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ROLE OF INCRETINS IN THE PATHOGENESIS OF TYPE 2 DIABETES

Abstract: OBJECTIVE: Incretin hormones secreted in the digestive tract (incretins) have an important role in regulating glucose concentrations, energy balance and preserving Langerhans islet cells. They regulate the glucose concentration, but they can also be predictors of diabetes in the near future if their secretion is reduced. The aim of the study is to determine the association between GLP-1 secretion and the occurrence of insulin resistance, which will lead to the onset of type 2 diabetes by comparing HOMA IR and GLP-1 values, as well as HOMA IR and BMI values. **MATERIAL AND METHODS:** Glucose, insulin and GLP-1 concentrations were measured for 29 participants in the study. HOMA IR were calculated, from values of glucose and insulin concentration, for the each participant in the study. For all participants in the study were measured body mass and height, and calculated BMI. The resultes were statistically procesed, the values of HOMA IR and GLP-1 were compared, as well as values of HOMA IR and BMI. **RESULTS:** According to the Bayes factor (4.589), there is moderate correlation between HOMA IR and GLP-1.The Pearson coefficient is negativ (r=-0.177), which means thet the increase of HOMA IR values results in a decrease in GLP-1 secretion and vice versa. It has to be noted that there are individual differences in the secretion of this incretin. The Bayes factor (5.732) indicates moderate correlation between HOMA IR and BMI. Positive Pearson coefficient (r=0.121) leads to the conclusion that with the increase of BMI, HOMA IR increases, and consenquently the possibility of insulin resistance. **CONCLUSION:** Some people with insulin resistance have suppression of release of the glucagon like peptide 1. Reduced GLP-1 secretion is individual and does not have to occure in all people with impaired glucose metabolism. The correlation between HOMA IR and GLP-1 concentrations is negative, which is in favore of the fact that pe-

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ople with insulin resistance have reduced secretion of incretin hormones. We found that the correlation between BMI and HOMA IR values can lead to insulin resistance and consequently to type 2 diabetes.

Keywords: insulin resistance, HOMA IR, BMI, GLP-1, DM

Introduction

Diabetes mellitus is a non-infectious disease, occurring with increasing frequency and probably frequency will tend to increase further. To be able to reduce the risk factors for this disease it is necessary to know the pathophysiology that leads to it.

Number of persons who were diagnosed with diabetes worldwide has increased from 108 million (1980) to 422 million (2014), which means that the global prevalence in this period increased from 4.7% to 8.5%. Diabetes causes complications that increase the risk of cardiovascular disease, limb amputation, renal disease, and blindness due to retinopathy.

Incretin hormones that is secreted in the digestive tract plays an important role in the regulation of glucose, energy balance and preservation of Langerhans islets cells.

Physiologically they regulate the glucose concentration, and if their secretion is impaired they can also be predictors of diabetes in the near future. If there is a decrease in the secretion of these hormones and presence of Diabetes, their replacement with the GLP-1 mimetics or DPP-4 inhibitor can lead to the better control of the disease.

Consequently, it is important to know the synthesis, function, physiological role and the degradation of these hormones and their role in development, early detection and control of diabetes and insulin resistance so the early treatment can be started and postpone, as far as possible, the development or complications of the disease (1,2).

The incretins are hormones which are secreted from the intestine into the bloodstream in response to nutrient intake and modulate insulin secretion. Insulin secretion under the influence of the incretins (incretin effect) explained up to 50% of the total insulin secretion after oral glucose intake. By definition, an incretin hormones are insulinotropic, and the common physiologic plasma concentrations is reached after a meal. The word ,, incretin,, was first used in 1932 by La Barre for extract from the upper part of the intestinal mucosa. Between 1964 and 1967 several researchers separately observed that the response of insulin is larger (greater secretion, measuring of insulin concentration) when glucose is administered orally compared to glucose given intravenously (up to 70%), even though the glucose concentrations were higher administrated intravenously. They found that glucose is administered orally induces the release of incretin from the intestine. Brown et al are observed and the dependence of GIP activity of glucose, respectively, of plasma glucose should be raised in order to induce insulin secretion GIP. A second peptide which is produced in the intestine, fragment of proglucagon and shows potent insulinotropic effect was found in 1985 and was named glucagone- like peptide 1 (GLP-1). GIP and GLP-1 together

