

## MORPHOFUNCTIONAL FEATURES CHANGE OF GASTRIC MUCOSA DURING DIFFERENTIAL TREATMENT IN PATIENTS WITH CHRONIC KIDNEY DISEASE II AND III STAGES ON BACKGROUND OF EROSIIVE AND ULCERATIVE LESIONS OF GASTRODUODENAL AREA

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Statement of the problem. This paper deals with the modern state of the problem concerning the mechanisms of gastropathy in patients with chronic kidney disease (CKD). Modern points of views of research nephrologists and gastroenterologists of inter relations between *Helicobacter pylori* (Hp)- mediated gastric and duod(0)enal lesions and a progression of CKD are stated. Various factors of damage of the mucus coat of the stomach and duodenum in with chronic renal disease are listed: *Helicobacter pylori*, a noctivation of lipid peroxidation and a decline of the activity of the processes of antioxidant defence, a derangement of lipid metabolism, anemia, imbalance of the factors of aggression and defence of the mucous coat of the stomach, a disturbanse of cytokine balance. Factors having an important role in determining the structural functional condition of the kidneyss and stomach as wellas in the pathogenesis of the development of nephropathies, induced by the ekstrarenal factors (the syndrome of systemic response and an inflammatory process in the kidnes). It is evident from the bibliographical review presented that a close connection exists the between development of erosive-ulcerous lesions of the gastro-duodenal area and the progression of the chronic renal disease.

**Keywords:** chronic kidney disease, chronic pyelonephritis, lipid peroxidation (LPO), *Helicobacter Pylori*.

**Analysis of recent researches and publications.** Nowadays, it has to be admitted that the problem of the diseases of the gastroduodenal area remains one of the highest priority not only in the field of gastroenterology, but also for clinical medicine whole. The corresponding state of affairs is stipulated by a number of preconditions. First of all, peptic ulcer and chronic gastritis belong to pathology, which traditionally has a significant prevalence in the population of people and an upward tendency of the disease incidence [8].

**The allocation of unsolved aspects of the problem.** Over the last two decades basic views on the pathogenesis of the overwhelming majority of the diseases of the gastroduodenal area have changed drastically. The substantiating etiologic role of *Helicobacter pylori* (Hp) in their origin is reflected in the treatment strategy [1], although a significant number of issues still remain unsolved and require some relevant researches.

**The purpose of the work.** In connection with significant social relevance of the topic, the aim of our work was based on the study of the state of peroxide oxidation LP – Dov, proteins, antioxidant defense system to improve the methodology of differentiated treatment of patients with combined CKD and for EVOS and duodenum by a proper individual selection of drugs.

**Formulation purposes of article (problem).** In the process of vital activity the human organism is constantly interacting with a host of microorganisms, resulting in a permanent selection of those strains that could colonize the mucous membranes (e.g., of the gastrointestinal tract or the urinary system), using it as a habitat medium. As a result of this selection a symbiosis is formed between mi-

cro-and macro-organisms, representing the normal microflora of the human body [1, 2].

The main material of the research. Thus with underlying Hp infection, apart from direct damage of the stomach, there occurs an abatement of the immunoprotective properties of the body and a multitude of systemic effects develops that cause adequate reactions on the part of other organs and systems, one of them being the urinary system. [4, 7].

One of the main damaging factors which lead to the development of lesions in the stomach and duodenum is hypersecretion of the gastric juice, which can be caused by an increased tonus of the parasympathetic tpartion of the central nervous system, an intensifieol gastrin hormone release from the hastrin producing cells in the pyloroantral part of the stomach, histamine from the mast cells of the gastric mucosa (GM) and the formation of cyclic nucleotides, a durease of the activity of the duodenal inhibitory mechanism or a reduction of the inhibitory hormones in the duodenum in atrophic duodenitis. Hyperplasia, of the with an increase of their mass in the fundic portion of the stomach is of patogenetic value. Activation of aggressive factors is mainly associated with the hypersecretion of hydrochloric acid, and a weakening of the protective factors of the gastroduodenal mucosa coat (MC) – with its inflammation. The principal role in both cases is played by a prolonged infection of the MC of the stomach and duodenum with *H. pylori* [9].

