Diagnostic value of blood urea and bilirubin levels determination in patients with gastroduodenal zone diseases

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The study of relationships of urea and bilirubin blood levels in patients with Helicobacter pylori associated gastroduodenal pathology (HP-aGDP) has the considerable relevance for clinicians, since these indicators represent the status and function of the gastroduodenal zone. The aim of this study was to estimate changes of bilirubin and urea blood levels in patients with HP-aGDP before and after treatment.

Materials and methods. Our study has included 59 patients of the main group with different HP-aGDP and 44 patients of the control group with community-acquired pneumonia (CAP).

Results. In patients with HP-aGDP the doubly severe reduction of urea concentration was observed in significantly greater number of patients, while half of the patients in the controls had an increase of its level by 10.4 %. The bilirubin concentration decrease was more pronounced (37.1 % vs. 3.5 %) and significant (P < 0.05) in patients with HP-aGDP. Its rate depended on the dynamics of urea exactly in patients with HP-aGDP and it was more pronounced in case of urea reduction (P < 0.05). Thus, the revealed association of bilirubin and urea levels changes, namely their decrease owing to the treatment, was inherent only to patients with HP-aGDP unlike to the patients with CAD. We also determined the involvement of lipid, carbohydrate and protein metabolism, electrolytes, composition of blood in the processes of local and systemic inflammation caused by HP and its relationship with adaptive reactions, which generally depended on other individual characteristics of patients in the study group (age, duration of disease, ulcer size, etc.).

Conclusions. The monitoring of urea and bilirubin blood levels in patients especially with HP-aGDP during the eradication has a specific diagnostic and prognostic value. The bilirubin level in such cases reflects the severity of cholestasis, inflammatory lesions of the duodenal mucosa, comorbid hepatobiliary disease, while the urea level reduction may be an additional criterion of efficacy of HP eradication.
It is well-known that gastric and duodenal disorders associated with Helicobacter pylori (HP) infection may have an impact on the content of ammonia and urea not only in gastric juice, but also in blood through urease activity of this microorganism [1]. On the other hand, blood bilirubin level is an important indicator, which characterizes the pigment metabolism, the state of biliary system, the function of organs of gastrointestinal zone, the intensity and effectiveness of metabolism, the state of biliary system, the function of the pancreas [2,3]. Therefore, the determination of these parameters and further study the mutual influence or associations of bilirubin and urea in the blood in patients with HP-associated gastroduodenal pathology (HP-aGDP) is the considerable subject of interest for clinicians, resulting in expediency of our study.

**Purpose**

The aim of this study was to estimate changes of bilirubin and urea blood levels and other metabolic parameters and blood indices in patients with HP-aGDP before and after treatment.

**Materials and methods**

Overall, we have examined 103 patients with internal diseases. The main group included 59 patients with HP-aGDP with the average age of 32.2 ± 1.6 years. Mean disease duration was 2.9 ± 0.53 years. Gastric or duodenal ulcer was diagnosed in 54 % of patients (the average ulcer size was 0.58 ± 0.05 cm); other participants had chronic gastroduodenitis (14 %), duodenitis (12 %), gastritis (5 %), non-ulcer dyspepsia (7 %) and gastroesophageal reflux disease (8 %). According to recommendations in the 4th edition of the Maaschtricht Consensus Report all patients underwent eradication antibiotic therapy. The control group included 44 patients with community-acquired pneumonia (CAP) with the average age of 23.8 ± 1.7 years, treated with etiotic antibiotic therapy (aminopenicillins and/or macrolides). Consequently, we compared changes in the concentration of bilirubin and blood urea in similar conditions (infectious nature of the disease, syndromes of local and systemic inflammation, and the use of similar groups of antibiotics). The study did not include people with liver or kidney dysfunction and changes in the parameters of nitrogen metabolism.

Total bilirubin count and its fractions in the serum was examined by colorimetric dazio method (normal 8.5–20.5 mcmol/L), urea – by enzymatic method (normal 2.5–8.3 mcmol/L). Patients were divided into three groups by the level of urea: up to 5.0 mmol/L (I); 5.0–5.4 mmol/L (II); 5.5 mmol/L or more (III). Results were processed by mathematical statistics, the level of significance was set to P < 0.05, the degree of linear correlation assessed using Pearson’s correlation coefficient (r).

