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Research Article

Prevalence of Toxigenic Strains of *Helicobacterious* Infection and Histological Changes of the Mucous Membrane in Patients with Duodenal Peptic Ulcer and Type 2 Diabetes

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Abstract

Introduction: The article highlights the assessment of the prevalence of Helicobacter infection strains in combination with type 2 diabetes. The effect of this main pathology, depending on the strain, on the state of the duodenal mucosa in the chambers of the poor pathology with concomitant disease is also highlighted.

The aim of the study: To evaluate the prevalence and histological changes of the mucous membrane under the influence of toxigenic strains of Helicobacter infection in patients with peptic ulcer of the duodenum with type 2 diabetes.

Research materials and methods: As a result of the screening, 48 patients with Hp - associated peptic ulcer of the DPK were involved in the study, including 28 patients with concomitant type 2 diabetes mellitus (T2DM). The control group consisted of 22 practically healthy persons (PZO) in whom no acute or chronic diseases were detected at the time of examination.

Examination results and their justification: In patients with PVDPK, presence of genotype cagA + vacA + occurred in 11 people (55%), genotype cagA + vacA- - in 1 person (5%), genotype cagA-vacA + - in 6 people (30%), respectively. The combination of cagA-/vacA- genes was observed in 2 people (10%), respectively. In the group of patients with PVDPK in combination with type 2 diabetes, it is observed in the presence of the cagA-vacA + genes that it occurs 4.67 times more often compared to the combination of cagA + vacA + and cagA + vacA- strains. Among examined patients with PVDPC in combination with T2DM, there is a combination of genes cagA– vacA- 2 individuals (7.14%), which were later removed from the study. At the same time, it should be noted that according to the data in SODPK, there is an increase in the R/B ratio in all studied structures of SODPK, and not only in endotheliocytes, and both in the group of patients with sensitivity of genes cagA + vacA + and genes cagA + or vacA + HP in patients. According to the morphological data, more pronounced signs of endothelial dysfunction are observed in SODPK in the presence of cagA + vacA + HP genes than in the presence of cagA + or vacA + HP, in particular, the percentage of vessels with endothelial desquamation phenomena was relatively higher, the volume of endothelial nuclei was reduced, and at the same time an increased coefficient of variation of the distribution of nuclear chromatin in the nuclei of endotheliocytes was found. When PV is combined with type 2 diabetes, endothelial dysfunction is enhanced both in cagA + vacA + and in cagA + or vacA + individuals, but more significantly in cagA + vacA + individuals. The optical density of the PAS-reaction is reduced in patients with PVS in the presence of cagA + vacA + genes compared to cagA + or vacA + patients, which indicates a more strongly impaired mucosa formation. Moreover, with peptic ulcer in combination with T2DM, a further deepening of saliva production disorders is noted. The analysis of the obtained data of histological and histochemical studies showed that in the association of PV with the cagA + vacA + genotype of Helicobacter pylori, more pronounced morphological changes are observed compared to the presence of the cagA + vacA- or cagA-vacA + genotypes, which are characterized by a higher percentage of vessels with endothelial desquamation phenomena (by 42 .1% - for PVDPK, by 19.35% - for PVDPK with T2DM, $p < 0.05$); a smaller volume of endotheliocyte nuclei (by 36% - in PVDPC, by 25.3% - in PVDPC with T2DM, $p < 0.05$), which indicates a deepening of cell alteration; a higher coefficient of variation of nuclear chromatin distribution in the nuclei of endotheliocytes (by 26.1%, by 17.6%,

spectively), with a decrease in the optical density of the surface mucus and the optical density in the cells of Brunner's glands of the duodenum.

Conclusion: 1. It was established that in the group of patients with PVDPK in combination with type 2 diabetes, it is observed in the presence of the cagA-vacA + genes that it occurs 4.67 times more often compared to the combination of cagA + vacA + and cagA + vacA- strains. 2. Evaluating the state of the endothelium, it was established that in the presence of genes cagA + vacA + in patients with PD, manifestations of impaired endothelial function were detected, in particular - an increased percentage of vessels with the phenomena of endothelial desquamation, a reduced volume of endothelial nuclei against the background of an increased coefficient of variation of nuclear chromatin distribution in the nuclei endotheliocytes in comparison with the group of patients with PD in the presence of cagA + or vacA + genes. When combining PVDPC with T2DM taking into account the genes cagA + vacA +, the indicators of endothelial dysfunction significantly increase in comparison with the group of patients with PVDPK combined with T2DM taking into account the genes cagA + or vacA +. 3. According to the results, it was established that the manifestations of inflammatory reactions, which are assessed not only by the level of inflammatory infiltration by polymorphonuclear leukocytes (PML), but also by taking into account such exudation phenomena as stroma swelling, blood stasis and erythrocyte soot, hemorrhages. The level of desquamation of the covering epithelium indicated the level of alteration (damage) of these cells. In patients with CKD in combination with T2DM, the condition of CKD is accompanied by pronounced changes in these parameters. 4. It was investigated that the optical density of the PAS- reaction in the presence of genes cagA + vacA + in patients with PV PDK in comparison with patients with PV PDK in the presence of genes cagA + or vacA + in all studied structures indicates a more pronounced impaired mucus formation. Moreover, in the presence of type 2 diabetes in combination with PVDPK, a further deepening of disorders of mucus formation processes is noted.

