Serum Levels of Incretin Hormones – GLP-1 and GIP in Patients with Type 1 Diabetes Mellitus

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Background:
The glucagon-like peptide-1 (GLP-1) and the glucose-dependent insulinotropic peptide (GIP) are natural incretin hormones, which are secreted respectively by the L- and K-cells of the intestinal mucosa in response to the physiological gastrointestinal glucose absorption. In patients with type 2 diabetes mellitus, the incretin effect is reduced, whereas the results in type 1 diabetes mellitus (T1DM) are heterogeneous, in some patients normal incretin response is observed.

Aim:
Comparative analysis of the basal serum levels of the incretin hormones GLP-1 and GIP in patients with type 1 DM and in individuals without carbohydrate disorders.

Materials and methods:
The study included 27 patients with diagnosed T1DM and a control group of 39 individuals without carbohydrate disorders. All participants in the study were subjected to the following clinical measurements and laboratory tests – height, weight, bioimpedance analysis of body composition, fasting blood sugar (BS 0’), postprandial blood sugar (PPBS), glycated haemoglobin (HbA1c) in T1DM patients, total cholesterol (TC), HDL cholesterol (HDL chol), triglycerides (TG), transaminase (AST and ALT), basal serum levels of GLP-1 and GIP.

Results:
The serum levels of GIP in the patients with type T1DM were significantly higher, compared to the individuals without carbohydrate disorders (P<0.05), while there was no statistically significant difference in the GLP-1 levels.

Conclusion:
The significantly higher GIP levels and the similar GLP-1 levels in our patients with type 1 DM, compared to the individuals without carbohydrate disorders, support the hypothesis of intact incretin effect in this type of diabetes mellitus

Key words: Glucagon-like peptide-1, Glucose-dependent insulinotropic peptide, Type 1 diabetes mellitus.

BACKGROUND
Glucagon-like Peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are incretin hormones, secreted by the intestinal tract during meals. GLP-1 and GIP are considered to be biologically active substances that contribute to the glucose-dependent secretion of insulin, and when acting together they have been demonstrated to fully account for the incretin effect.¹⁻³ The incretin effect itself is defined as a phenomenon whereby orally ingested glucose elicits a much greater insulin response than that obtained when glucose is infused intravenously in order to give identical blood glucose levels (the so-called isoglycemic glucose infusion).

Endogenous GLP-1 is a gastrointestinal hormone secreted from the L cells of the distal part of the small intestine. It is derived from a large proglucagon (i.e., glucagon precursor) that also encodes for glucagon. Endogenous GIP is a 42-chain amino acid peptide secreted by the lymphocyte K cells, which are located within the intestinal epithelium of the proximal duodenum and are regulated predominantly by fat consumption.² Receptors for GLP-1 and GIP can be found in a number of organs, including brain, duodenum, kidneys, liver, lungs, pancreas and stomach. The effect of these hormones is considered to be mediated by a G-protein-coupled adenylate cyclase, whose action results in an increase of cyclic adenosine monophosphate and a stimulation of the enzyme protein kinase A.¹,²
It is known that both GLP-1 and GIP are subjected to a rapid inactivation by the enzymes dipeptidyl peptidases-IV (DPP-IV). These peptidases are ubiquitous serine proteases that are widely distributed in a variety of human tissues. By cleaving N-terminal amino acids, they cause inactivation of GLP-1 and GIP - the substrate 'preferences' of DPP-IV. The effect of DPP-IV is associated with more than 50% inactivation of GLP-1 within 1 to 2 minutes, and more than 50% inactivation of GIP within 7 minutes.

The incretin hormones are characterized by a lot of physiological effects, including: an induction of the glucose-dependent secretion of insulin and a suppression of the glucagon secretion, respectively; a delay of the gastric emptying; a suppression of the glucose production in the liver; a stimulation of the beta-cells replication and neogenesis, an inhibition of the beta-cells apoptosis. It is thought that incretin effect determines about 50–70% of the postprandial insulin response. There is evidence that incretins' action is disturbed in type 2 diabetes mellitus (T2DM) – a condition which is associated with a combination of decreased GLP-1 levels and a reduced response towards both incretins – GLP-1 and GIP.

However, there is insufficient scientific information about the levels of the incretin hormones and the incretin effect in type 1 diabetes mellitus (T1DM). It is suggested that the remission phase of T1DM is associated with a significant restoration of the function of the residual β-cell apparatus leading to a noticeable improvement of the endogenous insulin response during meals in the early months after the diagnosis of the disease. Nevertheless, this process is accompanied by a mild or a lack of improvement in the insulin response towards parenteral glucose administration, which suggests that the function of the incretin hormones – GLP-1 and GIP, could be important for the regulation of the blood glucose during this phase of T1DM.