are responsible for the full incretin effect. It has been shown that GLP-1, but not GIP, administered intravenously, can increase insulin secretion, and reduced blood glucose in people with type 2 diabetes (3).

Glucose-dependent insulinotropic peptide (GIP) is the first incretin hormone that was described. In the fasting state its concentration is low compared to the concentrations after a meal. GIP is released into the bloodstream upon intake of food that contains glucose or fat. If you enter only fatty foods, secretion of GIP is induced, but its concentration is not enough to stimulate the secretion of insulin. GIP is synthesized in a K cell of the small intestine. Most of the K cells can be found in the duodenum and jejunum, while few in the distal ileum. In the fasting state circulating levels are low but it's concentration is increasing within a few minutes after food intake. Glucose, fats, sucrose, galactose and fructose stimulate secretion of GIP, and secretion isn't stimulate by mannose. Secreted GIP is degradated under the influence of dipeptidyl peptidase 4 (DPP4) within 5 to 7 minutes, this produce an inactive metabolite, GIP (3-42). After this inactive metabolite is excreted through kidneys (3–5).

It is shown that the primary function of GIP is to stimulate secretion of insulin from pancreatic beta cells. In type 2 DM its role is almost lost. It is speculated that this occurs as a result of chronic desensitization or reduction expression of GIPR in beta cells. In addition, GIP, complements insulin concentracion in the beta cells by increasing insulin gene transcription and biosynthesis of insulin. Prolonged exposure to GIP shows an increased expression of GLUT-1 and increased glucose uptake. Some data suggest that GIP has the role in the proliferation of beta cells and has antiapoptotic effect.

Glucagon- like peptid- 1 (GLP-1) is second peptide with incretin activity. Gene for proglucagon encoding two glucagon- like peptides (GLP-1 and glucagon- like peptide- 2). GLP-2 does not stimulate insulin secretion, so he is not the part of the incretin hormones. These two peptides are produced mostly in the enteroendocrine L cells, which are stored in the enterocytes of the small intestine and through the ascending colon. The primary physiological stimulus for the secretion of GLP-1 is a fatty food and food rich with carbohydrates. After a few minutes of food intake plasma concentration is increasing rapidly. Secretion is biphasic, with an early phase within 5 to 15 minutes, and the late phase after 30 to 60 minutes. The half-life of GLP-1 in blood is 1.5 to 2 minutes. Degradation is performed by cleaving the amino acids under the influence of DPP4 and neutral endopeptidase 24.11 (NEP 24.11), which results in obtaining an inactive metabolite. GLP-1 fragments are excreted by the kidneys. GLP-1 binds to receptors on pancreatic beta cells, leading to exocytosis of insulin secretory vesicles.

In addition to insulin secretion, GLP-1 acts on the expression of GLUT2 receptor, and proliferation, neogenesis, increasing beta cell mass and inhibition of apoptosis. This peptide regulates appetite, food intake and body weight. In muscles stimulates glycogen synthesis, in adipocytes stimulates glucose uptake, lipogenesis and lipolysis, while in the bone was not found, but its effect is achieved indirectly by stimulation of calcitonin

secretion, inhibiting bone resorption (3,5–11)”id”:”ITEM-1”,”issue”:”4”,”issued”:{“-date-parts”:[[“2008”]]},”page”:”470-512”,”title”:”The Role of Incretins in Glucose Homeostasis and Diabetes Treatment”,”type”:”article-journal”,”volume”:”60”},”uris”:[“http://www.mendeley.com/documents/?uuid=4bdf1687-c6fb-4f3b-9afa-7f685ea15d65”]},{“id”:”ITEM-2”,”itemData”:{“DOI”:”10.1016/S0003-4266(04.