Keywords: Toxigenic Strains; Helicobacter Infection; Histological Changes; Mucous Membrane; Peptic Ulcer; Duodenum; Diabetes

Introduction

The production of VacA (50-65%) and CagA toxins is the mechanism of pathogenic action of *H. pylori* (HP.). It is known that VacA can bind to receptors (RPTPα, RPTPβ) in epithelial cells [42,49], thus ensuring the interaction of the strain with G401 (human renal tumor cells) and AGS (adenocarcinoma cells) cell cultures [10], which enables interact with AZ-521 gastric carcinoma cells [28,29,41]. Increasing the sensitivity of the RPTPβ receptor in some cell lines increases the toxicity of VacA [42]. Absence of the RPTPβ receptor is known to increase resistance to CO ulceration caused by VacA [10,28]. Attachment of the VacA strain to receptors LFA1 (functional lymphocyte antigen type 1, known as integrin CD18/CD11a) and T cells, whose ligands are ICAM-1, ICAM-2 (ICAM3), increases the expression of leukocytes [47]. The presence of many receptors for the vacA gene can determine the diversity of its influence on CO [10,42].

As is known, the VacA toxin is a "conductor" of the cytotoxin-associated protein CagA and contains 2 regions - signal - (s, signal, allelic variants - s1 and s2) and middle (m, middle, m1 or m2). It is the different combination of presented regions of the CagA protein that causes the formation of pores on the cell membrane with the release of chlorine ions, inhibition of T- lymphocyte activity, and the occurrence of vacuolar degeneration of epithelial cells, which is the cause of apoptosis [14,35,50].

VacA cytotoxicity depends on the presence of genotypes s1 and s2 and m1 and m2, the combination of which (s1m1, s1m2, s2m1 and s2m2) determines the level of pathogenicity [10,15,50]. The signal sequence s1m2 encodes a signal protein (p33), which better penetrates the epitheliocyte membrane. The middle section of DNA is responsible for the synthesis of the p58 receptor domain, and cells with the m1 genotype are able to interact with a wider range of epithelial cells than those with the m2 genotype. This explains the high vacuolating activity of s1/m1 genotypes, moderate degree of vacuolation in the s1/m2 genotype and its absence in the s2/m2 genotype [10,23,46]. The intermediate i region between the s and m regions is considered a marker of disease severity [25,45], and the s1m1 genotype is considered to be most associated with high cytotoxicity and disease severity [34]. Strains containing a combination of s1, i1, m1 alleles are associated with the most severe diseases [33]. This relationship can be realized due to the increased

