JCHR (2021) 11, 173-178

Journal of Chemical Health Risks

www.jchr.org

ORIGINAL ARTICLE

Role of Incretin Levels in Controlling Diabetic Patients

Rasool Muayad Shukur Al-Obaidi

Department of Medical Laboratory Techniques, Faculty Medical and Health Technologies, Ahlulbyt University, Karbala, Iraq

(Received: 10 May 2021 Accepted: 20 August 2021)

KEYWORDS

Blood glucose;
Incretins;
Type 2 diabetes;
Insulin resistance;
HOMA IR.

ABSTRACT: Within extremely precise limitations, the management of blood glucose levels in healthy individuals can be achieved and maintained. The glucose level rises immediately after a meal is consumed. Incretin hormones, which are appeared in the digestive system, play an essential function in the order of glucose, the maintenance of energy balance, and the protection of Langerhans islets cells. They are involved in the regulation of glucose levels in the body, and if their secretion is hindered, they can be used to anticipate the development of diabetes as soon as possible.The overarching goal of the research is to identify the relationship between the production of GLP-1 and the development of insulin resistance , which ultimately results in type 2 diabetes.The case-control portion of current investigationdepends on a revision of medical records from patients at the Clinic for Endocrinology , Diabetes, and Metabolic Diseases at the Clinical Center of Serbia, and computing the relevant parameters and doing statistical analysis.In terms of glucose profile, there was a substantial statistical divergence between the two groups that was found in the study. The relationship between Glucagon-like peptide 2 (GLP-2) and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was found to be negative and statistically considerable (p=0.045). There was a statistically considerable positive association between DPP-IV and HOMA-IR (p=0.05).Our finding displays that insulin resistance can result in the suppression of glucagon-like peptide 1 production in persons with diabetes. According to the information presented here, reduction of GLP-1 secretion is detached and will not occur in all people with poor glucose metabolism . This is due to a condition known as prediabetes, which will be discussed further in this section.

INTRODUCTION

Type 2 diabetes represents a non-infectious condition that is becoming increasingly common, and the frequency of occurrence is likely to continue growing in the future as well. Being familiar with the biology of this disease is essential if one hopes to decrease the risk factors that contribute to the development of this condition. In accordance with the World Health Organization, the number of individuals who have been diagnosed with diabetes all over the world has raised from 108 million in 1980 to 422 million in 2014. This indicates that the global prevalence of diabetes has increased from 4.7% to 8.5% over this time period. Complications of diabetes include cardiovascular illness, amputation of lower extremities owing to limb amputation, kidney failure, and blindness as a result of retinopathy[1].

The discovery of a diverse variety of GLP-1 receptor agonists has been particularly productive, but investigation using GIP monotherapy in people with type 2 diabetes have been consistently disappointing . "Both GIP-GLP-1 coagents and GIP receptor antagonists used in combination with GLP-1R agonists appear to be" beneficial in terms of both weight loss and diabetes control, although the molecular mechanisms behind these advantages are still unknown [2].

A significant role is played by incretin hormones, which are released in the digestive system and are involved in

*Corresponding author: dr.rasoolobaidi@abu.edu.iq (R.M.Shukur Al-Obaidi)
DOI: 10.22034/jchr.2021.685648

the glucose regulation, the maintenance of energy balance, and the protection of Langerhans islets cells. They are involved in the regulation of glucose levels in the body, and if their secretion is hindered, they can be used to anticipate the development of diabetes as soon as possible. If there is a reduction in the production of these hormones and the existence of Diabetes , their substitution with GLP-1 mimetics or a DPP-4 inhibitor can result in improved control of the illness and lower blood glucose levels[3].

Many studies have been conducted on GLP-1 mimetics, with the result that patients who are treated with GLP-1 (mimetics) or DPP4 inhibitors may have a better prognosis with their illness. GLP-1 is a hormone that is involved in the management of glucose and energy balance and the regulation of weight gain and obesity. In the same experiments, the researchers came to the conclusion that, in the majority of cases, GIP secretion is retained or even enhanced, but the insulinotropic impact is reduced. It has been recommended by some researchers that patients with secondary diabetes have a decreased incretin impact. Overall, the findings of all investigations indicate that patients with type 2 diabetes have decreased GLP-1 production while maintaining GIP secretion [4].