In patients with type 2 DM we see reduced incretin effect. Several studies had been done on the subject: Whether the defect of incretin effect is causing disease or it occurs as a secondary phenomenon due to the development of the disease. In most cases, the conclusion was that the reduction of incretin effect is not a primary cause of type 2 DM. One study reported that the incretin effect in participants with impaired glucose tolerance in most of the subjects are preserved. It is shown that the disorder of incretin effect is early phenomenon in the pathogenesis of type 2 diabetes, and it is not the defect which leads to disease.

Many studies were made on the GLP-1 mimetics, and came to the conclusion that patients who were treated with GLP-1 (mimetics) or DPP4 inhibitors may improve outcome of the disease. GLP-1 plays an important role in the regulation of glucose and energy balance, as well as in the obesity regulation. In the same studies, they made conclusion that secretion of GIP is in the most cases preserved or even increased, but insulinotropic effect is decreased. Some researchers suggests that there is a reduced incretin effect in people with secondary diabetes. Conclusion of all studies is that people with type 2 diabetes have reduced secretion of GLP-1 and preserved GIP secretion (1,12–17).

Materials and Methods

The research part of this study is a retrospective, quantitative, observational study, based on a review of medical records, patients from Clinic for Endocrinology, Diabetes and Diseases of Metabolism, Clinical Center of Serbia, calculating the necessary parameters and statistical analysis.

The overall objective of the work is to determine the correlation between the secretion of GLP-1 and the appearance of insulin resistance leading to type 2 diabetes.

The objectives of this study were:

1. To compare the value of HOMA-IR and GLP-1 and calculate the correlation between them
2. To compare the value of BMI and HOMA IR and calculate the correlation between them for assessing the prediction of type 2 diabetes

Research study is examination of medical records of patients from obesity center, Clinical center of Serbia. The study included 29 participants, with no discrimination of gender and age. Weight and the height were measured for all participants and from it body mass index (BMI) was calculated.

Concentration of glucose, insulin and GLP-1 were measured. From concentration of glucose and insulin an index of insulin resistance, HOMA IR was calculated.

The obtained data were statistically analyzed in IBM SPPS Statistic. Statistical values were compared with HOMA IR and BMI, and HOMA IR and GLP-1. Statistical conclusions were obtained from the Bayes factor and the correlation coefficient (r).

Results

The study included patients of both sexes. Of the 29 patients who participated in the study, 21 people (72%) were female, and 8 people (28%) were male.

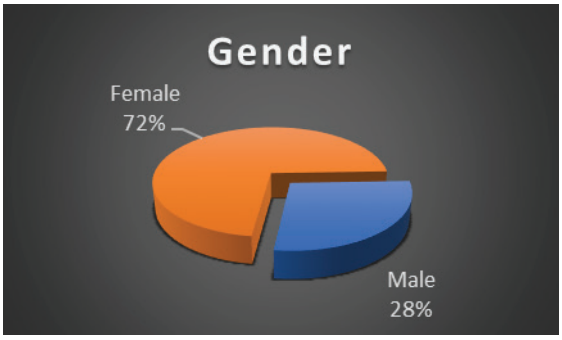

Figure 1. Classification of patients according to sex

The youngest participant research was 16 and the oldest 62 years old, with an average value of 37 years.