ability to form anion channels, vacuolating activity and wide cellular tropism of s1/i1/m1 genotypes [37]. Since vacA s1/m1 is closely associated with the cagA-positive genotype, this factor cannot be considered separately as a marker of disease severity [34]. In turn, the pathogenicity island of Cag (Cag RAI) of HP encodes up to 27 genes, 17 of which are necessary for encoding the type IV secretory system. Effector proteins, CagA penetrate through the formed pores into the epithelial cells of the host [1,50]. Interacting directly with PAR1/MARK kinases, which are regulators of cell polarity, they affect the process of mitosis, lead to the disruption of the phases of the mitotic cycle (G1 and G2) and the appearance of polyploid cells [17,18]. As a result of the above, the intracellular signaling system SHP-2 is stimulated with the production of pro-inflammatory chemokines IL-8, IL-6, activating the migration processes of neutrophils in the CSF, which contributes to the activation and translocation of the main pro-inflammatory protein NF-kB into the nucleus and the subsequent production of pro-inflammatory cytokines: IL - 1β, TNF – α and IFN – γ, IL – 12 [34]. However, the connection of the cytotoxic protein CagA with other isoforms of PAR1, which ensure the density of intercellular junctions, with the formation of microtubules and increased permeability on the one hand, and ensuring the stability of CagA on the other, is known. As a result, signal transduction is activated, the function of the mucous membrane epithelium is inhibited, intercellular connections are destroyed, cell polarity and their differentiation are disrupted [37], which leads to the development of PVS and DPK (91%) and chronic gastritis (CG) (48%) [4,36].The ability to directly damage the epithelium of the gastric mucosa is one of the characteristics of H. pylori, which have CagA - and VacA - phenotypes and, as a result, show the greatest cytolytic activity. And in the presence of the gene carA, Helicobacter pylori also affects the processes of systemic inflammation due to the activation of the processes of lipid peroxidation and the development of metabolic intoxication [12,15,20,24,43], disruption of the hemostasis system [8], subsequently leading to the development of atherosclerosis (AC) and hypertension [8,13,38], and, not excluded, and T2DM [4]. The obtained data on the influence of *H. pylori* infection on the course of the atherosclerotic process are focused on several aspects: epidemiological association, pathophysiological mechanisms, and the results of eradication therapy [16,17]. The connection between HR-seropositivity and the course of the atherosclerotic process has been proven in the presence of sagA [21,48,49]. One of the most immunogenic antigens of HR is its HSP, which belongs to the family of bacterial Gro-EL proteins and has broad cross-reactivity both with other bacterial Gro-EL (in particular, mycobacterial) and with human HSP65 [11,22,36]. This fact is of considerable importance, taking into account the fact that the possibility of induction of AS by HSP65 immunization has been proven [36,52], and the level of antibodies to HSP65 reliably correlates with the degree of risk of developing vascular events [53] and cross-reacts with antigens of atherosclerotic vascular walls [30], which may also be a link between HP infection and the risk of developing cardiovascular pathology in AS patients [5]. Another direction of research within the scope of the search for possible mechanisms of *H. pylori* infection interference in the course of the atherosclerotic process is the study of the effect on the exchange of biologically active substances, in particular, on the synthesis of nitrogen monoxide (NO) by the endothelium, which is an important regulator of vascular tone and hemostasis [20,39,50]. The question of the relationship between HP infection and pancreatic pathology remains an interesting and not fully clarified issue.

The direct influence of this microorganism on the development of pancreatitis and T2DM has been proven. The results of research on the spread of Helicobacter infection in patients with diabetes mellitus are ambiguous. So, N. Guicelik., *et al*. found *H. pylori* infection in 75.6% of patients with T2DM [31], the increased frequency of which is explained by the development of microangiopathy of SOS, which creates favorable conditions for the survival of the microorganism [3,12]. It is known that the vacuolating cytotoxin is capable of causing a pancreatotoxic effect by suppressing the exocrine secretory function of the pancreas. *H. pylori* infection inhibits the synthesis and release of somatostatin (which normally inhibits gastrin production and pancreatic secretion) from D-cells of the stomach, and, as a result, leads to an increase in the synthesis and secretion of gastrin [27,40], which is accompanied by a decrease in the antral density of D - cells, which returns to normal after eradication [40]. The pathogenetic connection of *H. pylori* with macroangiopathy, neuropathy, and microalbuminuria was also investigated, which is explained by immune-mediated damage to the endothelium, a pronounced systemic inflammatory response, and is the initial stage of the development of diabetes [2,26,44,50].

The aim of the study

To evaluate the prevalence and histological changes of the mucous membrane under the influence of toxigenic strains of Helicobacter infection in patients with peptic ulcer of the duodenum with type 2 diabetes.

Research Materials and Methods

As a result of the screening, 48 patients with Hp - associated peptic ulcer of the DPK were involved in the study, including 28 patients with concomitant type 2 diabetes mellitus (T2DM). The control group consisted of 22 practically healthy persons (PZO) in whom no acute or chronic diseases were detected at the time of examination.

All patients received inpatient treatment in the gastroenterology department of the Chernivtsi Regional Clinical Hospital and the Chernivtsi Regional Endocrinology Center in 2013-2016.

The diagnosis of type 2 diabetes was established according to WHO standards 2006/2011 (HbA1c> 6.5%, fasting plasma glucose ≥ 7.0 mmol/l, postprandial glycemia after 2 hours ≥ 11.0 mmol/l). The presence of PV of the DPC was verified on the basis of the clinical picture, anamnesis data, objective methods of examination of the patient, the results of endoscopic and morphological studies of the SO of the DPC.

Examination of patients was carried out during exacerbation of the disease. In addition to interviewing and collecting anamnesis of the disease, patients were subjected to modern, highly informative, generally accepted clinical, laboratory and instrumental research methods using physical examination methods. At the same time, the histological features of the SO of the DPC, the presence of *H. pylori*, were investigated. To verify the diagnosis of PPD, fibro gastroduodenoscopy was performed using the "GIF Q-40" apparatus of the "Olympus" company (Japan) with targeted biopsy according to the generally accepted methodology. Characterization of endoscopic changes in the mucous membrane of the stomach and duodenum was carried out using minimal standard terminology. Inflammatory and atrophic changes of CO were evaluated by degrees: 0 - no signs, 1 - minimal degree, 2- moderate and 3- pronounced.

