

***ОРИГІНАЛЬНІ СТАТТІ З КЛІНІЧНОЇ НЕФРОЛОГІЇ***

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УДК 617.16-004.3: 317.90-357.43-111

**IMPACT OF MUKOHEN ON DYNAMICS OF  
PROSTAGLANDIN E<sub>2</sub> IN PATIENTS WITH CHRONIC  
KIDNEY DISEASE STAGE II-III WITH THE PRESENCE  
OF LESIONS OF GASTROINTESTINAL TRACT**

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**SUMMARY. Introduction.** All processes in the stomach, which are under the influence of Hp, are systemic in nature and show a direct pathogenic effect on the kidneys in patients with chronic kidney disease (CKD). **The aim** was to study the dynamics of the systemic and local content of prostaglandin E<sub>2</sub> in patients with chronic kidney disease stage II and III, due to a long course of chronic recurrent pyelonephritis with the presence of erosive and ulcerative lesions of the stomach under the influence of mukohen. **Materials and Methods.** The study has involved 105 patients with CKD Stage II-III, due to a long course of chronic pyelonephritis with the presence of Hp-negative (and with the previous eradication of the pathogen) erosive and ulcerative lesions of the stomach (EULS) with preserved secretory function and patients with EULS without CKD. Patients with CKD were conducted examination and treatment according to clinical protocols of renal patients, were examined glomerular filtration rate (GFR) and daily level of proteinuria. The level of indicators PG E<sub>2</sub> was performed in serum, urine, gastric juice of patients and assessed by immunoenzymatic method. **Results and Discussion.** We proved the positive influence of mukohen, which manifests itself at the local (stomach, kidneys) and general (blood) levels. **Conclusions.** Pathological changes in combination of CKD stage II-III and EULS have interdependent progressive character. The positive effect of mukohen, which manifests itself on the local (stomach, kidneys)

and on a general (blood) levels can be successfully used in treatment of patients with CKD, combined with erosive lesions of the stomach.

**Key words:** chronic kidney disease, chronic pyelonephritis, prostaglandin E<sub>2</sub>, erosive and ulcerative lesions of the stomach, mukohen.

**Introduction.** Today it is known that prostaglandins (PG), including PgE<sub>2</sub>,PgI<sub>2</sub>, are able to contribute to the rehabilitation of damaged gastric mucosa (GM) that positively influence on the morphological changes, regression of rebuilding changes, the proliferative activity of epithelial cells and the depth of occurrence of Helicobacter pylori (HP) – simultaneously affect several elements of pathogenesis [1, 6, 7, 12, 13].

All processes in the stomach ,which are under the influence of Hp, are systemic in nature and show a direct pathogenic effect on the kidneys in patients with chronic kidney disease (CKD).

The damaging effects of aggressive systemic factors increase and cause acceleration of progression of CKD with the increasing degree of it. [4, 13].

The increase of the excretion of inflammatory mediators is observed in patients with CKD with the presence of erosive and ulcerative lesions of the stomach (EULS) – renal prostanoids (prostaglandins and thromboxanes), arachidonic acid, histamine, bradykinin and others. Some of them, especially PgE<sub>2</sub>, enhances mucus in GM and some other effects that are widely discussed in the literature and cause conflicting conclusions [1, 3, 7, 8, 16].

A respond of mucous membrane of renal pelvises and cups on pathogenic properties of microorganisms, as during colonization of gastric mucosa with Hp, are characterized by activation of proinflammatory cytokines of blood (precursor of arachidonic acid), macrophages (mast cells or labrocytes), lymphocytes, neutrophils and monocytes, which promotes the expression of inflammatory mediators -

renal prostanoids (prostaglandins including prostaglandin E2 and thromboxane), arachidonic acid [9, 14, 15].

Renal prostanoids (prostaglandins and thromboxanes) are involved in regulating renal hemodynamics, tubular transport of ions and renin secretion. In addition, they can be active participants as mediators of inflammation by the action of damaging factors (inflammatory substances, toxic changes at CKD) [2, 3, 4, 9].

Two forms of cyclooxygenase(COG)are expressed in the kidneys:

1. Structural (COG - 1).
2. Induced (COG - 2).

COG - 1 is synthesized in the body constantly under normal conditions and provides production of prostoglandin PgE<sub>2</sub>, Pg<sub>12</sub> that are improving the protective properties of gastric mucosa [7, 9].

