1 may also enhance LV contractile function in patients with chronic HF. An early analysis carried out on a small group of T2DM patients with chronic HF found that short-term GLP-1 infusion for three days tended to enhance both systolic and diastolic function, though these changes did not have statistical significance. However, longer-term GLP-1 treatment (5 weeks) in both diabetic and normoglycaemic chronic HF patients (New York Heart Association class III and IV) was reported to significantly enhance myocardial oxygen consumption, LV ejection fraction and functional status, whereas no impact of GLP-1 was observed in patients with normal cardiac function **(33).**

Conflicts of Interest: The authors declare no conflict of interest.

References:

1. Wewer Albrechtsen NJ, Kuhre RE, Pedersen J, et al. (2016): The biology of glucagon and the consequences of hyperglucagonemia. Biomarkers in medicine, 10(11), 1141-1151.
2. Solloway MJ, Madjidi A, Gu C, et al. (2015): Glucagon couples hepatic amino acid catabolism to mTOR-dependent regulation of α-cell mass. Cell reports, 12(3), 495-510.
3. Wang Q, Liang X & Wang S (2013): Intra-islet glucagon secretion and action in the regulation of glucose homeostasis. Frontiers in physiology, 3, 485.

4. Gromada J, Franklin I & Wollheim CB (2007): α-Cells of the endocrine pancreas: 35 years of research but the enigma remains. Endocrine reviews, 28(1), 84-116.
5. Cooperberg BA & Cryer PE (2010): Insulin reciprocally regulates glucagon secretion in humans. Diabetes, 59(11), 2936-2940.
6. Kawamori D, Kurpad AJ, Hu J, et al. (2009): Insulin signaling in α cells modulates glucagon secretion in vivo. Cell metabolism, 9(4), 350-361.
7. Habegger KM, Heppner KM, Geary N, et al. (2010): The metabolic actions of glucagon revisited. Nature Reviews Endocrinology, 6(12), 689-697.
8. Charron MJ & Vuguin PM (2015): Lack of glucagon receptor signaling and its implications beyond glucose homeostasis. Journal of Endocrinology, 224(3), R123-R130.
9. Ceriello A, Esposito K, Testa R, et al. (2011): The possible protective role of glucagon-like peptide 1 on endothelium during the meal and evidence for an "endothelial resistance" to glucagon-like peptide 1 in diabetes. Diabetes care, 34(3), 697-702.
10. Godoy-Matos AF (2014): The role of glucagon on type 2 diabetes at a glance. Diabetology & metabolic syndrome, 6(1), 1-5.
11. Menge BA, Grüber L, Jørgensen SM, et al. (2011): Loss of inverse relationship between pulsatile insulin and glucagon secretion in patients with type 2 diabetes. Diabetes, 60(8), 2160-2168.
12. Farah A & Tuttle R (1960): Studies on the pharmacology of glucagon. Journal of Pharmacology and Experimental Therapeutics, 129(1), 49-55.
13. Müller TD, Finan B, Bloom SR, et al. (2019): Glucagon-like peptide 1 (GLP-1). Molecular metabolism, 30, 72-130.
14. White CM (1999): A review of potential cardiovascular uses of intravenous glucagon administration. The Journal of Clinical Pharmacology, 39(5), 442-447.
15. Ali S & Drucker DJ (2009): Benefits and limitations of reducing glucagon action for the treatment of type 2 diabetes. American Journal of Physiology-Endocrinology and Metabolism, 296(3), E415-E421.
16. Rosic M, Pantovic S, Rosic G, et al (2010): Glucagon effects on ischemic vasodilatation in the isolated rat heart. Journal of Biomedicine and Biotechnology, 2010.
17. Andersen A, Lund A, Knop FK & Vilsbøll T (2018): Glucagon-like peptide 1 in health and disease. Nature Reviews Endocrinology, 14(7), 390-403.
18. Vilsbøll T & Holst JJ (2004): Incretins, insulin secretion and type 2 diabetes mellitus. Diabetologia, 47(3), 357-366.
19. Sandoval DA & D'Alessio DA (2015): Physiology of proglucagon peptides: role of glucagon and GLP-1 in health and disease. Physiological reviews, 95(2), 513-548.
20. Sonne DP, Rehfeld JF., Holst JJ, et al. (2014): Postprandial gallbladder emptying in patients with type 2 diabetes: potential implications for bile-induced secretion of glucagon-like peptide 1. European Journal of Endocrinology, 171(4), 407-419.
21. Holst JJ (2007): The physiology of glucagon-like peptide 1. Physiological reviews, 87(4), 1409-1439.

22. Nauck MA, Kemmeries G, Holst JJ & Meier JJ (2011): Rapid tachyphylaxis of the glucagon-like peptide 1–induced deceleration of gastric emptying in humans. Diabetes, 60(5), 1561-1565.
23. Gregg BE, Moore PC, Demozay D, et al. (2012): Formation of a human β-cell population within pancreatic islets is set early in life. The Journal of Clinical Endocrinology & Metabolism, 97(9), 3197-3206.
24. Fujitani Y (2018): How does glucagon-like peptide 1 stimulate human β-cell proliferation? A lesson from islet graft experiments. Journal of Diabetes Investigation, 9(6), 1255-1257.
25. Nystrom T, Gutniak MK, Zhang Q, et al. (2004): Effects of glucagon-like peptide-1 on endothelial function in type 2 diabetes patients with stable coronary artery disease. American Journal of Physiology-Endocrinology and Metabolism, 287(6), E1209-E1215.
26. Noyan-Ashraf MH, Momen MA, Ban K, et al. (2009): GLP-1R agonist liraglutide activates cytoprotective pathways and improves outcomes after experimental myocardial infarction in mice. Diabetes, 58(4), 975-983.
27. Nikolaidis LA, Doverspike A, Hentosz T, et al. (2005): Glucagon-like peptide-1 limits myocardial stunning following brief coronary occlusion and reperfusion in conscious canines. Journal of Pharmacology and Experimental Therapeutics, 312(1), 303-308.
28. Ban K, Noyan-Ashraf MH, Hoefer J, et al. (2008): Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor–dependent and–independent pathways. Circulation, 117(18), 2340-2350.
29. Asmar A, Asmar M, Simonsen L, et al. (2017): Glucagon-like peptide-1 elicits vasodilation in adipose tissue and skeletal muscle in healthy men. Physiological reports, 5(3), e13073.
30. Bremholm L, Andersen UB, Hornum M, et al. (2017): Acute effects of glucagon-like peptide-1, GLP-19–36 amide, and exenatide on mesenteric blood flow, cardiovascular parameters, and biomarkers in healthy volunteers. Physiological reports, 5(4), e13102.
31. Mannucci E & Monami M (2017): Cardiovascular safety of incretin-based therapies in type 2 diabetes: systematic review of integrated analyses and randomized controlled trials. Advances in therapy, 34(1), 1-40.
32. Crajoinas RO, Oricchio FT, Pessoa TD, et al. (2011): Mechanisms mediating the diuretic and natriuretic actions of the incretin hormone glucagon-like peptide-1. American Journal of Physiology-Renal Physiology, 301(2), F355-F363.
33. Grieve DJ, Cassidy RS & Green BD (2009): Emerging cardiovascular actions of the incretin hormone glucagon-like peptide-1: potential therapeutic benefits beyond glycaemic control? British journal of pharmacology, 157(8), 1340-1351.