Thus, *H. pylori* is involved in the pathogenesis of erosive-ulcerous lesions, affecting both the «defensive» and «aggressive» factors. In the first place, Hp directly damages the gastric affects stomach mucous membrane (YMM), which is especial-

ly characteristic for the *H. pylori* strains of type I that possess the highest cytological activity. Except the vacuolizing cyto-toxin, *H. pylori* produces urease, oxidase, catalase, alkaline phosphatase, glucose-phosphatase, protease, phospholipase, the HC1 secretion protein-inhibitor, superoxide dismutase and many other substances that destructively affect the gastric and duodenal tissues [2, 7]. The lipopolysaccharide of the *H. pylori* outer membrane interacts with the laminin of the stomach epithelium basement membrane, thus losing links with integrin and disturbing the epithelial cover integrity: epitheliocytes lose links with the basement membrane which results in the development of mucous membrane surface micro-defects [5].

Urease also possesses immunogenic properties. Monocytes and leukocytes, enlisted by it, produce pro-inflammatory cytokines which, in their turn, produce free radicals that damage the epithelium. *H. pylori* contributes to secretion of great deal of pro-inflammatory cytokines (IL-1, IL-6, IL-8, tumor necrosis factor (TNF- $\beta$ ), etc.) which initiate and sustain the processes of damaging the SMM [7]. However, the *H. pylori* direct influence on the epithelium is insufficient to form defects in the mucous membrane. *H. pylori* adhesion with the SMM results in an immediate signal transduction and a cytoskeleton reorganization in the epitheliocytes which react by way of producing cytokines, namely, IL-8. These cytokines make leukocytes migrate from the blood vessels, and an active stage of inflammation begins [6]. Activated macrophages secrete interferon-gamma (IFN- $\gamma$ ) and TNF- $\beta$  which, in their turn, involve new cells into the mucous membrane that take part in inflammatory reactions. *H. pylori* avoid phagocytosis owing to catalase and superoxide dismutase. At the same time, reactive oxygen and myeloperoxidase of activated leukocytes in the epithelium give rise to severe destructive changes in the SMM [5].

All the processes described above that take place in the stomach and duodenum are of systemic nature under the *H. pylori* influence and exert a direct pathogenic effect upon the kidneys in patients with chronic kidney disease (CKD). With an increased CKD degree, the damaging effect of aggressive systemic factors intensifies and leads to an accelerated CKD progression [8]. For example, an elevation of the blood proinflammatory cytokine level causes direct lesion of the renal structures. An elevated level of IFN- $\gamma$ , in its turn, provokes an increase of the level of T-lymphocytes with the killer and helper activity, and the expression of the CD95-proapoptotic factor, which leads to an enhancement of apoptosis in the kidneys, and, in our opinion, in the SMM [9]. According to some authors, an elevation of the TNF- $\beta$  level also contributes to the CD95 activation and an enhancement of the destructive activity in patients with CKD with the presence of erosive-ulcerous gastric and duodenal lesions that is revealed at the level of both systems of organs stomach and kidneys [6].

The influence of *H. pylori* also extends to the factors of aggression. The bacterium disturbs the system of intercellular relationships that regulate the gastrin secretion [4]. At the expense of a urease activity, *H. pylori* encircle themselves with an «alkaline cloud» of ammonium ions (*H. pylori* urease

dissolves urea into ammonia and carbonic dioxide), thus removing a normally existing inhibition of gastrin secretion by G cells in the acid medium [5].