COG - 2 is produced during the inflammation in the large quantities. It provides a synthesis of proinflammatory prostaglandins, causing its characteristic features – vasospasm of microcirculation, exudation in the inflammatory focus, pain and fever [5, 8, 9, 10].

Consequently, there is a close relationship between the development of erosive and ulcerative gastroduodenal lesions and progression of CKD. It should be noted that the progression of both pathological processes are interrelated, Hp infection causes a number of systemic effects (activation of proinflammatory cytokines, apoptosis, selection of biologically active substances that enhance ischemia, hypoxia of the affected tissue, activation of the hemostatic platelet level) that detect pathogenic effects on kidneys and progression of CKD. On the other hand, kidney disease, especially in reducing their function, are reduced the processes of COX-1 activation, resulting in reduced production of prostaglandins, which are important to support both local and systemic hemodynamics in normal and, in particular, take part in protecting the stomach from aggression factors (increased mucus, bicarbonate excretion, etc.). [5, 10, 13, 16].

**The aim** was to study the dynamics of the systemic and local content of prostaglandin E2 in patients with chronic kidney disease stage II and

III, due to a long course of chronic recurrent pyelonephritis with the presence erosive and ulcerative lesions of the stomach under the influence of mukohen.

**Materials and Methods.** The study has involved 105 patients with CKD Stage II-III, due to a long course of chronic pyelonephritis with the presence Hp-negative (and with the previous eradication of the pathogen) erosive and ulcerative lesions of the stomach with preserved secretory function and patients with EULS without CKD. Among the examined patients, there were 56 men and 49 women with the age from 27 to 60 years. There were also examined 20 healthy individuals of the similar age. The control group was consisted of patients with the presence of CKD II-III without EULS (29 people). Patients were divided into 2 groups: the first group was consisted of 39 patients with EULS and without CKD; II group - 37 patients with CKD stage II-III with the presence EULS before treatment. Patients were examined before the treatment and after 3 weeks of treatment with mukohen. Mukohen was taken by one tablet 3 times a day 30 minutes before the meal.

The clinical picture, radiological and endoscopic data, results histopathological study of biopsies of the gastric mucosa were taken into consideration during the verification of diagnosis EULS. Patients with CKD were conducted examination and treatment according to clinical protocols of renal patients, were examined glomerular filtration rate (GFR) and daily level of proteinuria.

The level of indicators PG E<sub>2</sub> was performed in serum, urine, gastric juice of patients and assessed by immunoenzymatic method using commercial test - kits (Kit) company "Assay Designs, Inc.", USA. The serum samples were centrifuged at 1500 rev. / min. for 10-15 minutes. Separated serum was taken and used in immunofluorescence analyzer ("Picon" number 01391409).

The data processed statistically using Student criterion. All indicators were presented as mean values from their mean error ( $M \pm m$ ). Significant was considered difference at  $p < 0.05$ .

**Results and Discussion.** As a result of the study it was revealed that in patients of the first group, decreased the levels of PgE<sub>2</sub> in serum ( $720,02 \pm 14,23$  pg / ml), which was credible compared with corresponding indicators in a group of healthy individuals (12.01 pg 1050.10 + / ml) ( $p < 0.05$ ) and control group ( $1028.33 + 11.04$  pg / ml).