Diagnosis of HP was carried out using a rapid urease test with biopsy material, polymerase chain reaction (PCR) with biopsy material, and urease breath test using the "Helik" test system with indicator tubes ("AMA"). Helicobacter pylori DNA was isolated from CO biopsies from the antral part of the stomach using special kits for DNA isolation ("Litekh"). Helicobacter pylori cagA and vacA genes in biopsies were determined using Helikopol reagent kits (Litekh). The intensity of the signal in the gel was determined using the following criteria: weak signal (+), moderate signal (++), strong signal (+++). The results with a weak, moderate and strong signal were taken into consideration. The assessment of detection of *H.pylori* cagA and vacA genes and their alleles was carried out according to the instructions, namely the presence of a DNA fragment of the cagA gene of 404 bp. light filter and vacA (alleles s1 + s2, m1, m2) on 259 bp. + 286 p.n., 290 p.n. and 352 p.n. respectively (Figure 1).

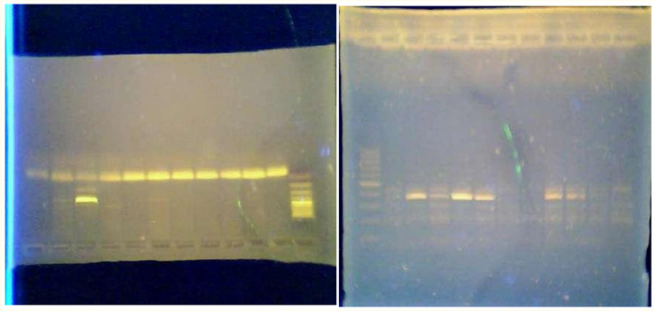

Figure 1: DNA - image of genes cagA and vacA of *H. pylori* in patients with peptic ulcer of the duodenum in combination with type 2 diabetes.

The level of glycemia was studied by the glucose oxidase method using standard sets of reagents produced by the "Filisit diagnostics" (Ukraine). Glycosylated hemoglobin (HbA1c) was determined using a photo colorimetric method using a set of reagents from the company "SpineLab" (Kharkiv, Ukraine).

When assessing histological and histochemical changes in the mucous membrane of the duodenum, biopsies were examined by staining with hematoxylin and eosin (for descriptive characterization of microscopic changes), azur-II-eosin (for the determination of HR-like microorganisms and for the diagnosis of apoptotic bodies), PAS-reaction (for evaluation of mucus- producing properties of various epithelial cells of the gastrointestinal tract) (F.º Venerucci, 2016), carried out a histochemical method of determining OMB (I.S.º Davidenko, 2013). Morphometry of the SOS and DPC was performed using the ImageJ program (T.ºFerreira, 2012). At this stage, patients with PD and those with type 2 diabetes in whom the cagA-/vacA- genotype of HP was detected were excluded from the study.

Statistical processing of the research results was carried out in the following order. The primary data of the examination of pa-

tients with PVS and DPK are entered into the database, which was developed for the unification of input, storage and calculation of data on the study of the condition of patients based on the Microsoft Excel 2003 software shell (Microsoft Corp., 1992- 1999).

Statistical analysis was performed using the SPSS Statistics 17 Multilanguage program.The results in the form of tables and diagrams were transferred to the database. In the process of statistical processing of the research results, the type of data distribution, descriptive indicators, the probability of the obtained results and other types of analysis were determined.

For data corresponding to a normal distribution, the arithmetic mean of the sample (M), standard error (m), maximum and minimum values were determined.

The results were calculated using parametric and non-parametric research methods (Student coefficient (p), Pearson coefficient (χ2), confidence interval (CI), Pearson correlation coefficient (r)). The probabilities of the difference between the obtained data were estimated by the Student's coefficient (t). A difference of $p < 0.05$ was considered probable.

Examination results and their justification

The assessment of the prevalence of *H.pylori* strains is presented in table 1. In patients with PVDPC, the presence of the sagA + vacA + genotype occurred in 11 people (55%), the sagA + vacA- genotype in 1 person (5%), and the sagA-vacA + genotype in 6 persons (30%), respectively. The combination of cagA-/vacA- genes was observed in 2 people (10%), respectively.

In the group of patients with PVDPK in combination with type

Disease	Prevalence of toxigenic *H.pylori*			
	cagA + vacA +	cagA + vacA-	cagA-vacA +	cagA- vacA-
Peptic ulcer of the duodenum (n = 20)	11(55%) *χ^2=9,23 1 p < 0.05	1 (5%) χ^2 = 0,360 p > 0.05	6 (30%) χ^2 = 2,500 p > 0.05	2 (10%)
Peptic ulcer of the duodenum in combination with type 2 diabetes mellitus (n = 28)	9(32,14%) *χ^2 = 5,543 p > 0.05	3 (10,72%) χ^2 = 0,220 p > 0.05	14 (50%) * χ^2=12,600 p < 0.05	2 (7,14%)

Table 1: Prevalence of toxigenic (cagA, vacA) HP strains in examined patients, %.