The objective of the present study was to compare the basal serum levels of the incretin hormones GLP-1 and GIP between patients with type 1 diabetes mellitus (T1DM) and individuals without carbohydrate disorders.

MATERIALS AND METHODS

This study was conducted in the Clinic of Endocrinology and Metabolic Diseases of St George University Hospital, Plovdiv as part of Project No R-2287 “Incretin effect in diabetes mellitus”, funded by the Medical University – Plovdiv, Scientific contest “Start of doctoral programmes”.

The study included 27 patients (16 women and 11 men) with diagnosed type 1 diabetes mellitus (T1DM) and a control group of 39 individuals (19 men and 20 women) without carbohydrate disorders. None of the T1DM patients was observed to achieve a spontaneous complete remission of the disease during the period of the investigation. All the participants were subjected to the following clinical measurements and laboratory tests – height, weight, bioimpedance analysis of body composition, fasting glucose, postprandial glucose, total cholesterol (TChol), HDL-cholesterol (HDL-chol), triglycerides (TG), transaminases (AST and ALT), basal serum levels of GLP-1 and GIP. Glycated haemoglobin (HbA1c) was measured in the group of T1DM patients. We calculated body mass index (BMI) = weight (kg) / height (m)^2 and LDL-cholesterol (LDL-chol), using the Friedewald formula: LDL-chol = TChol – (HDL-chol + TG/2.2). The carbohydrate tolerance of the control patients was determined by an oral glucose tolerance test measuring the levels of blood glucose and immunoreactive insulin at 0, 60 and 120 minute after oral intake of 75 g glucose.

The venous blood samples for laboratory tests were taken in standard conditions – early in the morning, after a 12-hour period of night fasting. All participants entered the study after signing an informed consent. The laboratory tests were performed in the Central Clinical Laboratory of St George University Hospital, Plovdiv. The serum levels of blood glucose were measured using a standard GOD-POD method. The concentrations of TChol were determined using ChOD-PAP; the TG concentrations with GPO, PAP, and the HDL-cholesterol with MgSO₄–dextran SO₄ precipitation (Schneiders Analysers; Netherlands test; Delta Kone Autoanalyser). A solid-phase sandwich immunoenzyme assay ELISA using 2 kinds of highly specific antibodies was performed. Serum GIP and GLP-1 concentrations were measured with Human GIP Elisa (Active form Assay Kit – IBL-Japan) and Human GLP-1 Elisa (Inactive form Assay Kit – IBL-Japan). The transaminases were analysed with chemical analyser Konelab 60i, Thermo Electron Corporation (Finland). The HbA1c concentrations were determined with immune-inhibition test.

In this study, the Bioimpedance Analysis (BIA) was performed with body composition analyser Tanita BC-420, which measures the following indexes: total body fat (%), fat-free mass FFM (kg),...
muscle mass (kg), bone mass (kg), basal metabolic rate (basal metabolism), approximate visceral fat, metabolic age. We used referent values for % body fat recommended by the licensed software for Tanita – Health Monitor, version 2.7.0.

The statistical analysis of the results was performed with SPSS, version 21.0 for Windows. A comparative analysis of the clinical, anthropometric and biochemical characteristics of the studied groups was performed using independent samples t-test. The results were shown as arithmetic mean ± standard deviation. Level of significance p<0.05 was chosen for all comparisons. Logarithmic transformation of the serum levels of GLP-1 and GIP was done due to their deviation from normal distribution, established with Kolmogorov-Smirnov test (K-S). Pearson correlation coefficient (r) for assessing correlations among the parameters was used.

RESULTS

The clinical, anthropometric and bioimpedance characteristics of the studied groups are shown in Table 1.

We determined mean values of HbA1c = 9.20±2.10% in the T1DM patients. There was no significant difference in the levels of TChol, HDL-chol, LDL-chol, TG, AST and ALT between the two investigated groups (Table 2). The serum levels of GIP were significantly higher in the patients with T1DM, compared to those in the individuals from the control group (p<0.05). No statistically significant difference in the GLP-1 levels between the patients with T1DM and the individuals without carbohydrate disorders was observed (Table 2).