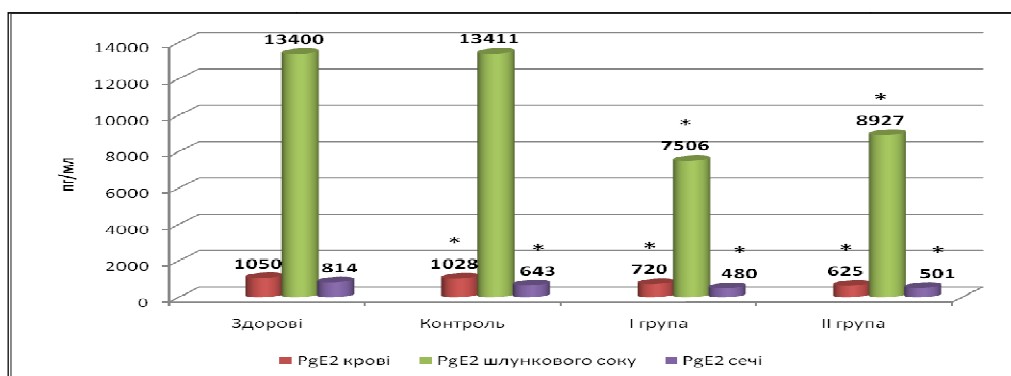
Dynamics of indicators of second group was similar and during its assessment it was discovered a credible reduction of PgE<sub>2</sub> in serum (respectively  $625.44 + 13.21$  pg / mL) compared with healthy indicators data ( $p < 0.05$ ) and control group ( $p < 0.05$ ) and patients of the first group ( $p < 0.05$ ). PgE<sub>2</sub> content in blood of patients of the control group did not differ from the norm ( $p > 0.05$ ). Due to the conducted treatment with inclusion of mukohen in patients of groups I and II, levels of PgE<sub>2</sub> in blood significantly increased in comparison with the corresponding data before treatment (I group -  $839.47 + 12.34$  pg / ml and group II -  $10.32$  pg  $898.04 +$  / ml), where in both cases ( $p < 0.05$ ).

In evaluating the indicators of PgE<sub>2</sub> in gastric juice was found it's probable decline in patients of I and II groups before treatment (respectively  $7506.13$  and  $8927.41 + 13.21 + 13.26$  pg / ml) ( $p < 0.05$ ) compared with norm and control (respectively  $13400,14 + 13,411.17 + 3.12$  and  $12.35$  pg / ml). This indicates that the local deficit of PgE<sub>2</sub> accompanies EULS can't be corrected without the use mukohen. As a result of a treatment was noted a significant increase of PgE<sub>2</sub> in gastric juice in I and II groups after 3 weeks of treatment ( $11,256.44 + 12,55$ ph / ml and  $11134,05 \pm 12,15$  pg / ml), which was credible compared with indicators of patients before treatment ( $p < 0.05$ ), but still far from the norm.

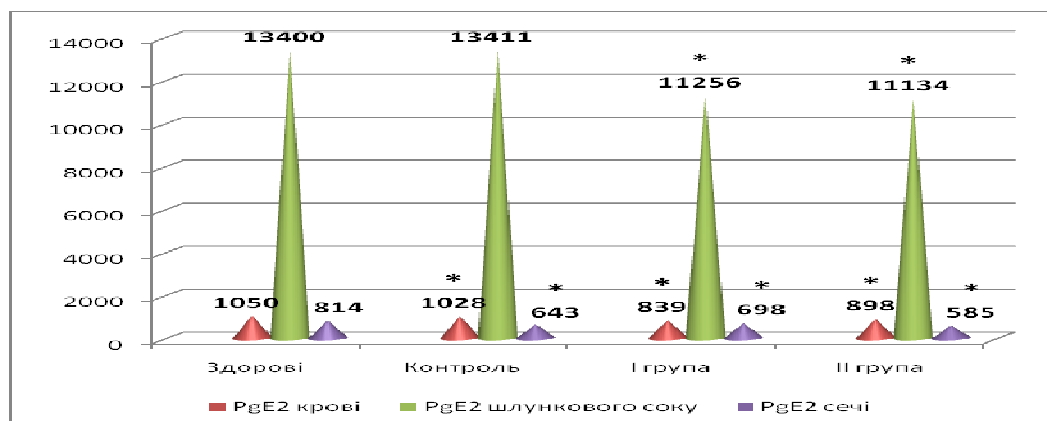
Results of the study of PgE<sub>2</sub> content in the urine of patients showed a possible decline of this indicator in patients of all groups (I group -  $480.19 + 12.38$ ; group II -  $13.51$  and  $501.16$ ; control group -  $643.41 + 13.22$  pg / mL) versus healthy ( $814,02 + 13.18$  pg / ml) ( $p < 0.05$ ). But it should be noted that after treatment with the inclusion of mukohen, PgE<sub>2</sub> content in the urine of patients increased (respectively in the above mentioned groups -  $698.14 + 12,11$ ph / ml;  $585,79 \pm 9,87$  pg /

ml and  $732,34 \pm 10,99$  pg / ml), which was credible compared to the relevant data of these groups of patients studied before adding mukohen treatment ( $p < 0.05$ ). In the studied patients of II group after 3 weeks of treatment were determined positive changes in the gastro-intestinal tract (from  $56,8 \pm 3.12$  ml / min.  $69,1 \pm 4$  to  $87$  ml / min.) as well as reducing the daily proteinuria ( from  $1.59 \pm 0.12$  to  $0.83 \pm 0.10$  ml / min.) ( $p < 0.05$ ). This demonstrates absence of negative impact of mukohen on renal function.