Lately, it is not so much the G cell activation as a reduction of the D cell quantity and an inhibition of the somatostatin (a gastrin antagonist) production that has been given attention to [3]. It seems evident that the decisive role in this process does not belong to a pH change, but to the cytokines of monocytes and lymphocytes of the inflammatory infiltrate that lead to a disharmony of the endocrine cellular apparatus, thus impairing the regulatory function of the somatostatin cells. *H. pylori* infection does not result only in an increase of IL-1, IL-6, IL-8, TNF- $\beta$  and IFN- $\gamma$ , as well as the thrombocyte activation factor, resulting in microthrombosis in both the kidney capillaries and the stomach vascular network [3]. Consequently, it leads to an enhancement of ischemia and hypoxia with the development of stomach erosive-ulcerous lesions and CKD progression the quantity of acting nephrons is reduced.

In vitro studies show that IL-1 and IFN- $\gamma$  lead to a release of SMM gastrin. Hypergastrinemia results in a growth of the mass of parietal cells and an increase of acidic production [1].

Arterial hypertension, oxidative stress, a derangement of lipid metabolism and anemia are outlined as major mechanisms of CKD accelerated development and its progression [6, 9].

The state of chronic ischemia, or prolonged stress remains today to be the basic theory of renal disease progression. This process is closely connected with a depletion of the system of the antioxidant defense (AOD) and an activation of lipid peroxidation (LPO) that cause derangements of the protein, electrolyte and lipid metabolisms. Under ordinary conditions, the functioning of the LPO system is a normal physiological process that results in the formation of intermediate and final products that become sources for synthesis and regeneration of vitally necessary biological substances. The regulation of these reactions is realized by the AOD system [2].

Under the conditions of a depletion of the AOD system, an LPO activation appears to be one of the factors that lead to structural-functional lesion of cellular membrane, causing a disorganization of the lipid phase of the biomembrane formations, which finally results in a disturbance of intercellular homeostasis [7]. An elevated level of the end products of the LPO reaction were revealed in the serum of patients with CKD [6]. Similar LPO changes were also found in patients who suffered from erosive-ulcerous lesions of the stomach and duodenum [3, 4, 5].

Thus, a considerable role in the progression of CKD is also played by Hp infection, as it appears from the above-said, apart from such endogenous factors as an accumulation of underoxidized products of nitrogen metabolism and well-known factors-proteinuria, arterial hypertension which is conducive to the maintenance of the pathological process in the kidneys [1, 2, 3, 7].

The inflammation develops as a response to a lesion and invasion of the tissue by pathogens with the participation of cytokines which are synthesized at the site of the original the process pri-

marily by macrophages activated by the components of the pathogen cellular walls and as a result of damaged tissues. Besides, combined infections processes (pyelonephritis and stomach Hp infection) add to enhanced endothelium penetrability, a elevated expression of adhesive molecules and an enhancement of the procoagulant activity. At the same time, an inflow of low-molecular weight inflammatory mediators – histamine, prostaglandins, etc. , responsible for the development of an inflammation in the mucous membrane of the stomach and kidneys, is observed [4, 6].

Ducto the action of systemic effects by helicobacter infection in combination with the stomach and kidney diseases, there appear gross changes in the vascular and capillary walls, resulting in an increase of their penetrability; the extravasal space accumulates glycolized albumin, neutrophils, immu-

noglobulins, immune complexes that lead to changes in immune homeostasis the, development of immune auto-aggression with the formation of antibodies to the glomerular basement membrane [6, 9].

**The findings from this study.** Many problems concerning a study of a combined pathology of the stomach, duodenum and chronic kidney disease remdin unstudied and disputable. For example, the question of a positive or negative PGE<sub>2</sub> effect in patients with a combined stomach and kidney pathology is actively discussed today. The question of today H. pylori content in patients suffering from CKD of degrees III-IV is broadly discussed, since the stomach environment in these individuals is favorable for the development of H. pylori infection, though, according to some authors, the universally accepted tests, when applied, did not reneal the presence of said H. pylori [9].