Note: % - from the total number of patients, taking into account HR genotypes; χ2 is a reliable Pearson test $p < 0.05$.

2 diabetes, it is observed in the presence of the cagA-vacA + genes that it occurs 4.67 times more often compared to the combination of cagA + vacA + and cagA + vacA- strains.

Among examined patients with PVDPC in combination with T2DM, there is a combination of genes cagA–vacA- 2 individuals (7.14%), which were later removed from the study.

When studying the structures of the mucous membrane of DPC with T2DM in combination with Helicobacter pylori infection, there are features of proteins that are associated with the processes of oxidative modification of proteins and glycation [5]. With this technique, proteins in which carboxyl groups predominate over amino groups are colored red, and proteins in which amino groups predominate over carboxyl groups are colored blue. Quantitatively and accurately with a high degree of reproducibility, it can be estimated by computer micro spectrophotometry based on the R/B ratio. The predominance of the red color in the color is evidenced by the increase of this indicator above one, and the blue color in the color is indicated by the decrease of the R/B ratio below one and below [6].

In the table 2 presents the results of measuring the R/B ratio in various structures of the mucous membrane of the DPC before treatment. From the given data, it can be seen that in the group of patients with PD with the presence of the cagA + vacA + genes both without the combination of T2DM and in combination with T2DM in patients compared to the group of patients with the presence of

Indexes	cagA + vacA + n = 11	cagA + або vacA + n = 7
R/B ratio in the cytoplasm of endotheliocytes	1.21 ± 0.034	1.12 ± 0.022 p < 0.05
R/B ratio in cytoplasm of enterocytes	1.14 ± 0.024	1.06 ± 0.020 p < 0.05
The R/B ratio in the cytoplasm of the epithelium of Bruner's glands	1.24 ± 0.033	1.16 ± 0.021 p < 0.05

Table 2: R/B ratio in various structures of the mucous membrane in patients with peptic ulcer of the duodenum, M ± m.

Note: p < 0.05 - the reliability of the differences in indicators between these groups.

the cagA + or vacA + genes, the R/B ratio is increased in all studied structures Such research results indicate that the processes of oxidative modification of proteins, which are known to be activated during inflammation in response to infection, play a significant role in pathology in the examined patients.

At the same time, it should be noted that according to the data in the table, there is an increase in the R/B ratio in all studied structures of SODPK, and not only in endotheliocytes, and both in the group of patients with absence of genes cagA + vacA + and genes cagA + or vacA + HP in patients.

The above-mentioned features of changes in the R/B ratio when staining histological sections with bromophenol blue according to Mikel Calvo are illustrated with the help of figure 2,3.

Indexes	cagA + vacA + n = 9	cagA + або vacA + n = 17
R/B ratio in the cytoplasm of endotheliocytes	1.29 ± 0.018	1.16 ± 0.025 p < 0.05
R/B ratio in cytoplasm of enterocytes	1.18 ± 0.020	1.09 ± 0.021 p < 0.05
The R/B ratio in the cytoplasm of the epithelium of Bruner's glands	1.29 ± 0.024	1.24 ± 0.023[НВ]

Table 3: R/B ratio in various structures of the mucous membrane in patients with duodenal peptic ulcer in combination with type 2 diabetes, M ± m.

Note: p < 0.05 - the reliability of the differences in indicators between these groups. HB - reliability between indicators was not found.

In connection with the fact that the ratio R/B showed the most

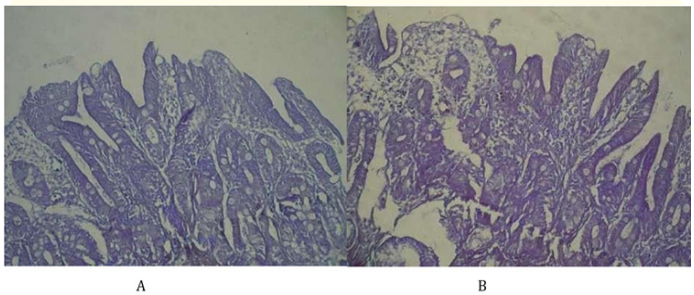

Figure 2: Observation of duodenal peptic ulcer without combination and type 2 diabetes.

- A: With agA + vacA + Helicobacter pylori.
- B: With cagA + or vacA + Helicobacter pylori.

Mucous membrane of the duodenum.

Staining with bromophenol blue by Mikel Calvo Rev. 20x. Approx. 10x.

