Changes in prostaglandin levels in the blood serum of patients with gastroesophageal reflux disease on the background of type 2 diabetes mellitus

Abstract. Background. Digestive organ damage in patients with diabetes mellitus (DM) is based on several mechanisms: autonomic nervous system dysfunction, angiopathy, dysregulation of secretion and inactivation of hormones and increments. The purpose was to study the features of changes in prostaglandin (Pg) levels (I₂ and F₂α) in the blood serum of patients with gastroesophageal reflux disease (GERD) on the background of type 2 DM depending on the body mass index violation. Materials and methods. The study involved 54 patients with type 2 DM and GERD (group I). The comparison group included 22 patients with GERD (group II). The patients had their blood serum examined and indicators of Pg F₂α and 6-keto-prostaglandin F₁α (blood prostacyclin — Pg I₂) determined. Results. Increased levels of prostaglandins in both groups of patients were detected, but more significant changes were observed in group I. Attention is called to a more significant increase in Pg I₂ concentration compared with Pg F₂α, especially in patients with GERD on the background of type 2 DM (3.4 times compared with 2.1 times in group I). Patients with GERD revealed the increased levels of Pg I₂ by 2.2 times, while Pg F₂α is only 1.6 times higher. In the combination of several pathological states (type 2 DM, GERD, increased body mass index), there is a more significant increase in the concentration of prostacyclin, which also depends on the duration of the disease. Conclusions. In patients with GERD, an increase in the levels of prostaglandins F₂α and I₂ in the blood serum has been detected. The combination of GERD and type 2 DM is accompanied by a more significant increase in the concentration of prostaglandins, especially Pg I₂, in the blood serum. The correlation was established between the duration of type 2 DM mellitus, excessive body weight and the dynamics of Pg I₂ level in the blood serum of patients with GERD on the background of type 2 diabetes mellitus.

Keywords: gastroesophageal reflux disease; type 2 diabetes mellitus; prostaglandins

Introduction

Gastroesophageal reflux disease (GERD) is a topical problem of modern gastroenterology due to its high prevalence, the development of severe complications, the need for long-term therapy, and a significant deterioration in the quality of life of patients [1–3].

As it is known, the etiopathogenesis of GERD is based on the imbalance between the protective (barrier function of the lower esophageal sphincter, effective esophageal clearance, normal resistance of the esophageal mucosa) and aggressive factors (hydrochloric acid, pepsin, bile, pancreatic enzymes, etc.) [4, 5]. The emergence of pathological gastroesophageal reflux is also promoted by an increase in the intraabdominal (obesity, pregnancy) and intragastric pressure (gastric stasis, duodenostasis of functional or organic nature) [1].

In clinical practice, 75% of patients with diabetes mellitus (DM) have symptoms of damage to the gastrointestinal tract, with almost all sections of the digestive tract being affected [6].

Digestive organ damage in patients with DM is based on several mechanisms: autonomic nervous system dysfunction, dysregulation of secretion and inactivation of hormones and increments, as well as electrolyte disorders associated with
uremia and ketoacidosis [7]. Many hormones and biologically active substances in the body (estrogen, progesterone, prostaglandins, somatostatin, cholecystokinin, etc.) affect the tension of the lower esophageal sphincter [8].

Consequently, in diabetes mellitus, the changes in regulatory substances due to metabolic disorders combined with the changes in the neurotropic control of the lower esophageal sphincter on the background of diabetic autonomic neuropathy creates conditions for the contact of aggressive contents in the stomach and duodenum with esophageal mucosa and leads to the emergence of clinical manifestations of GERD. Studying the features of changes in regulatory biologically active substances in patients with type 2 DM can reveal new pathogenetic mechanisms for the formation of organ damage in the digestive system, including the esophagus, in these persons.

**Purpose** of the research was to study the features of changes in serum prostaglandin (I\(_2\) and F\(_2\alpha\)) levels in patients with GERD on the background of type 2 diabetes mellitus depending on the body mass index violation.