MATERIALS AND METHODS

The case-control investigation was based on the examination of medical records of patients from the Clinic for Endocrinology, Diabetes, and Metabolic Diseases, Clinical Center of Imam Al Hassan in Karbala, the calculation of the required parameters, and statistical analysis. The research portion of this study was divided into three parts: the research portion, the clinical portion, and the administrative portion.

The current investigation's objectives were to "compare the values of HOMA-IR and GLP-1 and compute the correlation between them, as well as to compare the values of BMI and HOMA IR and calculate the correlation between them" in order to analyze the prediction of type 2 diabetes in the participants. As part of the investigation, medical data from patients at an obesity center are being analyzed.

A number of 80 individuals were participated in the investigation, who were separated into two groups: Cases group consisted of 40 type 2 diabetes patients, whereas the Control group composes of 40 apparently healthy individuals who were age and sex matched. All of the participants' weight and height were measured, and their BMI was calculated based on the results.

Measurements were made of the condensations of glucose, insulin, and GLP-1. The HOMA IR was developed based on the condensations of glucose and insulin in the blood and an indicator of insulin resistance. IBM SPPS Statistic was used to conduct a statistical analysis of the data collected. A comparison was made between the statistical data and the HOMA IR and BMI, and between the statistical data and the HOMA IR and GLP-1. For the purpose of making statistical conclusions about the data (r), the Bayes factor and the correlation coefficient were employed.

RESULTS

Regarding LDL and Triglyceride levels, there was a large statistically considerable variance between the examined groups, and there was a statistically considerable variance between the studied groups in relation to HDL Table 1.

GLP-2 and DPP-IV levels were significantly variance between the two study groups, which was statistically significant. Table 2.

There was high statistically considerable variance between the studied groups as regard Glucose profile Table 3.

There was negative correlation between GLP-2 and HOMA-IR with significance (p=0.045). There was Positive correlation between DPP-IV and HOMA-IR with significance (p=0.05) Table 4.

Table 1. Comparing studied groups

	Cases (n = 40)		Control (n = 40)		p	Sig.
Age (years)	54.98 ± 11		54 ± 12.8		0.716	NS
Sex	No.	%	No.	%		
Male	20	50.0	24	60.0	0.369	NS
Female	20	50.0	16	40.0		
BMI	28.07 ± 4.06		29.13 ± 4.12		0.250	NS
Systolic BP(mmHg)	130.25 ± 18.04		129.25 ± 16.7		0.798	NS
Diastolic BP(mmHg)	72.25 ± 8.91		72.5 ± 11.27		0.913	NS
Cholesterol ($mgdl^{-1}$)	195.22 ± 44.73		209.95 ± 36.92		0.112	NS
HDL ($mgdl^{-1}$)	54.68 ± 27.75		67.75 ± 16.33		0.012	S
LDL ($mgdl^{-1}$)	90.2 ± 39.19		117.65 ± 22.26		<0.001	HS
Triglyceride($mgdl^{-1}$)	244.52 ± 96.91		126.2 ± 53.62		<0.001	HS

χ^2: Chi square test t: student-t test;p: p value for comparing between the studied groups

*: Statistically significant at $p \leq 0.05$

Table 2. Comparing studied groups as regard Incretins

	Cases (n = 40)	Control (n = 40)	p	Sig.
GLP-1 ($ngml^{-1}$)	13.55 (2.2 – 25.58)	9.05 (1 – 27.28)	0.364	NS
GLP-2 ($ngml^{-1}$)	15.45 (3.85 – 19.28)	8.05 (1 – 21.58)	0.015	S
GIP ($pgml^{-1}$)	4166.05 (737.73 – 6959.1)	4099.3 (360.43 – 7848.6)	0.945	NS
DPP-IV($ngml^{-1}$)	16.95 (7.1 – 19.48)	8.2 (2.93 – 13.93)	0.005	S

U: Mann-Whitney test;p: p value for comparing between the studied groups ;