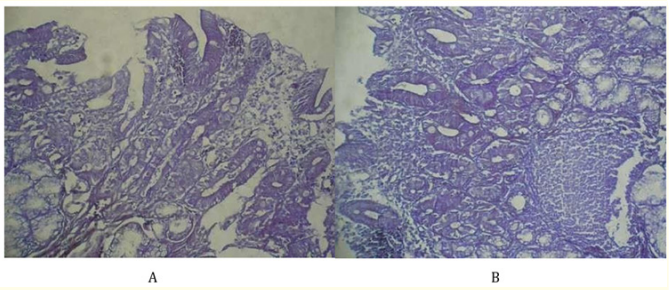

Figure 3: Observation of duodenal peptic ulcer in association with type 2 diabetes mellitus.

A: with agA + vacA + Helicobacter pylori;

B: with cagA + or vacA + Helicobacter pylori. Mucous membrane of the duodenum.

Staining with bromophenol blue according to Mikel Calvo Ob. 20x. Approx. 10x.

constant changes on the part of endotheliocytes both in relation to various organs and in relation to various pathologies, it was intended to study some features of endothelial dysfunction by morphological methods, for which the three most informative indicators were chosen (1- Coefficient of variation of nuclear chromatin distribution (%) in endotheliocyte nuclei, 2- Volume of endotheliocyte nuclei, 3 - Percentage of vessels with endothelial desquamation phenomena) data on which are given in table 4.

From the data presented in the tables, it can be seen that, according to the morphological data more pronounced signs of endothelial dysfunction are observed in SODPK in the presence of cagA + vacA + HP genes than in the presence of cagA + or vacA + HP, in particular, the percentage of vessels with the phenomena of endothelial desquamation was relatively higher, and the percentage of vessels with endothelial desquamation phenomena was lower the volume of endothelium nuclei, and at the same time, an increased coefficient of variation of the distribution of nuclear chromatin in the nuclei of endotheliocytes was found. When PV is combined with type 2 diabetes, endothelial dysfunction increases both in sagA + vacA + and in sagA + or vacA + individuals, but more significantly in sagA + vacA + individuals (Table 5).

Indexes	cagA + vacA + n = 11	cagA + абоvacA + n = 7
Coefficient of variation of nuclear distribution chromatin (%) in the nuclei of endotheliocytes	19.0 ± 1.3	13.0 ± 1.1 p < 0.05
The volume of endotheliocyte nuclei (μm3)	19.0 ± 1.2	29.7 ± 1.3 p < 0.05
The percentage of vessels with desquamation phenomena endothelium (%)	27.0 ± 1.5	19.0 ± 1.4 p < 0.05

Table 4: Morphological indicators of endothelial dysfunction in various structures of the mucous membrane in patients with peptic ulcer of the duodenum, M ± m.

Note: p < 0.05 - the reliability of the differences in indicators between these groups.

Based on the staining of the preparations with hematoxylin and eosin, other morphometric indicators of the state of SODPK were obtained, the data of which are given in tables 6-7.

Indexes	cagA + vacA + n = 9	cagA + абоvacA + n = 17
Coefficient of variation of nuclear distribution chromatin (%) in the nuclei of endotheliocytes	20.0 ± 1.6	17.0±1.4^{нв}
The volume of endotheliocyte nuclei (μm3)	18.0 ± 1.3	24.1 ± 1.2 p < 0.05
The percentage of vessels with desquamation phenomena endothelium (%)	37.0 ± 1.8	31.0 ± 1.3 p < 0.05

Table 5: Morphological indicators of endothelial dysfunction in various structures of the mucous membrane in patients with peptic ulcer of the duodenum combined with type 2 diabetes, M ± m.

Note: p < 0.05 - the reliability of the differences in indicators between these groups.
HB - the reliability of the indicators was not revealed.

In general, the analysis of these tables allows us to come to the conclusion that in sagA + vacA + patients the condition of SODPK is worse than in sagA + or vacA + patients. This is especially evident from the manifestations of inflammatory reactions, which are assessed not only by the level of inflammatory infiltration by polymorphonuclear leukocytes (PML), but also by taking into account such exudation phenomena as stroma swelling, blood stasis and erythrocyte sludge, hemorrhages. The level of desquamation of the covering epithelium indicated the level of alteration (damage) of these cells. In patients with peptic ulcer with T2DM, the damage of the SODPK was more pronounced according to individual indicators.

Separate studies have also been carried out to study the processes of mucus formation in SODPK, which were based on the his-

Indexes	cagA + vacA + n = 11	cagA + абovacA + n = 7
Desquamation of enterocytes (scores: from 0 to 5)	2.4 ± 0.05	1.8 ± 0.04 p < 0.05
Percentage of vessels with stasis phenomena and (or) erythrocyte sugar (%)	32.0 ± 1.6	7.0 ± 0.4 p < 0.05
Edema of the stroma (points: from 0 to 5)	3.7 ± 0.07	1.2 ± 0.02 p < 0.05
Hemorrhages into the stroma (points: from 0 to 5)	2.4 ± 0.05	1.1 ± 0.02 p < 0.05
The degree of infiltration of PML (points: from 0 to 5)	2.8 ± 0.07	1.1 ± 0.04 p < 0.05
Percentage of goblet cells (%)	14.0 ± 0.9	24.0 ± 1.2 p < 0.05

Table 6: Morphometric indicators of the state of the mucous membrane in patients with peptic ulcer of the duodenum without concomitant pathology, M ± m.