Scientific research is a fragment of a state-funded topic of the department of surgical diseases and the department of propaedeutics of internal diseases of the medical faculty of the SHEI “UzhNU” No. 815 “Mechanisms of complications formation in liver and pancreatic diseases, methods of their treatment and preventive measures”, state registration number: 0115U001103.

**Materials and methods**

At the premises of the department of propaedeutics of internal diseases (gastroenterological and endocrinological departments of A. Novak Transcarpathian Regional Clinical Hospital) of the medical faculty of the SHEI “UzhNU” No. 815 “Mechanisms of complications formation in liver and pancreatic diseases, methods of their treatment and preventive measures”, state registration number: 0115U001103.

The comparison group consisted of 22 patients with GERD (group II) — 12 males (54.5%) and 10 females (45.5%). Their average age was (48.3 ± 5.7) years. The control group included 20 apparently healthy individuals (12 males (60.0%), 8 females (40.0%)), their average age was (47.6 ± 5.8) years.

All studies were conducted with patient’s consent, and the methodology of conducting the study complied with the Declaration of Helsinki and its 2013 revision [9, 10].

Patients underwent general clinical examination according to local protocols. Anthropometric, general clinical, laboratory and instrumental methods of investigation were used. In the verification of the diagnosis, attention was paid to the nature of the complaints, anamnesis of the disease.

During the anthropometric examination, the body mass index (BMI), waist circumference (WC), hip circumference (HC) were measured, and the waist/hip index (WHI = WC/HC) was calculated. According to the obtained data, in compliance to World Health Organization recommendations, patients were distributed by their BMI: BMI 16.0 and less corresponded to the expressed deficient body weight; 16.0–18.5 — insufficient body weight; 18.5–24.9 — normal weight; 25.0–29.9 — excessive weight; 30.0–34.9 — class I obesity; 35.0–39.9 — class II obesity; 40.0 and more — class III obesity (morbid obesity) [11].

The diagnosis of type 2 DM has been made according to the International Diabetes Federation (2005) guidelines and to the criteria of the unified clinical protocol (Ministry of Health order No. 1118 issued 21.12.2012) [12, 13]. The severity of type 2 DM has been evaluated according to the level of glycated hemoglobin (%), which was determined by a chromogenic assay on the Sysmex 560 analyzer (Japan) using Siemens reagents. The patients also had electrocardiographic examination.

GERD was diagnosed according to the criteria of the unified clinical protocol (Ministry of Health order No. 943 issued 31.10.2013) taking into account patients’ complaints, endoscopic examination data, etc. [14]. In order to prove the diagnosis, the patients underwent esophagogastroduodenoscopy conducted with the help of endoscopic equipment — Pentax EPM-3300 video processor and Pentax E-2430 elastic fiberscopes GIF-K20. The patients also had daily pH-monitoring (according to prof. V.N. Chernobrovyov).

All patients had their serum 8-iso-prostaglandin F\(_{2\alpha}\) (Pg F\(_{2\alpha}\)) and 6-keto-prostaglandin F\(_{1\alpha}\) (blood prostacyclin — Pg I\(_\alpha\)) levels examined using immunoassay analysis with the help of Enzo Life Sciences test systems (USA).

The criteria for patients’ inclusion into the study were: type 2 diabetes mellitus, erosive form of GERD.

The criteria for patients’ exclusion from the study: type 1 diabetes mellitus, functional or organic diseases of the esophagus, stomach and duodenum, non-erosive form of GERD.

Results of the patients’ examination were analyzed and processed by means of computer program Statistica 10.0 (StatSoft Inc., USA) using parametric and non-parametric methods.

**Results**

In all patients in group I (GERD and type 2 DM), an excessive body weight or obesity of varying degrees were found while analyzing anthropometric measurements. The vast majority of patients (54.5%) in group II (GERD) had normal body weight, and only 36.4% — excessive body weight (Table 1).

The determination of prostaglandin F\(_{2\alpha}\) and prostacyclin (Pg I\(_\alpha\)) serum levels in patients of both groups and healthy individuals was performed. The results are presented in Table 2.