*: Statistically significant at $p \leq 0.05$

Table 3. Comparison between studied groups as Glucose profile

	Cases (n = 40)	Control (n = 40)	p	Sig.
HbA1c (%)	7.39 ± 0.6	5.02 ± 0.38	<0.001	HS
FBG ($mgdL^{-1}$)	137.15 ± 13.47	90.33 ± 6.01	<0.001	HS
F. insulin	5.59 ± 1.51	6.47 ± 1.21	0.005	S
HOMA-IR	1.87 ± 0.46	1.44 ± 0.27	<0.001	HS

t: student-t test;p: p value for comparing between the studied groups

*: Statistically significant at $p \leq 0.05$

Table 4. CorrelatingIncretins and HOMA-IR

	HOMA-IR	
	R	p
GLP-1	-0.066	0.559
GLP-2	-0.225	0.045
GIP	0.087	0.445
DPP-IV	0.220	0.050

r: Pearson correlation;p: p value for comparing between the studied groups

*: Statistically significant at $p \leq 0.05$

DISCUSSION

The regulation of blood glucose level in normal individual is controlled by very strict limits. Immediately after food ingestion, the glucose level increases. This will trigger insulin secretion from pancreatic β cell and will lower the glucagon secretion from pancreatic β cell; and the contrariwise. Insulin will reduces the glucose level by lowering the glycogenolysis and gluconeogenesis in liver and increasing the glucose uptake in the peripheral tissue,

as well as by lowering glucagon secretion in pancreas. This does not occur in diabetes mellitus, one of its causes is pancreatic β cell defect[5].

Incretin hormones, which are secreted in the digestive system and are involved in glucose control, energy balance, and the protection of Langerhans islets cells, play a vital role. They have a role in the body's glucose control, and if their secretion is hampered, they can be utilized to predict the onset of diabetes in the near future. Their substitution with GLP-1 mimetics or a DPP-4 inhibitor can result in improved control of the illness and lower blood glucose levels if there is a decline in the synthesis of these hormones and the presence of Diabetes [6].

When it comes to LDL and Triglyceride levels, we observed a substantial statistically considerable variance between the examined groups, as well as a statistically significant difference when it comes to HDL levels in the current study. In terms of age, gender, and body mass index (BMI), there was no statistically considerable variance between the examined groups.

Identical findings were reflected by Toft-Nielsen et al. [7]who detected that there is no statistically considerable variances between the investigated groups regarding age, sex and BMI. There was statistically considerable variances between the investigated groups regarding LDL.

According to a previous study, greater BMI values are related with a higher value of the Homeostatic Model Assessment for Insulin Resistance (HOMA IR). In the lengthier research, BMI was shown to be accompanied with HOMA IR in a manner that was independent of the other variables. A number of researchers have demonstrated that BMI has an independent positive connection with insulin resistance indicators and an inverse association with the activity of beta cells that have been acclimated to insulin resistance in individuals with newly diagnosed type 2 diabetes [8].

Subjects with IFG + IGT and NIDDM, as well as those at a more severe stage of glucose metabolism disorders , had considerably lower total GLP-1 levels, as with certain studies, than those at a less severe stage. Patients with prediabetes, particularly those with IFG + IGT, may have lower overall GLP-1 concentrations and a reduced sensitivity to glucose, which may suggest that they already have GLP-1 abnormalities. However, it is not yet clear what function it plays in the development of type 2 diabetes. Multiple experts, on the other hand, referred that GLP-1 levels in individuals with IGT or type 2 diabetes have not been found to be decreased. Although the exact reason and method of this difference are unknown, there is a potential that this assertion is dependent on the type of prediabetes that is being discussed[9].

GLP-1 and DPP-IV levels were found to be statistically significantly different between the two groups in this investigation, according to the findings. According to Nauck et al. [10], who investigated the impact of intravenous infusions of GIP and GLP-1 in moderately type 2 diabetic patients and matched controls, the insulinotropic effect of GIP was almost completely lost in the patients, whereas the insulin response to GLP-1 was almost identical to that seen in the controls. Elahi and colleagues came at the same conclusion [11].