**Results and discussion**

We have found and analysed significant correlation between the studied biochemical and blood parameters in patients with HP-aGDP in order to obtain an overall characteristic of the main group. The persistent correlation of patients’ age of the study group and duration of disease proved to be obvious (r = 0.475). Increased levels of triglycerides (r = 0.387) and cholesterol of very low density lipoprotein (r = 0.387) and greater erythrocyte sedimentation rate (r = 0.378) and the increased number of eosinophils (r = 0.356) were often detected in older patients, what can generally display different aspects and severity of both local and systemic inflammation.

Direct correlation between urea and cholesterol (r = 0.373), cholesterol of very low density lipoprotein (r = 0.399), which have been determined, may also be an evidence of lipid metabolism involvement in the processes of systemic inflammation, particularly due to HP. In return, our data show that the increase of creatinine level was associated with higher levels of high density lipoprotein cholesterol (r = 0.316). An interesting fact was a positive association of the urea level with disease duration (r = 0.394), which may indirectly indicate a greater prevalence of HP-infection in patients with long course of HP-aGDP. Direct correlation of the urea level (r = 0.328), blood creatinine (r = 0.308) with glucose levels may be associated with older age of patients, comorbid pathology or pathophysiological changes in the function of pancreas.
Inverse correlation of the urea concentration ($r = -0.366$) and creatinine ($r = -0.437$) with the number of white blood cells may indicate the peculiarities of leukocyte reactivity in the processes of local and systemic inflammation caused by HP. Also, urea concentration significantly positively correlated with concentrations of potassium and sodium ($r = 0.363; r = 0.425$) that can generally illustrate changes of electrolyte balance in patients with HP-aGDP. Increased potassium in blood serum may reflect the degree of tissue damage as a result or directly during inflammation or renin-angiotensin system activity reduction, and increased sodium level is often caused by loss of water containing little salt, resulting from vomiting with varying degrees of severity – a major specific symptom in patients with HP-aGDP.

A significant correlation between bilirubin and total blood protein levels ($r = 0.521$) can be complex reflection of liver function. Positive correlation between bilirubin concentration and the age of patients looks natural ($r = 0.539$), which indicates age-related changes of the liver function. Relationship between bilirubin level and blood monocyte count ($r = 0.369$) shows one of the parts of its production, namely, the conversion of heme into biliverdin involving macrophages.

According to many studies [4, 5] it is known that free bilirubin has marked antioxidant properties due to its ability to prevent lipid peroxidation of cell membranes and membrane protein oxidation, showing particular tropism for nerve tissue and heart muscle. Thus, according to the findings of M. K. Akboga, U. Canpolat, A. Sahinarslan et al. in 2015, serum bilirubin has significant inverse correlation with specific and non-specific markers of systemic inflammation such as C-reactive protein, a neutrophil and lymphocyte ratio (NLR) etc. allowing us to consider its concentration as a predictor to prevent the development of atherosclerosis, ischemic heart disease, systemic inflammation. Our study can illustrate these properties of free bilirubin as inverse correlation of its level with segmented neutrophil count ($r = -0.358$) and direct one with lymphocyte count. The direct significant correlation of bilirubin concentration with adaptation index ($r = 0.326$) and the frequency of favourable adaptive reactions ($r = 0.339$) seems quite logical and natural taking into account its antioxidant and anti-inflammatory properties. This also may explain the inverse relationship of bilirubin level and the size of ulcer ($r = -0.562$), which we have defined, that is especially marked after eradication.

Significant correlations were most frequently diagnosed between the size of ulcer and other indicators. Thus, the presence and extent of HP-associated lesions of gastric or duodenal mucosa were inversely correlated with the age of patients ($r = -0.371$) and directly correlated with the frequency of antibiotic therapy ($r = 0.528$), i.e. mucosal ulceration in our study was more often encountered in younger patients, which implies greater frequency of prescribed eradication therapy. Also, increased degree of lesion, more severe medical conditions were associated with an increase in blood glucose ($r = 0.325$), which may also be associated with older age of patients that was also positively correlated with blood glucose level ($r = 0.329$) or metabolic syndrome manifestations. Increased ulcers size was significantly associated with a decrease in total protein ($r = -0.587$), probably as a manifestation of associated protein-producing liver function disorder (Fig. 1).