Note: p < 0.05 - the reliability of the differences in indicators between these groups.

Indexes	cagA + vacA + n = 9	cagA + абovacA + n = 17
Desquamation of enterocytes (scores: from 0 to 5)	3.2 ± 0.05	2.0 ± 0.04 p < 0.05
Percentage of vessels with stasis phenomena and (or)erythrocyte sugar (%)	39.0 ± 1.6	19.0 ± 0.4 p < 0.05
Edema of the stroma (points: from 0 to 5)	3.9 ± 0.07	2.8 ± 0.02 p < 0.05
Hemorrhages into the stroma (points: from 0 to 5)	2.9 ± 0.05	1.8 ± 0.02 p < 0.05
The degree of infiltration of PML (points: from 0 to 5)	3.9 ± 0.08	2.1 ± 0.05 p < 0.05
Percentage of goblet cells (%)	12.0 ± 0.8	21.0 ± 1.1 p < 0.05

Table 7: Morphometric indicators of the state of the mucous membrane in patients with peptic ulcer of the duodenum in combination with type 2 diabetes, M ± m.

Note: p < 0.05 - the reliability of the differences in indicators between these groups.

tochemical method (PAS-reaction), which allows for the detection and quantitative evaluation of mucus glycoproteins and polysaccharides. The results of these studies are highlighted in table 8.

According to the given data, the optical density of the PAS reaction is reduced in patients with PVS in the presence of cagA + vacA + genes compared to cagA + or vacA + patients, which indicates a more severely impaired mucosa formation. Moreover, in the case of peptic ulcer in combination with T2DM, a further deepening of disturbances in the processes of mucus formation is noted (Table 9, Figure 4-7).

The analysis of the obtained data of histological and histochemical studies showed that in the association of PV with the cagA + vacA + genotype of Helicobacter pylori, more pronounced morphological changes are observed compared to the presence of the cagA + vacA- or cagA-vacA + genotypes, which are characterized by a higher percentage of vessels with endothelial desquamation phenomena (by 42 .1% - for PVDPK, by 19.35% - for PVDPK with

Indexes	cagA + vacA + n = 11	cagA + або vacA + n = 7
The optical density of the PAS reaction in goblet cells (relative to optical density)	0.290 ± 0.0019	0.291 ± 0.0022^{НВ}
The optical density of the PAS-reaction in the cells of Bruner's glands (relative toopt. density)	0.381 ± 0.0028	0.394 ± 0.0028 p < 0.05

Table 8: Morphological indicators of mucus formation of the mucous membrane in patients with peptic ulcer of the duodenum without hypertension and type 2 diabetes mellitus, M ± m.

Note: p < 0.05 - the reliability of the differences in indicators between these groups. HB - reliability between indicators was not found.

Indexes	cagA + vacA + n = 9	cagA + абовacA + n = 17
The optical density of the PAS reaction in goblet cells (relative to optical density)	0.264 ± 0.0014	0.278 ± 0.0024 p < 0.05
The optical density of the PAS-reaction in the cells of Bruner's glands (relative to opt. density)	0.342 ± 0.0024	0.364 ± 0.0021 p < 0.05

Table 9: Morphological indicators of mucus formation of the mucous membrane in patients with peptic ulcer of the duodenum in combination with type 2 diabetes mellitus, M ± m.

Note: p < 0.05 - the reliability of the differences in indicators between these groups. The given data are illustrated with the help of figures. 4-7.

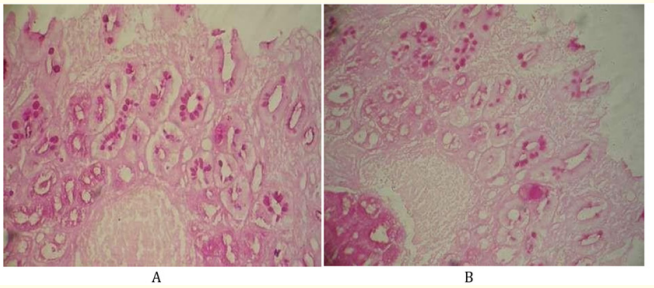

Figure 4: Observation of peptic ulcer of the duodenum. Mucous membrane of the duodenum.
A: With agA + vacA + Helicobacter pylori;
B: With cagA + or vacA + Helicobacter pylori. PAS reaction. Around 8 p.m. About 10 p.m.