Although the anthropometric characteristics (height, weight and BMI) were determined to be significantly higher in the male T1DM patients as compared to those in the female T1DM individuals (p<0.001), no significant difference in the serum levels of LogGLP-1 (0.93±0.31 vs. 1.13±0.37 pmol/l) and LogGIP (1.42±0.41 vs. 1.34±0.38 pmol/l) between the male and the female T1DM patients was found (p>0.05). As far as the male and female subjects without carbohydrate disorders were concerned, we established comparable values of height (1.73±0.07 vs. 1.66±0.04 m), weight (86.00±15.92 vs. 70.45±12.61 kg), BMI (29.45±6.26 vs. 25.66±5.87 kg/m²); LogGLP-1 (0.93±0.15 vs. 0.95±0.29 pmol/l) and LogGIP (1.11±0.25 vs. 1.18±0.40 pmol/l), (p>0.05).

No correlations between LogGLP-1 concentrations and the other investigated parameters were determined in the group of T1DM patients. Interestingly, LogGIP showed a positive correlation with HbA1c values (r=0.592, p=0.001).

DISCUSSION

The growing interest of incretin hormones’ effect in patients with type 1 diabetes mellitus has been originated from the results of a number of studies with experimental animals, which suggest that referent or relatively high levels of GLP-1 and GIP in T1DM might be a sign of β-cell preservation or improvement, resulting in a major increase of residual insulin secretion. The data of the present study shows significantly higher levels of GIP in the patients with T1DM, compared to those in the individuals without carbohydrate disorders. However, there is no significant difference in the GLP-1 levels between the two studied groups.

GLP-1 and GIP have the ability to protect the beta-cells from apoptosis, and to extend their lifespan. The inhibition of the apoptosis of the human islet cells by the GLP-1 and exendin-4 is associated, on the one hand with the process of down-regulation of Caspase-3 at mRNA level of the active protein, and on the other hand, with the up-regulation of the anti-apoptotic Bcl 2 protein.

Studies with experimental animals have shown that GLP-1 increases the beta-cell mass in a different way than the anti-apoptotic mechanism, namely through stimulation of the islet-cell neogenesis from the precursor cells. GLP-1 and exendin-4 induce the cellular proliferation of insulin-expressing cells, which is registered with the incorporation of marked thymidine or bromodeoxyuridine in vivo in mice.
Various authors discuss and hypothesize the use of GLP-1 in patients with onset of type 1 diabetes mellitus, for regeneration and decrease of the beta-cell apoptosis and improvement of the residual insulin secretion.

There is evidence suggesting that the human beta-cells can also potentially react to incretin agents. In the first place, the regeneration of the human islet cells continues long after the onset of T1DM, which suggests that even when the beta-cell mass is almost completely depleted, the human pancreas still responds to therapies that increase the beta-cell mass. This concept is supported by recent observations of increasing concentration of C-peptide in pregnant women with a long history of T1DM, a known beta-cell trophic stimulus.

### Table 1. Age, anthropometric and bioimpedance characteristics of the studied groups by gender

| Characteristics       | Without carbohydrate disorders | With T1DM |
|-----------------------|---------------------------------|-----------|
|                       | Male   | Female | Total | Male | Female | Total |
| n                     | 19     | 20     | 39    | 11   | 16     | 27    |
| Age (years)           | 39±13  | 35±13  | 35±13 | 37±9 | 32±11  | 34±10 |
| Height (m)            | 1.71±0.07 | 1.69±0.04 | 1.67±0.07 | 1.79±0.06 | 1.62±0.05 | 1.68±0.10 |
| Weight (kg)           | 86.00±15.92 | 78.45±12.61 | 73.29±24.24 | 82.40±11.16 | 54.47±7.38 | 64.18±16.10 |
| BMI (kg/m²)           | 29.45±6.26 | 25.66±5.87 | 26.37±8.89 | 25.72±3.00 | 20.84±2.92 | 22.54±3.73 |
| Fat (%)               | 23.90±9.80 | 33.22±11.05 | 31.45±11.24 | 20.11±5.89 | 22.98±8.93 | 21.71±7.66 |
| Visceral fat (level)  | 12.25±10.08 | 5.71±5.44 | 6.95±6.77 | 6.38±3.7 | 2.00±1.89 | 3.94±3.54 |
| FFM (kg)              | 70.60±28.92 | 45.50±6.95 | 50.28±16.31 | 65.54±7.62 | 41.93±2.71 | 52.42±13.17 |
| Muscle mass (%)       | 72.28±9.24 | 63.37±10.47 | 65.07±10.64 | 75.94±5.58 | 73.07±8.49 | 74.34±7.29 |
| Bone mass (kg)        | 3.48±1.34 | 2.31±0.33 | 2.53±0.76 | 3.26±0.37 | 2.15±0.14 | 2.64±0.62 |
| Metabolic age (years) | 40.00±22.11 | 36.88±20.91 | 37.48±20.61 | 34.38±16.69 | 20.90±9.31 | 26.89±15.16 |

