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V.V.Vivsiannyk, L.O.Zub, L.D.Kushnir, N.R.Velyhorska

MECHANISMS OF GASTRIC LESION IN PATIENTS SUFFERING FROM CHRONIC KIDNEY DISEASE

Department of Internal Medicine and Endocrinology (Prof. O.I.Fediv – Head)
City of Chernivtsi (Ukraine)

Abstract. 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 interrelations between Helicobacter pylori (Hp)-mediated gastric and duodenal lesions and a progression of CKD are stated. Various factors of damage of the mucus coat of the stomach and duodenum in patients with chronic renal disease are listed: Helicobacter pylori, an activation of lipid peroxidation and a decline of the activity of the processes of the antioxidant defence, a derangement of lipid metabolism, anemia, inbalance 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 kidneys and stomach as well as in the pathogenasis of the development of nephropathies, induced by the estrarenal factors (the syndrome of systemic response and an inflammatory process in the kidneys) have been singled out. It is evident from the bibliographical review presented that a close connection exists between the development of erosive-ulcerous lesions of the gastro-duodenal area and the progression of the chronic renal disease.

Key words: chronic kidney disease, chronic pyelonephritis, lipid peroxidatio (LPO), Helicobacter pylori, gastric and duodenal erosive-ulcerous lesions.

Nowadays, it has to be admitted that the problem of the diseases of the gastroduodenal area remains one of the highest priorities not only in the field of gastroenterology, but also for clinical medicine as a 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, 11, 21]. 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, 8, 22], although a significant number of issues still remain unsolved and require some relevant researches.

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 micro-and macro-organisms, representing the normal microflora of the human body [1, 2, 7, 9, 13].

Thus, with underlying Hp infection, apart from direct damage of the stomach, there accurse an abatement of the immunoprotective properties of the body and a multitude of systemic effects develop that cause adequate reactions on the part of other organs and systems, one of them being the urinary system [4, 7, 9, 13].

One of the main damaging factors which lead to the development of lesions in the stomach and duodenum is a hypersecretion of the gastric juice, which can be caused by an increased tonus of the parasympathetic portion of the central nervous system, an intensified 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 disease of the activity of the duodenal inhibitory mechanism or a reduction of the inhibitory hormones in the duodenum in atrophic duodenitis. Hyperplasia, with an increase of their mass in the fundic portion of the stomach is of patogenetic value. An activation of aggressive factors is mainly associated with the hypersecretion of hydrochloric acid, and a weakening of the protective factors of the gastroduodenal mucousa 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, 13, 17].

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 mucous membrane (GMM) which is especially characteristic of the H. pylori strains of type I that possess the highest cytological activity. Except the vacuolizing cytotoxin, 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, 9, 14]. 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, 6, 8, 9, 13].

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 the secretion of a great deal of pro-inflammatory cytokines (IL-1, IL-6, IL-8, tumor necrosis factor (TNF-b), etc.) which initiate and sustain the processes of damaging the SMM [7, 9, 14]. 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 cy-

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toskeleton 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, 8, 9, 16]. Activated macrophages secrete interferon-gamma (IFN-c) and TNF-b 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 [17, 20, 21].

All the processes described above, taking 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, 10, 14]. For example, an elevation of the blood proinflammatory cytokine level causes a direct lesion of the renal structures. An elevated level of IFN-c, 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, 21]. According to some authors, an elevation of the TNF-b 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 the systems of organs the stomach and kidneys [6, 15, 17].

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 the powerful 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, 7, 9].

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 [10, 12, 16]. 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-b and IFN-c, as well as the thrombocyte activation factor, resulting in microthrombosis in both the kidney capillaries and the stomach vascular network [10, 13, 15]. 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-c lead to a release of SMM gastrin. Hypergastrinemia results in a growth of the mass of parietal cells and an increase of acidic production [10, 11].

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, 10, 11, 13, 21].

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, 4, 19, 20].

Under the conditions of a depletion of the AOD system, an LPO activation appears to be one of the factors that lead to a structural-functional lesion of the cellular membrane, causing a disorganization of the lipid phase of the biomembrane formations, which finally results in a disturbance of intercellular homeostasis [17]. An elevated level of the end products of the LPO reaction were revealed in the serum of patients with CKD [6, 13]. Similar LPO changes were also found in patients who suffered from erosive-ulcerous lesions of the stomach and duodenum [3, 4, 5, 7, 15, 16].

Thus, a consideralle 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 origin of the inflammatory processes, primarily 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 penetratibility, 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, 8, 9].

Due to 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 penetratibility; the extravasal space accumulates glycolized albumin, neutrophils, immunoglobulins, 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, 7, 9, 12].