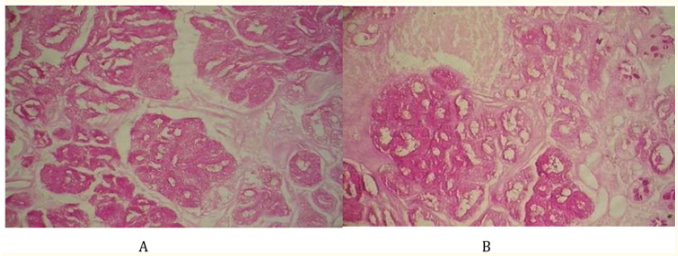

Figure 5: Observation of peptic ulcer of the duodenum. Location of Bruner's glands of the duodenum.
A: With agA + vacA + Helicobacter pylori;
B: With cagA + or vacA + Helicobacter pylori. PAS reaction. Rev. 20h Approx. 10x.

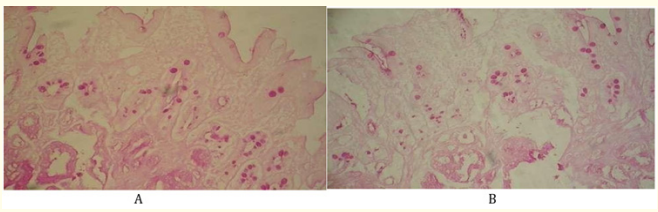

Figure 6: Observation of duodenal peptic ulcer in combination with type 2 diabetes mellitus. Duodenal mucosa.
A: With agA + vacA + Helicobacter pylori;
B: With sagA + and vacA + Helicobacter pylori. PAS reaction. Rev. 20h Approx. 10x. SOD.

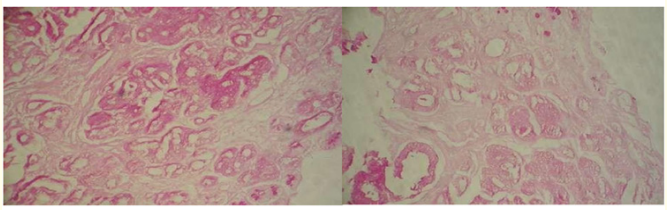

Figure 7: Observation of peptic ulcer of the duodenum with arterial hypertension and type 2 diabetes.
Location of Bruner's glands of the duodenum. A) With agA + vacA + Helicobacter pylori; B) With cagA + or vacA + Helicobacter pylori.PAS- reaction. Rev. 20h Approx. 10x.

T2DM, $p < 0.05$); a smaller volume of endotheliocyte nuclei (by 36% - in PVDPC, by 25.3% - in PVDPC with T2DM, $p < 0.05$), which indicates a deepening of cell alteration; a higher coefficient of variation of nuclear chromatin distribution in the nuclei of endotheliocytes (by 26.1%, by 17.6%, respectively), with a decrease in the optical density of the surface mucus and the optical density in the cells of Brunner's glands of the duodenum.

Conclusion

- It was established that in the group of patients with PVDPK in combination with type 2 diabetes, it is observed in the presence of the cagA-vacA + genes that it occurs 4.67 times more often compared to the combination of cagA + vacA + and cagA + vacA- strains.
- Evaluating the state of the endothelium, it was established that in the presence of genes cagA + vacA + in patients with PD, manifestations of impaired endothelial function were detected, in particular - an increased percentage of vessels with the phenomena of endothelial desquamation, a reduced volume of endothelial nuclei against the background of an increased coefficient of variation of nuclear chromatin distribution in the nuclei endotheliocytes in comparison with the group of patients with PD in the presence of cagA + or vacA + genes. When combining PVDPC with T2DM taking into account the genes cagA + vacA +, the indicators of endothelial dysfunction significantly increase in comparison with the group of patients with PVDPK combined with T2DM taking into account the genes cagA + or vacA +.
- According to the results, it was established that the manifestations of inflammatory reactions, which are assessed not only by the level of inflammatory infiltration by polymorphonuclear leukocytes (PML), but also by taking into account such exudation phenomena as stroma swelling, blood stasis and erythrocyte soot, hemorrhages. The level of desquamation of the covering epithelium indicated the level of alteration (damage) of these cells. In patients with CKD in combination with T2DM, the condition of CKD is accompanied by pronounced changes in these parameters.
- It was investigated that the optical density of the PAS-reaction in the presence of genes cagA + vacA + in patients with PV PDK in comparison with patients with PV PDK in the presence of genes cagA + or vacA + in all studied structures indicates a more pronounced impaired mucus formation. Moreover, in the presence of type 2 diabetes in combination with PVDPK, further deepening of disorders of mucus formation processes is noted.

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