### Table 2. Lipid parameters and incretin hormones

| Parameters         | Without carbohydrate disorders | With type 1 diabetes mellitus |
|--------------------|---------------------------------|-------------------------------|
|                    | (n=39)                          | (n=27)                        |
| Total cholesterol (mmol/l) | 5.09±1.09                      | 5.13±1.56                     |
| HDL-cholesterol (mmol/l)     | 1.49±0.30                      | 1.44±0.49                     |
| LDL-cholesterol (mmol/l)     | 3.13±0.94                      | 2.95±1.18                     |
| Triglycerides (mmol/l)       | 1.05±0.59                      | 1.63±1.69                     |
| LogGLP-1              | 0.95±0.28                      | 1.05±0.36                     |
| LogGIP                | 1.17±0.38                      | 1.37±0.39^a                   |

^a p<0.05, ^aa p<0.01, ^aaa p<0.001
Second, exenatide improves the function of transplanted islet cells in patients with T1DM. Third, in metformin-treated type 2 diabetic patients, those who take also exenatide have 2.4 times higher beta-cell function over one year, compared to those who receive insulin.

There are a growing number of reports on the therapeutic use of GLP-1 analogues in T1DM as an addition to the insulin therapy. A pilot study of exenatide and anti-CD25 monoclonal antibodies in patients with long history of T1DM has shown that these have no effect on the residual beta-cell function. The negative results of this study suggest that in T1DM, the recovery of the beta-cell function in long-standing patients could be difficult, since in autopsy studies the residual beta-cell mass is calculated to be about 10% in T1DM with more recent onset, and about 1% in long-standing T1DM. Therefore, the perfect window to use incretin-based agents is probably before or immediately after the diagnosis, when significant beta-cell mass is still viable.

Similar to our data concerning GLP-1 and GIP levels in patients with T1DM is that presented by Huml et al. They conducted a study which aimed to evaluate plasma levels of gut hormones (amylin, GLP-1, GIP, ghrelin, leptin, pancreatic polypeptide, and polypeptide YY) in children with T1DM in comparison with healthy controls and to correlate plasma concentrations of gut hormones with different metabolic and anthropometric parameters. GIP levels were found to be higher (p<0.05) in the T1DM patients compared to those in the healthy controls. Plasma levels of GLP-1 did not differ statistically between the studied groups. It was found that plasma levels of the studied hormones correlated positively with HbA1c, BMI, actual glycemia, serum concentration of TChol, HDL-chol, LDL-chol, and TG, dosage of insulin per kilo (IU/D), age, sex, age at time of diagnosis, and years of T1DM duration. Furthermore, the investigators determined a positive correlation between GIP and GLP-1 (r=0.4903; p<0.05).

There are studies which describe the presence of normal circulating levels of GIP in newly diagnosed T1DM young adults. Controversially, we and Huml et al. found significantly elevated GIP levels in patients with T1DM. These results might be partially explained by the influence of the following factor – the duration of the diabetes in the studied subjects. Our T1DM patients were definitely not newly diagnosed whereas the two aforementioned studies examined newly diagnosed cohorts. It is well known that once insulin treatment is initiated, most likely the β-cell function improves for a certain period of time. It could be suggested that the elevated GIP levels may occur as a compensatory mechanism for the low number of β-cells along with either chronic desensitization of GIP receptors or a reduction in the expression of GIP receptors on pancreatic β-cells. Furthermore, we found a positive correlation between GIP and HbA1c values in the T1DM patients. However, the mechanism by which glucose control influences GIP (or GIP influences glucose control) is not fully understood. Therefore, further investigation is needed to reveal the precise pathophysiological mechanisms by which GLP-1 and GIP might influence the carbohydrate metabolism.