When conducting the study of linear correlations between the studied parameters was revealed a direct correlation dependence between the content of  $PgE_2$  in blood and GFR ( $r = 0,58$ ) ( $p < 0.05$ ), which proves that with decreasing of GFR due to progression of CKD, reduces production of local  $PgE_2$  by kidneys, which reduces its admission to the general bloodstream.



Pic.1. Dynamics of  $PgE_2$  of blood, urine and gastric juice in patients with CKD, combined with EULS before treatment.



Pic.2. Dynamics of  $PgE_2$  of blood, urine and gastric juice in patients with CKD, combined with EULS after three weeks of treatment with mukohen.

In addition, we found a direct correlation between the level of PgE<sub>2</sub> of gastric juice and PgE<sub>2</sub> of blood ( $r = 0,67$ ) ( $p < 0.05$ ). We revealed a strong inverse correlation dependence between indicators of PgE<sub>2</sub> of urine and daily proteinuria levels ( $r = -0,78$ ) ( $p < 0.05$ ). This proves that progressive kidney damage is accompanied by a shortage of general and local PgE<sub>2</sub>.

Therefore, the study of dynamics of PgE<sub>2</sub> content in blood, gastric juice and urine of patients showed that with the presence of EULS, content of local (in gastric juice) and general PgE<sub>2</sub> is significantly reduced. Lack of its content in the organism helps to maintain inflammation and worsens local regeneration. In patients with CKD stage II-III in our study was observed an expressed shortage of content of PgE<sub>2</sub> of urine and blood serum which also indicates the suppression of local recovery processes in kidneys and in the whole organism. In patients with chronic kidney disease II-III degree due to the presence of morphological (sclerosis) and functional disorders decreases a production of PgE<sub>2</sub> by kidneys. Consequently are compounded ischemic changes of kidney vessels, are supported the processes of inflammation, as described above, that is causing the progression of CKD.

In this way, pathological changes with combined CKD stage II-III and EULS have interdependent progressive character and contribute to deepening of pathological lesions in the stomach and in kidneys. Due to a strong positive effect of mukohen, as shown in our study, which appears on the local (stomach, kidneys) and on a general (blood) levels, due to entering of unchanged drug in into the bloodstream, it can be successfully used in treatment of patients with CKD, combined with erosive lesions of the stomach.

### **Conclusions**

1. In case of EULS, a content of local (in gastric juice) and general PgE<sub>2</sub> is significantly reduced.
2. In CKD patients stages II-III, is marked an expressed shortage of PgE<sub>2</sub> content in urine and blood serum.

3. Pathological changes in combination of CKD stage II-III and EULS have interdependent progressive character.
4. The positive effect of mukohen, which manifests itself on the local (stomach, kidneys) and on a general (blood) levels can be successfully used in treatment of patients with CKD, combined with erosive lesions of the stomach.

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РЕЗЮМЕ

**ВПЛИВ МУКОГЕНУ НА ДИНАМІКУ  
ПРОСТАГЛАНДИНУ E<sub>2</sub> У ХВОРИХ НА ХРОНІЧНУ  
ХВОРОБУ НИРОК II-III СТАДІЇ З НАЯВНІСТЮ  
УРАЖЕНЬ ШЛУНКОВО-КИШКОВОГО ТРАКТУ**