The findings of Bagger et al.[12]revealed that there were no statistically considerable variations in baseline levels between OGTTs and IIGIs in either group . When comparing patients with type 2 diabetes to healthy control participants, GIP levels were substantially greater in the diabetic patients. It was discovered that there were no changes in GIP responses between the groups during OGTTs (P = NS). In the study, it was shown that there were no considerable variances in mean fasting values across the groups. As oral glucose loading raised, raising GLP-1 responses were detected in both groups, with no statistically significant differences identified between the groups (P = NS).

GIP secretion has been observed to be normal or slightly impaired in the majority of cases. Toft-Nielsen et al. [7]conducted a prior research in individuals with type 2 diabetes who represented a fairly broad clinical spectrum of the illness and observed near-normal fasting levels and meal responses, as well as no associations between metabolic markers and GIP responses in this population. In the same investigation, it was discovered that the secretion of GLP-1 had been significantly decreased. Using multiple regression analysis, it was discovered that the impairment was associated with disabled -cell function. People with poor glucose tolerance exhibited an intermediate GLP-1 response, which was detected.

When type 2 diabetes individuals were subjected to a 15 $mmoll^{-1}$ hyperglycemic clamp, Vilsböll et al. [13]investigated the differential effects of high dosages of GIP and GLP-1 on their glucose metabolism. GLP-1 infusion was shown to be effective in restoring the late-phase (30–120 min) insulin response to glucose (which had been almost nonexistent in those patients) to levels that were indistinguishable from those found in healthy controls in those trials. For want of a better phrase, the individuals had a perfectly normal insulin response to glucose when given GLP-1. Kjems et al.[14] made a similar discovery (that GLP-1 can restore -cell response to glucose in individuals with type 2 diabetes) but used a completely different strategy to do it. According to the findings of this study, there was a substantial statistical difference between the examined groups when it came to glucose profile.

Radojčin et al.[15]pointed out that HOMA IR values are ordered from 0.09 to 21.67, with an average value of 2.86. Values less than 2.5 had nineteen patients (65.52%), whereas ten patients (34.48%) had values that correspond to insulin resistance (> 2.5). The average HOMA IR in obese individuals was 3.26, while the average HOMA IR in patients with a BMI of less than 25 was 1.82. The current study displays that there was negative correlation between GLP-2 and HOMAIR with considerable (p=0.045). There was Positive correlation between DPP-IV and HOMA-IR with considerable (p=0.05).

HOMA IR and GLP-1 have a moderate connection, according to Radojčin et al.[15], who found that the Bayes factor (4.589) indicates a moderate correlation between the two measures. The Pearson coefficient (r = -0.177) indicates a negative relationship between these two parameters, indicating that an increase in HOMA IR readings findings in a reduction in GLP-1 and vice versa.

The HOMA model has proved to be a valid clinical and epidemiologic tool in the description and etiology of diabetes, and it has since become a standard tool in clinical Endocrinology. The HOMA index is a sensitive method for estimating beta cell activity, insulin sensitivity, and glucose intolerance status . This document goes into great depth on how glucose intolerance can lead to type 2 diabetes [16].

Recent years have seen a tremendous increase in the development of the incretin biotechnology area. GIP, frequently referred to as the "forgotten twin" of GLP-1, is now being researched as a potential novel medication for the treatment of diabetes when used in conjunction with GLP-1. In clinical practice, GLP-1R agonists and DPP-4 inhibitors have demonstrated excellent results in the treatment of type 2 diabetes . In a study of 18 individuals with i-IFG, the effects of GLP-1R agonists and DPP-4 inhibitors on hepatic and peripheral insulin action , as well as glucagon and incretin hormone secretion, were examined[17].

CONCLUSIONS

Our finding demonstrates that insulin resistance can result in the suppression of glucagon-like peptide 1 production in persons with diabetes. According to the information presented here, reduction of GLP-1 secretion is detached and will not happen in all people who suffer poor glucose metabolism . This is due to a condition known as prediabetes, which will be discussed further in this section. We observed a link between BMI and HOMA IR values throughout the research, implying that excess body fat mass and increased body weight may lead to the development of insulin resistance and, as a result, the appearance of type 2 diabetes .

Conflict of Interest

The author decleared no conflict of interest

REFERENCES

1. Bano A, Pera A, Almoukayed A, Clarke TH, Kirmani S, Davies KA, Kern F. CD28 null CD4 T-cell expansions in autoimmune disease suggest a link with cytomegalovirus infection. F1000Research. 2019;p1-8. last page?