T. Vilsboll et al. investigated the levels of GLP-1 and GIP as well as the relationship between the incretin concentrations and the size of the meal in obese type-1 and type-2 diabetic patients. The plasma levels of the incretin hormones were measured during two meal tests (260 kcal and 520 kcal) in 8 type 1 diabetic patients, 8 lean healthy individuals, 8 obese type 2 diabetic patient and 8 obese healthy individuals. The early total GLP-1 responses (intact peptide plus primary metabolite) were identical in the four groups during the two meal tests, while the late responses were significantly higher when the size of the meal was bigger, compared to the small size meal. In type-1 diabetes patients there was a normal reaction of the total and intact GLP-1, compared to that of the healthy subjects with similar body weight. The early GIP responses were significantly higher in the type-1 diabetic patients and in the lean healthy subjects during large meals – a fact that proved the presence of an intact incretin effect. As a conclusion, the data is consistent with our results in respect to the basal incretin secretion in type-1 diabetic patients.

CJ Greenbaum et al. studied a special group of patients with T1DM, presented with normal fasting glycaemia and postprandial hyperglycaemia. All the participants were subjected to an oral glucose tolerance test and an insulin-modified intravenous glucose tolerance test evaluating the incretin effect. There were no differences in the fasting and postprandial GIP and GLP-1 levels between the control group and the T1DM group, which, again, is consistent with our data. In both groups the insulin secretion was significantly higher during oral intake of glucose, compared to that during the intravenous glucose administration. However, the incretin effect...
represented significantly higher percentage of the postprandial insulin secretion in the control group, compared to the T1DM group. The decrease of the incretin effect in the T1DM group was most evident on the 60th minute after the glucose intake – in half, compared to the response in the control group.27 This experimental arrangement shows complex and ambiguous impairments of the incretin effect in patients with type 1 diabetes, whose evaluation depends on the direction and the design of the performed studies. We can point out several limitations of our study, namely: a relatively small cohort of participants; a presence of intergroup differences in the values of weight, body fat percentage and metabolic age; an assessment of only the fasting levels of GLP-1 and GIP. Therefore, we think that further investigations for more precise evaluation of incretin hormones’ metabolic role in patients with type 1 diabetes mellitus are needed.

CONCLUSIONS
In our study the significantly higher GIP levels in the patients with T1DM and the similar GLP-1 concentrations between the two groups of subjects support the hypothesis of an existing intact incretin effect in type 1 diabetes mellitus. The data supposes a novel favourable incretin-based therapy combined with insulin application in T1DM patients in order to achieve a better glycemic control. Our results confirm the necessity of a more precise evaluation of the ‘incretin effect’ in T1DM requiring a wider range of analyses and additional specific tests including measuring the postprandial GIP and GLP-1 levels.

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Сывороточные уровни гормонов инкретина - GLP-1 и GIP у пациентов с сахарным диабетом 1 типа

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Ключевые слова: glucagon-like peptide-1, glucose-dependent insulinotropic peptide, type 1 diabetes mellitus

Введение: Глюкагоноподобный пептид-1 (GLP-1) и глюкозозависимый инсулинотропный полипептид (GIP) представляют собой природные инкретино- гормоны, которые секретируются соответственно L- и K-клетками слизистой оболочки кишечника в ответ на физиологическое желудочно-кишечное всасывание глюкозы. У пациентов с сахарным диабетом 2 типа, инкретиновый эффект редуцируется, а результаты при сахарном диабете 1 типа (СДТ 1) являются разнородными - у некоторых пациентов установлен нормальный инкретиновый ответ.

Цель: Сравнение базальных уровней сыворотки инкретиновых гормонов GLP-1 и GIP у пациентов с диабетом 1 типа и субъектов без нарушений углеводного обмена.

Материалы и методы: В исследование были включены 27 пациентов с диагностированным СДТ 1 и контрольная группа из 39 лиц без нарушений углеводного обмена. Все участники исследования прошли следующие клинические измерения и лабораторные исследования - рост, вес, биоимпедансный анализ состава тела, глюкоза крови натощак (BS 0’), уровень сахара в крови после еды (PPBS), гликозилированный гемоглобин (HbA1c) у больных с СДТ 1, общий холестерин (TC), HDL холестерин (HDL хол.), триглицериды (TG), трансаминасы (AST и ALT), базальные сывороточные уровни GLP-1 и GIP.

Результаты: Сывороточные уровни ГП у пациентов с СДТ 1 были относительно выше у пациентов с сахарным диабетом 1-го типа по сравнению с лицами без нарушений углеводного обмена (P <0,05), но не имели статистически значимые различия в уровнях GLP-1.
Выводы: Значительно более высокие уровни GIP и близкие уровни GLP-1 у наших пациентов с сахарным диабетом 1-го типа по сравнению с субъектами без нарушений углеводного обмена подтверждают гипотезу интактного инкретинового эффекта при этом типе сахарного диабета.