Increased levels of prostaglandins were detected in both groups of the examined patients, but more significant changes were observed in group I (combination of type 2 DM and GERD). Attention is called to a more significant increase in Pg I\(_\alpha\) concentration compared to Pg F\(_{2\alpha}\) in the blood serum, especially in patients with GERD on the background of type 2 DM (3.4 times vs 2.1 times in group I).

Levels of Pg I\(_\alpha\) in patients with GERD were increased by 2.2 times, while Pg F\(_{2\alpha}\) is only 1.6 times higher.
Changes in prostaglandin levels in the examined patients were evaluated depending on the violation of BMI (Table 3).

A more significant increase of \( P_g I_2 \) was found in the blood serum of patients with GERD on the background of type 2 DM and excessive body weight, as compared to the patients of the same group with class I and II obesity. While assessing the changes in serum \( P_g F_{2\alpha} \) in patients of group I, the same tendency was not established. In patients with GERD, the lowest concentration of \( P_g I_2 \) in the blood serum was detected in those with normal body weight, and in persons with excessive weight and class I obesity, there was no significant difference between these indices.

According to the results of the analysis of anamnestic data, as well as the data of preliminary medical documentation (extracts from the clinical record, records in outpatient cards), the duration of the disease in the examined patients was evaluated (Table 4).

In patients with obesity, the clinical signs of GERD are detected almost simultaneously with the diagnosis of type 2 DM. In patients of the same group with excessive body weight, GERD is diagnosed only 5–5.5 years after the diagnosis of type 2 DM.

**Discussion**

Digestive organ damage in case of type 2 DM, including the upper gastrointestinal tract, is actively discussed in the professional literature. Scientific research is aimed at determining the prevalence of GERD in patients with type 2 DM, as well as studying various factors underlying the formation of GERD in these patients. H. Sun et al. (2014) indicate a high prevalence of GERD among patients with type 2 DM, while the relationship between diabetic neuropathy, metabolic disorders on the background of diabetes and the occurrence of clinical manifestations of GERD was not revealed.
according to their data [15]. On the contrary, Korean scientists (S.D. Lee et al., 2014) argue that diabetic neuropathy plays an important role in the formation of GERD with type 2 DM, especially in the development of erosive esophagitis (31.5 versus 10.5 %, P = 0.022) [6]. The study of J.O. Ha et al. (2016) has also proven the role of diabetic neuropathy in the development of GERD in type 2 DM, moreover, the correlation has been established between GERD and the duration of diabetes, as well as the age of patients [16].

It should be noted that the performed research is mainly aimed at identifying the relationship between diabetic neuropathy and the formation of GERD with type 2 DM. We have not found any scientific works that discuss the role of prostaglandins in patients with the combination of GERD and type 2 DM.

The analyzed publications are devoted to the study of prostaglandins, separately in type 2 DM and separately in case of damage to the upper gastrointestinal tract, including GERD. K. Takeuchi (2010) highlights the role of prostaglandins, predominantly type E, in GERD and chronic gastritis. At the same time, the authors have proven that Pg E2 protects the esophagus from acid reflux and provides cytoprotection of the stomach [17]. In his review paper, V.A. Chernyshov (2013) discusses changes in the expression of 8-iso-prostaglandin F2α in the daily urine depending on the performed hypoglycemic therapy in patients with type 2 DM [18].

The research of V.O. Serhienko et al. (2017) is aimed at studying the influence of combination therapy consisting in the use of omega-3 polyunsaturated fatty acids and statins on the lipidogram dynamics and the levels of various biologically active substances, including 6-keto-prostaglandin F1α, in patients with type 2 DM associated with diabetic cardiovascular autonomic neuropathy. In this case, the initially increased levels of 6-keto-prostaglandin F1α were detected in these patients [19]. E.H. Dorosh and N.A. Kravchun (2013) determined the level of 8-iso-prostaglandin F2α in the daily urine depending on the performed hypoglycemic therapy in patients with type 2 DM [18].