2. Boer, G.A. and Holst, J.J., 2020. Incretin Hormones and Type 2 Diabetes—Mechanistic Insights and Therapeutic Approaches. Biology. 9(12), 473. last page?

3. English A., Irwin N., 2019. Nonclassical islet peptides: pancreatic and extrapancreatic actions. Clinical Medicine Insights: Endocrinology and Diabetes. 12, 1179551419888871.

4. Lafferty R., O'Harte F.P., Irwin N., Gault V.A., Flatt P., 2021. Proglucagon-derived peptides as therapeutics. Frontiers in Endocrinology. 12, 585.

5. Grüneis V., Schweiger K., Galassi C., Karl C.M., Treml J., Ley J.P., König J., Krammer G.E., Somoza V., Lieder B., 2021. Sweetness Perception is not Involved in the Regulation of Blood Glucose after Oral Application of Sucrose and Glucose Solutions in Healthy Male Subjects. Molecular Nutrition & Food Research. 65(2), 2000472.

6. Gonzalez-Campoy J.M., 2019. Hormonal regulation of energy balance and energy stores. Bariatric Endocrinology.Springer.37-57:

7. Toft-Nielsen M.B., Damholt M.B., Madsbad S., Hilsted L.M., Hughes T.E., Michelsen B.K., Holst J.J., 2001. Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. The Journal of Clinical Endocrinology & Metabolism. 86(8), 3717-3723.

8. Ji B., Qu H., Wang H., Wei H., Deng H., 2017. Association between the visceral adiposity index and homeostatic model assessment of insulin resistance in participants with normal waist circumference. Angiology. 68(8), 716-721.

9. Weng, J., Ji, L., Jia, W., Lu, J., Zhou, Z., Zou, D., Zhu, D., Chen, L., Chen, L., Guo, L. and Guo, X., 2016. Standards of care for type 2 diabetes in China. *Diabetes/metabolism Research and Reviews*. *32*(5), 442.last page?

10. Nauck M.A., Heimesaat M.M., Orskov C., Holst J.J., Ebert R., Creutzfeldt W., 1993. Preserved incretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. The Journal of Clinical Investigation. 91(1), 301-307.

11. Elahi D., McAloon-Dyke M., Fukagawa N.K., Meneilly G.S., Sclater A.L., Minaker K.L., Habener J.F., Andersen D.K., 1994. The insulinotropic actions of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (7–37) in normal and diabetic subjects. Regulatory Peptides. 51(1), 63-74.

12. Bagger J.I., Knop F.K., Lund A., Vestergaard H., Holst J.J., Vilsbøll T., 2011. Impaired regulation of the incretin effect in patients with type 2 diabetes. The Journal of Clinical Endocrinology & Metabolism. 96(3), 737-745.

13. Vilsbøll T., Krarup T., Madsbad S., Holst J., 2002. Defective amplification of the late phase insulin response to glucose by GIP in obese Type II diabetic patients. Diabetologia. 45(8), 1111-1119.

14. Kjems L.L., Holst J.J., Vølund A., Madsbad S., 2003. The influence of GLP-1 on glucose-stimulated insulin secretion: effects on β-cell sensitivity in type 2 and nondiabetic subjects. Diabetes., 52(2), 380-386.

15. Radojin D., Polovina S.P., 2018. Role of incretins in the pathogenesis of type 2 diabetes. Medical Gazette of the Special Hospital for Thyroid and Metabolism Zlatibor**.** 23(70), 53-65.

16. Johnston L. W., Harris S.B., Retnakaran R., Giacca A., Liu Z., Bazinet R.P., Hanley A. J., 2018. Association of NEFA composition with insulin sensitivity and beta cell function in the Prospective Metabolism and Islet Cell Evaluation (PROMISE) cohort. Diabetologia. 61(4), 821-830.

17.de Araújo, Ana Francisca Lopes Correia., 2017. Glucagon-like peptide-1 and glucagon-like peptide-1 analogs nanotechnology-based systems for prevention and therapy of diabetes.Thesis.