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*(Чернівці)*

**Вступ.** Всі процеси, що відбуваються у шлунку під впливом Нр мають системний характер та проявляють безпосередній патогенний вплив на нирки у хворих на хронічну хворобу нирок. **Мета.** Вивчити динаміку системного та локального вмісту простагландину E<sub>2</sub> у хворих на хронічну хворобу нирок II та III стадії, обумовлену тривалим перебігом хронічного рецидивуючого пієлонефриту з наявністю ерозивно-виразкових уражень шлунка під впливом мукогену. **Матеріал та методи.** Обстежено 105 хворих на ХХН II-III стадії, обумовлену тривалим перебігом хронічного пієлонефриту з наявністю Нр-негативних (та з попередньою ерадикацією цього збудника) ерозивно-виразкових уражень шлунка із збереженою секреторною функцією та хворих з ЕВУШ без ХХН. При верифікації діагнозу ЕВУШ враховувалася клінічна картина, рентгенологічні та ендоскопічні дані, результати патогістологічного дослідження біоптатів слизової оболонки шлунка. Пацієнтам з наявністю ХХН проводилося обстеження та лікування згідно клінічних протоколів нефрологічних хворих, обов'язково досліджували швидкість клубочкової фільтрації (ШКФ) та рівень добової протеїнурії. Рівень вмісту показників P<sub>g</sub>E<sub>2</sub> проводили у сироватці крові, сечі, шлунковому соці пацієнтів та оцінювали за допомогою імуноферментного методу. **Результати та їх обговорення.** Доведено позитивний вплив мукогену, який проявляється на місцевому (шлунок, нирки) та загальному (кров) рівнях. **Висновки.** Патологічні зміни при поєднанні ХХН II-III стадії та ЕВУШ мають взаємообумовлюючий прогресуючий

характер. Позитивна дія мукогену, яка проявляється на місцевому рівні (шлунок, нирки) і на загальному (кров) дозволяє з успіхом використовувати даний препарат при лікуванні хворих на ХХН, поєднану з ерозивними ураженнями шлунка.

**Ключові слова:** хронічна хвороба нирок, хронічний пієлонефрит, простагландин E<sub>2</sub>, ерозивно-виразкові ураження шлунка.

## РЕЗЮМЕ

### ВЛИЯНИЕ МУКОГЕНА НА ДИНАМИКУ ПРОСТАГЛАНДИНА E<sub>2</sub> У БОЛЬНЫХ ХРОНИЧЕСКОЙ БОЛЕЗНЬЮ ПОЧЕК II-III СТАДИИ С НАЛИЧИЕМ ПОРАЖЕНИЙ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА

*Зуб Л. О., Кушнир Л. Д., Вивсянник В. В., Дахно А. И.*

**Вступление.** Все процессы, которые осуществляются в желудке под влиянием Нр имеют системный характер и выявляют непосредственное патогенное влияние на почки у больных хронической болезнью почек. **Цель.** Изучить динамику системного и локального содержания простагландина E<sub>2</sub> у больных хронической болезнью почек II и III стадии, которая обусловлена длительным течением хронического рецидивирующего пиелонефрита с наличием эрозивно-язвенных поражений желудка под влиянием мукогена. **Материал и методы.** Обследовано 105 пациентов с ХБП II-III стадии, обусловленную длительным течением хронического рецидивирующего пиелонефрита с наличием Нр-негативных (и с предварительной эрадикацией этого возбудителя) эрозивно-язвенных поражений желудка с сохраненной секреторной функцией и больных с эрозивно-язвенными поражениями желудка без ХБП. Для верификации диагноза эрозивно-язвенных поражений желудка учитывали клиническую картину, рентгенологические и эндоскопические данные, результаты патогистологического исследования биоптатов слизистой оболочки желудка. Пациентам с наличием ХБП проводилось обслед-

дование и лечение согласно клинических протоколов нефрологических больных, обязательно исследовали скорость клубочковой фильтрации и уровень суточной протеинурии. Содержание P<sub>gE</sub><sub>2</sub> исследовали в сыворотке крови, мочи, желудочном соке пациентов и оценивали с помощью иммуноферментного метода. **Результаты и обсуждение.** Доказано положительное влияние мукогена, которое проявляется на местном (желудок, почки) и общем (кровь) уровнях. **Выводы.** Патологические изменения при сочетании ХБП II-III стадии и эрозивно-язвенных поражений желудка имеют взаимообуславливающий характер. Позитивное влияние мукогена, которое проявляется на местном уровне (желудок, почки) и на общем (кровь) дает возможность с успехом использовать данный препарат при лечении больных с ХБП, сочетанную с эрозивными поражениями желудка.

**Ключевые слова:** хроническая болезнь почек, хронический пиелонефрит, простагландин E<sub>2</sub>, эрозивно-язвенные поражения желудка.

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Ключові слова:  
Примітки:  
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Кількість збережень: 481  
Дата збереження: 24.06.2016 15:54:00  
Збережено: Т  
Повний час редагування: 11 228 хв  
Дата друку: 13.09.2016 11:15:00  
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