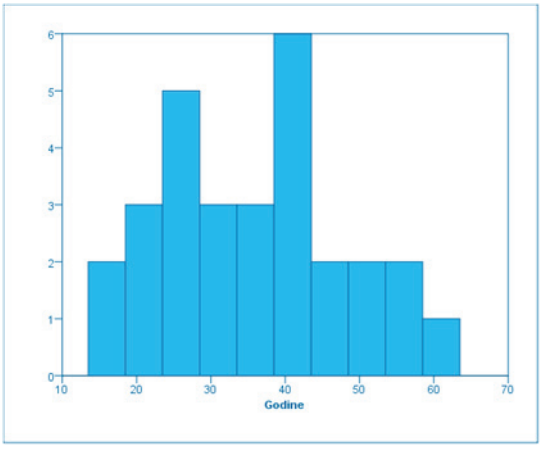

Figure 2. Distribution of age of patients

The lowest body weight was 50 kg, while the highest value of the body weight was 186 kg, with a mean value of 109 kg.

BMI was between 18.4 to 53.3, with a mean value of 37.2. Of the 29 patients eight patients not categorized as obese; one (3.45%) was categorized as underweight with a BMI of less than 18.5; seven participants (24.14%) had normal body weight with BMI values from 18.5 to 24.9. Twenty-one patients (72.41%) was categorized as obese with values of BMI above 30.

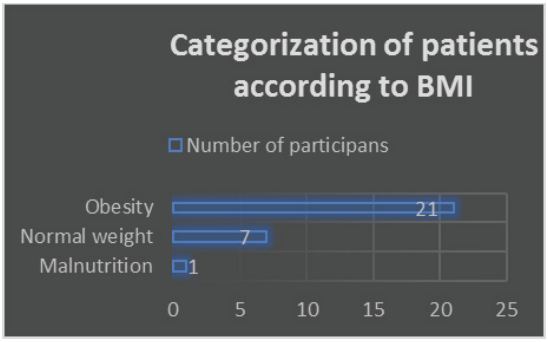

Figure 3.Classification of patients according to BMI

Glucose levels varied from 2.9 mmol/l to 6.6 mmol/l with an average value of 4,45 mmol/l. Five patients (17.24%) had a value of glucose less than 3.9 mmol/l (hypoglycemia). Twenty-two patients (75.86%) had a normoglycemic value, while two patients (6.9%) had hyperglycemia with values greater than 6.1 mmol/l. Glucose in individuals categorized as obese averaged 4.52 mmol/l, while in non-obese as categorized averaged 4.26 mmol/l.

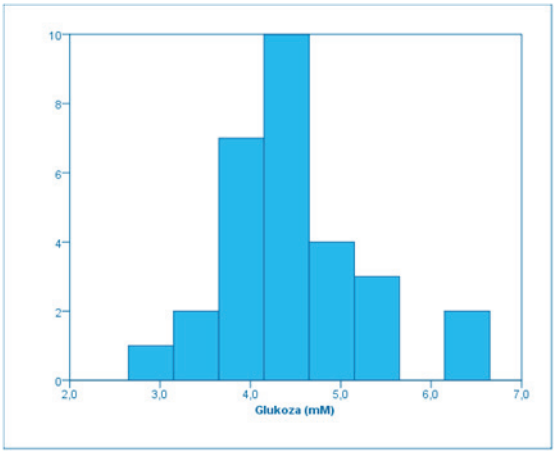

Figure 4. Distribution of glucose concntration

The minimum value of the insulin was 0.4 mU/mL, while the highest value was 73.9 mU/ml, with the mean value is 11.95 mU/ml. Normal levels of insulin (< 25 mU/ml) was found in twenty-seven persons (93.1%), while the two persons had hyperinsulinemia (6.9%). In obesity we see higest concentrations of insulin, on average, 12.98 mU/ml, then in individuals with a normal weight (an average of 9.23 mU/ml).