The results of their studies indicate an increase in 8-iso-prostaglandin level to (386.3 ± 42.2) pg/ml in patients with the combined pathology (type 2 DM and NAFLD), which is significantly higher compared to the patients with type 2 diabetes without NAFLD ((202.2 ± 54.5) pg/ml, p < 0.05) and 10 times higher compared to healthy persons ((38.8 ± 6.0) pg/ml, p < 0.001). On the basis of their research, it was also concluded that patients with type 2 DM and associated pathology (type 2 DM and NAFLD) have excessive weight and obesity of varying degrees [20].

We have studied the levels of F2α and I2 prostaglandins, which have a divergent effect on the body, namely: Pg F2α exhibits a constrictive effect, while prostaglandin I2, on the contrary, has relaxing properties. According to the results of our study, increased serum levels of prostaglandins F2α and I2 in patients with GERD were determined. At the same time, more significant changes were detected in the combined pathology (GERD and type 2 DM).

When characterizing the changes in prostaglandins by classes, a predominant increase in serum prostacyclin was detected. In patients with the combination of GERD and type 2 DM, it is 1.5 times higher than that in patients with GERD not suffering from type 2 DM.

The obtained data also indicate that in case of combination of several pathological states (type 2 DM, GERD, increased BMI), a more significant increase is observed in the concentration of prostacyclin, and Pg I2 depends on the disease duration.

High level of prostaglandin, which has a relaxing effect on smooth muscles, including the digestive system, suggests its influence on the formation of GERD, especially on the background of type 2 DM. It is plausible that the loss of physiological balance between prostaglandins, which have opposite effects on the internal organs on the background of metabolic disorders in obesity and diabetes, may be considered as one of the components affecting the lower esophageal sphincter, leading to its relaxation and the formation of GERD manifestations. The obtained data require further investigation, analysis of changes in prostaglandins in type 2 DM and their probable effect on the formation of GERD in these patients.

Conclusions

1. In patients with GERD, an increase in the levels of prostaglandins F2α and I2 in the blood serum was detected (up to (119.68 ± 9.26) pg/ml and (115.22 ± 7.84) pg/ml, respectively).
2. The combination of GERD and type 2 DM is accompanied by a more significant increase in serum concentration of prostaglandins, especially I2, (up to (176.94 ± 8.41) pg/ml as compared to the control group — (52.17 ± 6.44) pg/ml; p < 0.01), than in patients with GERD without type 2 DM.
3. In patients with GERD on the background of type 2 DM, the maximum concentration of prostacyclin in the blood serum ((192.61 ± 10.54) pg/ml) was detected in excess body weight, as well as of prostaglandin F2α (165.41 ± 6.89) pg/ml — in patients with class II obesity.

Conflicts of interests. Authors declare no conflicts of interests that might be construed to influence the results or interpretation of their manuscript.

Information on contribution of each author:
Ye.S. Sirchak — concept and design of the research, analysis of the data; M.P. Stan — collection and processing of materials, writing the text.

References

Зміни рівнів простагландинів у сироватці крові в пацієнтів із гастроезофагеальною рефлюксною хворобою на фоні цукрового діабету ІІ типу

Резюме. Актуальність. В основі ураження органів травлення в пацієнтів із цукровим діабетом (ЦД) лежать декілька механізмів: дисфункція вегетативної нервової системи, дисрегуляція секреції та інактивація гормонів і інкретомових. При ЦД відбувається зниження рівнів простагландинів (Pg), особливо F2α, особливо у пацієнтів із ГЕРХ на фоні ЦД ІІ типу у 3,4 раза проти 2,1 раза в групі. У пацієнтів із ГЕРХ встановлено зниження рівнів Pg I1, в 2,2 раза, а Pg F2α — лише в 1,6 раза. При поєднанні декількох патологічних станів (ЦД ІІ типу, ГЕРХ, хронічний апноєвий синдром) збільшення концентрації простагландинів може вплинути на трофіку та регенерацію слизової оболонки ГЕРХ.