A universally accepted present-day concept to the effect that prostaglandins, in particular, PgE_2 and PgI_2, are able to help rehabilitate damaged SMM by way of a positive effect on morphological changes, a regress of restructured changes, the LPO state, epitheliocyte proliferative activity and H. pylori occurence depth, i.e., to influence simultaneously upon several pathogenetic components is a universally accepted present-day theory [11, 12, 22]. However, this problem is insufficiently studied in terms of combined pathology, both in Ukraine and neighbouring countries, stipulating the expediency of its further research [8, 14, 17].

Today, H. pylori is regarded as an alternating agent, capable to both directly cause a local inflammatory reaction in the gastric and duodenal mucous membranes, and indirectly influence upon the processes of systemic inflammation by way of its effect upon the biochemical components of metabolism [11, 13, 16].

Thus, having found themselves in the stomach due to a highly active urease enzyme which breaks up endogenous urea into ammonia and CO_2 and creates round the microbe a protective «zone» of alkaline products and protein an inhibitor of the hydrochloric acid secretion, the microorganisms get over the stomach acid barrier. Glucophoshatase, produced by H. pylori, destructs the protective sulphomucopolysaccharide of the mucous membrane, while phospholipase and protease break the integrity of the epithelial stratum. Having colonized the mucous membrane of the stomach antral compartment, helicobacters start a quick propagation and secrete a great number of catalase and alcohol dehydrogenase enzymes. Thus formed, peroxide radicals and alcohol are able to protect the microbe from phagocytosis and damage the UM epithelium [1, 3, 6, 9].

The present review is the evidence of a close interrelation between the development of erosive-ulcerous lesions of the gastro-duodenal zone and CKD progression. It is necessary to note that the progression of both pathologic processes is mutually dependent. On the one hand, H. pylori infection causes a number of systemic effects (an activation of LPO, pro-inflammatory cytokines, apoptosis; the secretion of biologically active substances that result in an enhancement of ischemia, tissue hypoxia, of affected organs and an activation of the thrombocytic component of homeostasis) that pathologically affect the kidneys and add to CKD progression. On the other hand, with kidney disease, especially with reduced renal function, COX-1 activation processes also reduce, thus leading to a decrease of the production of prostaglandins which are essential for sustaining both local and systemic hemodynamics in health and, in particular, they take part in the stomach protection from the factors of aggression (an enhancement of the mucus secretion, bicarbonate excretion, etc.).

Many problems concerning a study of a combined pathology of the stomach, duodenum and chronic kidney disease remain unstudied and disputable. For example, the question of a positive or negative PgE_2 effect in patients with a combined stomach and kidney pathology is actively discussed today. The question of the 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 reveal the presence of said H. pylori [16, 22].

Thus, the problem regarding a study of the mechanisms of mutually conditioned pathological disorders in patients with CKD and erosive-ulcerous stomach and duodenum lesions is exceptionally interesting, though insufficiently studied and requires further active research in this direction.

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МЕХАНИЗМЫ ПОРАЖЕНИЯ ЖЕЛУДКА У БОЛЬНЫХ С ХРОНИЧЕСКОЙ БОЛЕЗНЬЮ ПОЧЕК

В.В.Вивсянныk, Л.А.Зуб, Л.Д.Кушнир, Н.Р.Велигорская

Резюме. 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 –опосредоваными поражениями желудка и двенадцатиперстной кишки и прогрессированнием 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 индуцурованы 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.

МЕХАНІЗМИ УРАЖЕННЯ ШЛУНКА У ХВОРИХ НА ХРОНІЧНУ ХВОРОБУ НИРОК

В.В.Вівсянник, Л.О.Зуб, Л.Д.Кушнір, Н.Р.Велигорська

Резюме. У даній роботі подано сучасний стан проблеми щодо механізмів ураження шлунка у хворих на хронічну хворобу нирок (ХХН). Викладено сучасні погляди вчених нефрологів та гастроентерологів на взаємозв'язок між Helicobacter pylori (HP)-опосередкованими ураженнями шлунка та дванадцятипалої кишки та прогресуванням хронічної хвороби нирок. У роботі наведено різноманітні фактори ушкодження слизової оболонки шлунка та дванадцятипалої кишки у хворих на хронічну хворобу нирок: Helicobacter pylori, активація перекисного окиснення ліпідів та зниження активності процесів антиоксидантного захисту, порушення ліпідного обміну, анемію, порушення рівноваги факторів агресії та захисту слизової оболонки шлунка, порушення цитокінового балансу. Виділено фактори, що мають важливе значення в детермінації структурно-функціонального стану нирок і шлунка, а також у патогенезі розвитку нефропатій, що індуковані екстраренальними факторами (синдром системної відповіді та запальний процес у нирках). З наведеного огляду літератури видно, що існує тісний зв'язок між розвитком ерозивно-виразкових уражень гастродуоденальної ділянки та прогресуванням хронічної хвороби нирок.

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

Bukovinian State Medical University (Chernivtsi)

Рецензент – проф. О.І.Волошин

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