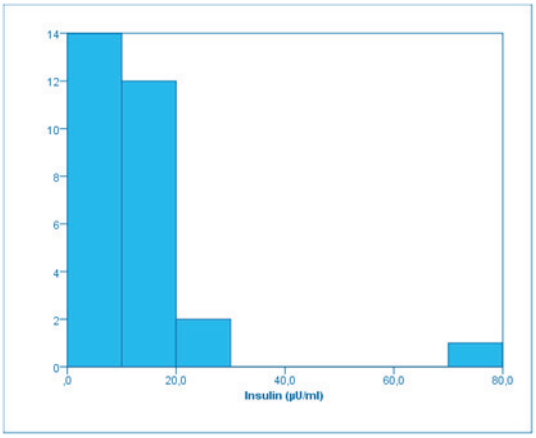

Figure 5. Distribution of fasting insulin concentrations

HOMA IR values are ranged from 0.09 to 21.67, with an average value of 2.86. Values less than 2.5 had nineteen patients (65.52%), while ten patients (34.48%) had values that correspond to insulin resistance (> 2.5). In obese patients average HOMA IR was 3.26, while in those with a BMI of less than 25 average HOMA IR 1.82.

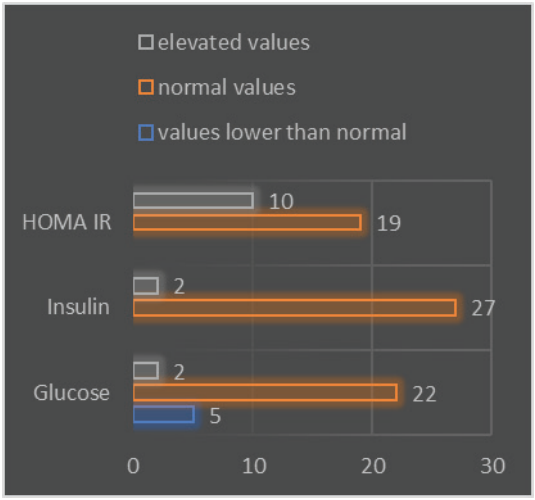

Figure 6. Glucose, insulin and HOMA IR

The values of the bioactive GLP-1 ranged from 0.01 pmol/l to 8.74 pmol/l with mean value of 1.92 pmol/l. In obesity, of GLP-1 on average, of 1.62 pmol/l, and in people with normal BMI of 2.69 pmol/l.

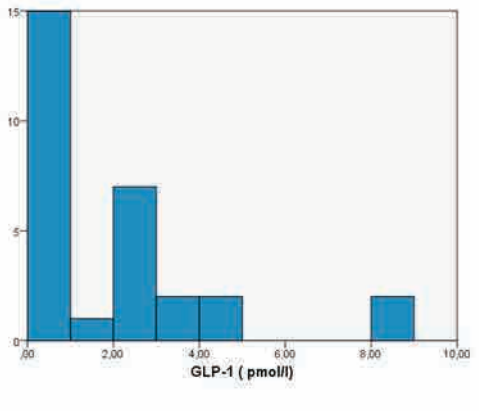

Figure 7. Distribution of GLP-1 concentrations

According to Bayes factor (4.589) there is the moderate correlation between HOMA IR, and GLP-1. The correlation between these two parameters is negative, the Pearson coefficient (r = -0.177), which means that the increase of HOMA IR values results in a decrease of GLP-1 and vice versa. Although it must be noted that there are individual differences in the secretion of the incretin.

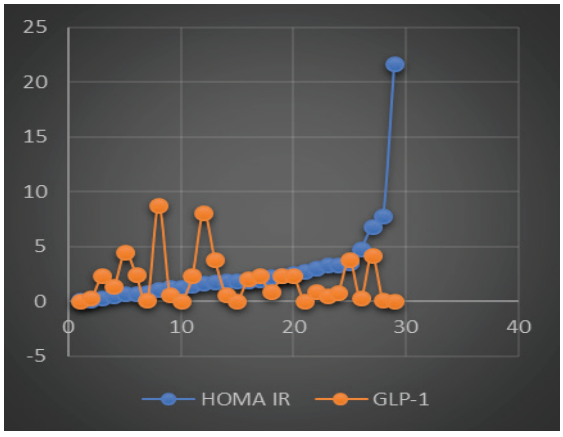

Figure 8 Interrelation HOMA IR and GLP-1

Bayes factor (5.732) indicates the existence of the moderate correlation between BMI and HOMA IR, which is the Pearson coefficient (r = 0.121) positive, suggesting

that increase in BMI increases HOMA IR and therefore the elevate possibility of insulin resistance.