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## МОРФОФУНКЦІОНАЛЬНІ ОСОБЛИВОСТІ ЗМІНИ СЛИЗОВОЇ ОБОЛОНКИ ШЛУНКА ДИФЕРЕНЦІЙНОГО ЛІКУВАННЯ ХВОРИХ З ХРОНІЧНОЮ ХВОРОБОЮ НИРОК II І III СТУПЕНЯ НА ТЛІ ЕРОЗИВНО-ВИРАЗКОВИХ УРАЖЕНЬ ГАСТРОДУОДЕНАЛЬНОЇ ОБЛАСТІ

### Анотація

У даній роботі відображено сучасний стан проблеми, що стосується механізмів ураження шлунка у хворих з хронічною хворобою нирок. Викладено сучасні погляди вчених нефрологів і гастроентерологів на взаємозв'язок між Helicobacter Pylori-опосередованими ураженнями шлунка, і дванадцятипалої кишки і прогресуванням хронічної хвороби нирок. У роботі наведені різні фактори ураження слизової оболонки шлунка та дванадцятипалої кишки у хворих з хронічною хворобою нирок: Helicobacter Pylori, активація перикисного окислення ліпідів і зниження активності процесів антиоксидантного захисту, порушення ліпідного обміну, анемія, порушення рівноваги чинників агресії та захисту слизової оболонки шлунка, порушення цитокинового балансу. Виділено фактори, що мають важливе значення в детермінації структурно-функціонального стану нирок і шлунка, а також у патогенезі розвитку нефропатій, які індуцуювані екстрауренальними факторами (синдром системної відповіді на запальний процес у нирках). Наведений огляд літератури показує тісний зв'язок між розвитком ерозивно-виразкових уражень гастродуоденальної зони і прогресуванням хронічної хвороби нирок.

**Ключові слова:** хронічне захворювання нирок, хронічний пієлонефрит, перекисне окислення ліпідів (ПОЛ), Helicobacter Pylori.

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## **МОРФОФУНКЦИОНАЛЬНЫЕ ОСОБЕННОСТИ ИЗМЕНЕНИЯ СЛИЗИСТОЙ ОБОЛОЧКИ ЖЕЛУДКА ДИФФЕРЕНЦИАЛЬНОГО ЛЕЧЕНИЯ БОЛЬНЫХ С ХРОНИЧЕСКОЙ БОЛЕЗНЬЮ ПОЧЕК II И III СТЕПЕНИ НА ФОНЕ ЭРОЗИВНО-ЯЗВЕННЫХ ПОРАЖЕНИЙ ГАСТРОДУОДЕНАЛЬНОЙ ОБЛАСТИ**

### **Аннотация**

В данной работе отображено современное состояние проблемы, касающейся механизмов поражения желудка у больных с хронической болезнью почек. Изложены современные взгляды ученых нефрологов и гастроэнтерологов на взаимосвязь между *Helicobacter pylori* – опосредованными поражениями желудка, и двенадцатиперстной кишки и прогрессированием хронической болезни почек. В работе приведены различные факторы поражения слизистой оболочки желудка и двенадцатиперстной кишки у больных с хронической болезнью почек: *Helicobacter pylori*, активация перекисного окисления липидов и снижение активности процессов антиоксидантной защиты, нарушение липидного обмена, анемия, нарушение равновесия факторов агрессии и защиты слизистой оболочки желудка, нарушение цитокинового баланса. Выделены факторы, имеющие важное значение в детерминации структурно-функционального состояния почек и желудка, а также в патогенезе развития нефропатий, которые индуцированы экстраренальными факторами (синдром системного ответа на воспалительный процесс в почках). Приведенный обзор литературы показывает тесную связь между развитием эрозивно-язвенных поражений гастродуоденальной зоны и прогрессированием хронической болезни почек.

**Ключевые слова:** хроническое заболевание почек, хронический пиелонефрит, перекисное окисление липидов (ПОЛ), *Helicobacter Pylori*.