Larger defects in patients with HP-aGDP also had significant inverse correlation with hemoglobin and erythrocyte count ($r = -0.623; r = -0.624$) due to greater frequency of current or previous haemorrhagic complications. Significant erythrocyte sedimentation rate increase in patients with larger ulcers ($r = 0.539$) turned out to be logical due to greater severity of inflammation, which is probably also related to a significant increase in segmented neutrophil count ($r = 0.717$). Instead, increasing ulcer severity leads to significant reduction in lymphocyte count and adaptation index ($r = -0.490; r = -0.548$), which is clearly associated with increasing frequency of adverse adaptive reactions ($r = -0.589$). In our opinion, inverse significant correlation of the degree and size of ulceration of gastric and duodenal mucosa with blood monocyte count after eradication ($r = -0.611$) is important, because low levels of the latter may be indirect evidence of regenerative processes failure and healing of ulcerative lesion caused by HP [6].

Then we used different ways to actually analyse and compare the dynamics of urea and blood bilirubin concentrations over time following the treatment in patients with HP-aGDP and CAP.

Differences in the frequency of different levels of blood urea were observed both before and after treatment in the main and control groups. Before treatment (Fig. 2) by the level of urea was most often determined as ≥5.5 mmol/L (42.4 ± 6 %) in patients with HP-aGDP, while patients in the control group before treatment often referred to the I subgroup by the level of urea (45.5 ± 8 %).

The amount of urea of 5.0–5.4 mmol/L was diagnosed significantly less frequently before treatment both in the study and control groups (P < 0.05) (Fig. 2). It should be noted that after treatment the number of patients in the I subgroup in terms of urea was significantly lower in the controls compared with the rate in the I and III subgroups (P < 0.05).

The frequency of urea different levels after treatment differed in the study and control groups. One of the similarities was that the number of patients in the I subgroup increased both in the main and the control groups (7.6 % and 6.9 %). The rate of urea concentration of 5.0–5.4 mmol/L increased slightly in the study group, but it decreased in the controls by 6.9 %. The main difference was that urea concentration of ≥5.5 mmol/L was detected 1.3 times less in patients of
the main group than it was before treatment, while the rate remained unchanged in the III subgroup of the controls (Fig. 2). Thus, in contrast to the control group, the rate of urea concentration of ≥5.5 mmol/L decreased after treatment in patients with HP-aGDP, and the number of patients in the II subgroup remained almost unchanged, which may be indirect evidence of greater severity and intensity of blood urea concentration reduction than in patients with CAP.

The mean level of urea decreased by 3.3 % in the main group (by 0.18 mmol/L) and its decrease was twice as little in the controls (by 0.09 mmol/L). Generally, the number of patients in the study group, whose level of urea decreased as a result of the treatment, was significantly greater compared with patients, whose level increased: its level decreased on an average of 0.46 mmol/L in 67 % of the main group patients (P < 0.05), and it slightly increased by 0.64 mmol/L in the rest (33 %). In contrast to the above mentioned, mean urea concentration decreased slightly (by 1.8 %) only in half of the patients (52.3 %) in the control group, while in 47.7 % of patients with CAP its level increased by 10.4 % (by 0.97 mmol/L), apart from that the changes were insignificant. Thus, reduction of urea in patients with HP-aGDP after treatment was more specific, marked and significant compared to the control group.

Assessing changes in the mean concentrations of blood bilirubin in patients with HP-aGDP and controls in the settings of different dynamics of urea due to treatment, it should be noted that they all occurred within the physiological norm. Initial median bilirubin concentration in the study group patients was 15.03 mcmol/L, and after treatment it was 11.60 mcmol/L. Mean level of bilirubin was determined as 9.04 mcmol/L before treatment and 8.40 mcmol/L after treatment in controls.

Blood bilirubin decreased after treatment in both main and control groups, but this process largely depended on nosology. Bilirubin decreased significantly in HP-aGDP patients by 23.1 % (by 3.44 mcmol/L) compared with the initial level, whereas in the control group its decline was 3.2 times smaller (only by 7.2 %) and insignificant.