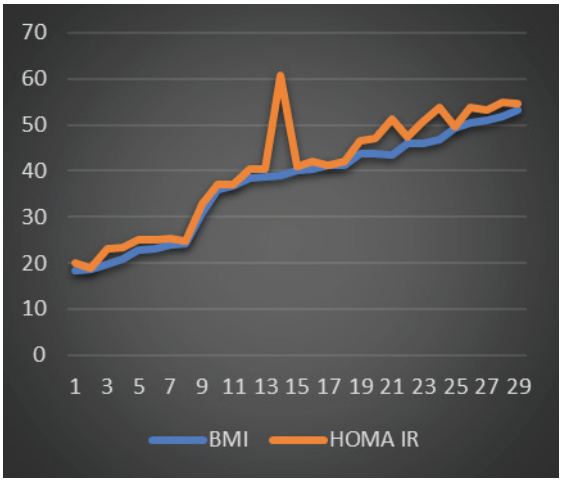

Figure 9. Interrelation between BMI and HOMA IR

Discussion

After oral glucose intake, insulin secretion depends on the secretion and effect of incterin hormones. Many authors have shown that the levels of GIP and GLP-1 may vary significantly between different prediabetic phenotypes, and the results should be interpreted with caution. When assessing secretion of insulin, it is also important to assess insulin resistance to obtain an accurate estimate of beta cell dysfunction.

In patients with severe type 2 diabetes, we observe an increased, normal and reduced secretion of GLP-1. Although these results could be explained by a number of different factors (eg. variations in the tests, the duration of diabetes, ethnicity), there is a possibility that the incretin hormone secretion differs from different diabetic phenotypes of type 2 DM which are generated from various prediabetic state.

In this study it is shown that insulin secretion in prediabetes is almost normal, some authors explain this with the increased secretion of the hormone GLP-1. Some of the studies suggested that the disorder of secretion of GLP-1 in type 2 diabetes is just a secondary phenomenon. It is believed that a compensatory mechanism for the reduction of glucose reduces the secretion of insulin, inducing hypersecretion of GLP-1 and that it can be formed at the earliest stages of glucose homeostasis disorders , but this compensation can again be lost when postprandial glucose levels are increased.

Work on clarifying mechanisms that are basically the relationship between obesity and insulin resistance in humans continues to support the concept that visceral obesity, but not subcutaneous, results in insulin resistance and an increased risk of DM type 2.Storing excess fat in the subcutaneous warehouses reduces the risk of resistance insulin and type 2 DM, possibly by preventing the accumulation of fat in the visceral adipose tissue, liver and skeletal muscles.

This study has shown that the higher values of BMI is associated with a higher value of Homeostatic Model Assessment for Insulin Resistance (HOMA IR). In the longer study, BMI had an independent positive association with HOMA IR. Some authors had shown that BMI has an independent positive associations with indications of insulin resistance and an inverse association with the function of beta cells adapted for insulin resistance in patients with new diabetes type 2.

The levels of total GLP-1, according to some studies, were significantly lower in subjects with IFG + IGT and NIDDM, followed with more severe stage of glucose metabolism disorders. Reduced total concentration of GLP-1 and its response to glucose may indicate that the GLP-1 defects already present in patients with prediabetes, particularly those with IFG + IGT. But its specific role in the process of type 2 diabetes is not yet known. However, several scientists pointed out that levels of GLP-1 have not been reduced in patients with IGT or type 2 diabetes. Although the cause and mechanism for this discrepancy are not clear, there is a possibility that this claim depends on the category of prediabetes.