Мета дослідження: вивчити особливості зміни рівнів простагландинів (Pg) (I1 та F2α) в сироватці крові в пацієнтів із гастроезофагеальною рефлюксною хворобою (ГЕРХ) на фоні ЦД ІІ типу залежно від порушення індексу маси тіла. Матеріали та методи. Обстежено 54 пацієнти з ЦД ІІ типу та ГЕРХ (I1 група). У групу порівняння включено 22 пацієнти з ГЕРХ (II група). У обстежених хворих визначали показники Pg F2α та б-кето-простагландину F3, (простациклін крові — Pg I1) в сироватці крові. Результати. Встановлено підвищення рівнів простагландинів в обох групах пацієнтів, але більш виражені зміни спостерігаються у I групі. Звертає на себе увагу більш суттєве зростання концентрації Pg I1, порівняно з показником Pg F2α, особливо в пацієнтів із ГЕРХ на фоні ЦД ІІ типу (в 3,4 раза проти 2,1 раза в групі). У пацієнтів із ГЕРХ встановлено знищення рівнів Pg I1, в 2,2 раза, а Pg F2α — лише в 1,6 раза. При поєднанні декількох патологічних станів (ЦД ІІ типу, ГЕРХ, порушення індексу маси тіла) спостерігається більш виражене підвищення концентрації простагландинів, що також залежить від тривалості захворювання.

Висновки. У пацієнтів із ГЕРХ встановлено знищення рівнів простагландинів F2α та I1 в сироватці крові. Посідання ГЕРХ та ЦД ІІ типу сприяє більш вираженому зростанню концентрації простагландинів, особливо у пацієнтів із ГЕРХ на фоні ЦД ІІ типу.

Ключові слова: гастроезофагеальна рефлюксна хворoba; цукровий діабет ІІ типу; простагландини.
Изменения уровней простагландинов в сыворотке крови у пациентов с гаstroзофагеальной рефлюксной болезнью на фоне сахарного диабета II типа

Резюме. Актуальность. В основе поражения органов пищеварения у пациентов с сахарным диабетом (СД) лежат несколько механизмов: дисфункция вегетативной нервной системы, ангиопатия, дисрегуляция секреции и инактивация гормонов и инкрегментов. Цель работы: изучить особенности изменения уровня простагландинов (Pγ (I, и F,- ) в сыворотке крови у пациентов с гастроэнзимальной рефлюксной болезнью (ГЭРБ) на фоне СД II типа в зависимости от нарушения индекса массы тела. Материалы и методы. Обследовано 54 пациента с СД II типа и ГЭРБ (I группа). В группу сравнения вошло 22 пациента с ГЭРБ (II группа). У обследованных пациентов определяли показатели Pγ F,- и 6-кето-простагландин F,- (простациклин крови — Pγ I,) в сыворотке крови. Результаты. Установлено повышение уровня простагландинов в обеих группах пациентов, но более выраженные изменения наблюдаются в I группе. Обращает на себя внимание более существенное увеличение концентрации Pγ I, по сравнению с показателем Pγ F,- особенно у пациентов с ГЭРБ на фоне СД II типа (в 3,4 раза против 2,1 раза в I группе). У пациентов с ГЭРБ установлено повышение уровня Pγ I, в 2,2 раза, а Pγ F,- — только в 1,6 раза. При сочетании нескольких патологических состояний (СД II типа, ГЭРБ, нарушение индекса массы тела) наблюдается более выраженное увеличение концентрации именно простациклина, что также зависит от продолжительности заболевания. Выводы. У пациентов с ГЭРБ установлено повышение уровня простагландинов F,- и I, в сыворотке крови. Сочетание ГЭРБ и СД II типа сопровождается более выраженным увеличением концентрации простагландинов, особенно Pγ I, в сыворотке крови. Установлена зависимость между продолжительностью СД II типа, избыточной массой тела и динамикой уровня простагландинов Pγ I, в сыворотке крови у пациентов с ГЭРБ на фоне СД II типа. Ключевые слова: гастроэнзимальная рефлюксная больезнь; сахарный диабет II типа; простагландины.