The analysis of changes in the level of bilirubin in patients of the study and control groups with regard to dynamics (increase or decrease) in the urea level proved to be of greater interest (Fig. 3). Mean level of blood bilirubin decreased significantly by 37.1 % (6.06 mcmol/L) in the main group compared to its initial level specifically in patients with decrease of urea (P < 0.05), whereas it remained almost unchanged in those with increased levels of urea (Fig. 3). Moreover, the percentage of bilirubin reduction in HP-aGDP patients in the settings of urea reduction was significantly greater than in patients with an increase in its' concentration (P < 0.05). This reported information may indicate a direct dependence of the bilirubin reduction intensity on the dynamics in the level of blood urea, namely, on its reduction in HP-aGDP patients after eradication.

Instead, in contrast to our results in the main group, other changes in blood bilirubin occurred in patients with CAP depending on the dynamics of urea (Fig. 3). Bilirubin just slightly decreased by 3.5 % (by 0.30 mcmol/L; P > 0.05) in the settings of decreasing level of urea, while bilirubin levels decreased by 10.4 % (to 0.97 mcmol/L; P < 0.05) when urea concentration increased. Therefore, the level of bilirubin in patients with CAP did not depend on the dynamics of blood urea, and its concentration decreased significantly in the settings of the urea level reduction in the main group of patients.

An interesting and indicative was the fact that the reduction in bilirubin level was associated with a decrease in the concentration of urea after treatment in patients with HP-aGDP, however when it increased the changes in bilirubin level either did not occur or they were minor and insignificant.

It seems that the revealed dependence of bilirubin level decrease intensity on the dynamics in urea concentration in the study group of patients is quite natural. It is obvious that the decrease of bilirubin in patients with HP-aGDP is caused by a decrease in the severity of duodenal mucosa inflammation, its swelling, improved function and, as a result improved passage of bile due to performed HP eradication [7]. Thus, changes in urea and bilirubin concentrations can characterize the degree of impairment of function or reparative processes in gastroduodenal region, despite the fact that these parameters indicate different aspects of metabolic disorders.

According to the data of various authors the level of urea both in gastric juice and serum is associated with the activity and prevalence of HP-infection, and hence with the degree
Влияние уровня мочевины на гепатобилиарную систему при гастродуоденальной патологии.

В исследованиях было показано, что уровень мочевины в крови может быть индикатором активности хронического гепатитов и заболеваний дуоденальной непроходимости [1]. Уровень мочевины в крови также является маркером инфекции Helicobacter pylori и может быть использован в качестве прогностического показателя [2].

Конечно, как контрольная группа, динамика уровня мочевины в пациентов с гастроудоденальной патологией может быть иллюстрирована негативным значением и функциональным состоянием HP-инфекции и эффективности ее устранения, а уровень билирубина может служить показателем реакции гепатобилиарной системы и инфекционной активности дуоденальной непроходимости их динамики.


Conclusions

1. Dynamics of changes in blood urea level in patients with HP-associated gastroduodenal pathology and patients with community acquired pneumonia differed significantly: reduction of urea concentration was observed in significantly greater number of the study group patients, while half of the patients in the control group had an increase of its level by 10.4 %.

2. Bilirubin concentration in the blood decreased both in the study and control groups after treatment, but only after HP eradication its reduction was more marked (37.1 % vs. 3.5 %) and significant (P < 0.05).

3. The intensity of bilirubin decrease in the blood of patients with HP-associated gastroduodenal diseases depended on the dynamics of urea and it was more marked in the settings of its’ reduction (P < 0.05). Changes in bilirubin level did not depend much on the dynamics of the urea concentration in patients with infectious pneumonia being minor, insignificant and having the opposite direction.

4. Association of bilirubin and urea levels changes was inherent only to patients with HP-associated disorders, indicating the involvement of nitrogen metabolism and liver function in the pathogenesis of given nosology, so monitoring these parameters in patients, especially in the main group, during the eradication has a specific diagnostic and prognostic value.

5. The level of bilirubin in the blood of patients with HP-associated gastroduodenal pathology can reflect the severity of cholestasis, inflammatory lesions of the duodenal mucosa, comorbid hepatobiliary disease.

6. In addition to the above mentioned, we also determined the involvement of lipid, carbohydrate and protein metabolism, electrolytes, composition and function of blood in the processes of local and systemic inflammation caused by HP and its relationship with adaptive reactions, which generally depended on other individual characteristics of patients in the study group (age, duration of disease, ulcer size, etc.).

It is perspective to examine changes in other metabolic factors in the settings of different dynamics of urea and bilirubin in the blood of patients with HP-associated gastroduodenal pathology for further study of the characteristics of inflammation caused by HP.

References


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