Most studies have been done on small samples, like this, but those studies who were done on large samples have the same conclusions, ie. releasing of total GLP-1 is reduced in subjects with IFG, IGT or IFG + IGT. Many types of drugs that reduces glucose have a positive effect on the release of GLP-1, such as metformin, thiazolidinedione and insulin etc. Some authors came to the conclusion that overall levels of GLP-1 (at each time point) is correlated with the function of the beta cells, the degree of insulin resistance and insulin secretion. Other studies suggest that of GLP-1 secretion may be bonded to IR or its risk factors. Antisecretory GLP-1 can cause dysfunction of beta cells, reduce deterioration of the IR and insulin secretion. This could represent a vicious circle that can steadily deteriorate disorder of glucose metabolism. Some authors point out that there is no detectable relationship between the levels of GLP-1 and age, BMI or waist circumference, while some authors found a correlation between these parameters. The same authors provide a potential explanation for this differences, which is that the general characteristics of their patients had not achieved sufficient scope to influence the secretion of GLP-1, and that the choice of different statistical methods can lead to differences (18–21)hepatic and peripheral insulin action, and glucagon and incretin hormone secretion in individuals with i-IFG (n = 18.

HOMA model has proven to be a robust clinical and epidemiologic tool in description and pathophysiology of diabetes, it has become a standard tool of clinical

Endocrinology. Calculating HOMA index is a sensitive method that allows estimation of beta cell function, insulin sensitivity, and glucose intolerance condition provides useful information about the potential progression of glucose intolerance to diabetes type 2 diabetes.

In recent years, the field of biotechnology of incretin significantly developed. GIP, often seen as neglected twin GLP-1, are now actively developing as a potential new drug for the treatment of diabetes, in combination with GLP-1. GLP-1R agonist and the DPP-4 inhibitors have shown a good results in clinical practice for the treatment of type 2 diabetes (1,18,19,22)hepatic and peripheral insulin action, and glucagon and incretin hormone secretion in individuals with i-IFG (n = 18.

To carry out statistically safer and more significant conclusions we need new studies on the role of incretin in the diagnosis of abnormal glucose regulation and diabetes therapy with larger samples.

Conclusion

This study, and research of many other authors, show that in individuals with insulin resistance can lead to suppressing secretion of glucagon-like peptide 1. As described herein, suppression of secretion of GLP-1 is detached and will not occur in all individuals with impaired glucose metabolism. The reason for this can be categorized prediabetes, as explained in the discussion.

The correlation between the concentration GLP-1 and HOMA IR is negative, as indicated by the fact that in individuals with insulin resistance are decreased secretion of incretin hormones.

During the study we found correlation between values of BMI and HOMA IR, which indicates that excess body fat mass, and increased body weight, may lead to the occurrence of insulin resistance and consequently to the appearance of diabetes type 2 diabetes.

Abbreviations

BMI - Body Mass Index
DM - Diabetes Mellitus
DPP4 - dipeptidyl peptidase-4
GIP - gastric inhibitory polypeptide / glucose-dependent insulinotropic peptide
GIPR - receptors for glucose-dependent insulinotropic peptide
GLP-1 - glucagon-like peptide 1
GLP-1 R- receptors for glucagon- like peptide 1
GLP-2 - glucagon-like peptide 2

GLUT-1 - glucose transporter 1
GLUT-2 - glucose transporter 2
HOMA IR - homeostatic model assessment function β cells of the pancreas and insulin resistance
IDDM - insulin dependent diabetes mellitus
IFG – Impaired Fasting Glucose
IGT - Impaired Glucose Tolerance
IR - Insulin resistance
NEP 24.11 - Neutral endopeptidase 24.11
NIDDM -non-insulin-dependent diabetes mellitus

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