Chapter 2

PROGNOSTICATING ALTERATIONS IN LIVER FUNCTION INDICATORS AND ASSESSING THE EFFICACY OF COMBINED THERAPY IN INDIVIDUALS WITH STABLE ANGINA PECTORIS ACCOMPANIED BY NON-ALCOHOLIC FATTY LIVER DISEASE

Karpyshyn N. V.

DOI https://doi.org/10.30525/978-9934-26-430-6-2

INTRODUCTION

Cardiovascular disease stands as the primary concern within morbidity statistics, frequently impacting individuals in their prime working years. Within this category, Coronary Heart Disease (CHD) holds the top position as the leading cause of mortality globally[1]. One-third of patients experience the onset of CHD alongside excess body weight or obesity, exacerbating the progression of the condition, deteriorating prognosis, and fostering complications. This association intertwines with conditions such as non-alcoholic fatty liver disease (NAFLD), arterial hypertension, dyslipoproteinemia, insulin resistance, hyperinsulinemia, and diabetes[2,3].

In individuals diagnosed with CHD, the presence of NAFLD significantly increases the manifestations of ischemia, the frequency of ventricular rhythm disturbances, deteriorates markers of autonomic regulation in cardiac function, and impedes their improvement over time[4]. NAFLD is currently a growing clinical and epidemiological problem worldwide. Its prevalence is 24%, 30% and 32% in Europe, America and the Middle East, respectively,

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and correlates with the level of development in a particular society, but worldwide the problem increasingly affects different age and social groups[5,6]. According to the data of various studies, NAFLD was recognized as a risk factor for the development of cardiovascular diseases. Currently, there are no evidence-based drugs recommended for the treatment of NAFLD, underscoring a significant clinical demand for further research in this field. Nevertheless, within clinical practice, pharmacotherapy targeting heightened cardiovascular risk often employs medications aimed at addressing obesity, diabetes, and hypolipidemic agents[7].

Statins are powerful cholesterol-lowering agents and drugs proven to reduce the risk of adverse or life-threatening cardiovascular events. Their effectiveness due to lowering the cholesterol level will also be favorable for NAFLD, which is characterized by the aggregation of free cholesterol in hepatocytes[8]. Besides, statins offer a spectrum of lipid-independent pleiotropic advantages, encompassing antioxidant, antithrombotic, antifibrotic, and anti-inflammatory properties, alongside enhancing endothelial function. In addition to a protective role against atherothrombosis, these effects may also play a significant role in the prevention and treatment of NAFLD[9].

In the current treatment approach for patients managing stable angina pectoris alongside NAFLD, when prescribing statins, a key consideration for liver function is assessing liver transaminase levels. A three-fold elevation in transaminase levels warrants a reduction in recommended doses of HMG-CoA reductase inhibitors. Given that liver damage constitutes one of the pathogenic factors in this synergy, a potential solution involves combining statin therapy with hepatoprotective agents. In this regard, the combination of statins and ursodeoxycholic acid (UDCA) emerges as a promising approach. Only a few studies have demonstrated the correcting effect of UDCA on the blood lipid profile due to the hepatoprotective properties, when administered alongside low therapeutic doses of statins in patients with stable angina

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pectoris coupled with NAFLD. Notably, this approach does not necessitate an increase in statin dosage[10]. According to the results of another study, two years of UDCA treatment effectively reduced liver dysfunction in patients with NAFLD[11], and a high dose of UDCA lowered the level of alanine aminotransferase (ALT) in patients with non-alcoholic steatohepatitis, which indicates multiple hepatoprotective effects of the drug[12]. UDCA effectively improves liver function by regulating bile acids, metabolism and appropriate remodeling of the microbiome, as well as an antioxidant effect similar to that of vitamin E[13]. Nevertheless, despite numerous investigations, the efficacy of UDCA in patients with NAFLD remains controversial and not thoroughly explored[14,15]. Therefore, further investigation of combined statin and UDCA therapy in patients with cardiovascular disease and NAFLD is important.

1. Research methodology and dynamic analysis of the obtained results

The study included patients with stable angina pectoris and accompanying non-alcoholic fatty liver disease, in whom, according to the results of the ^{13}C-methacetin breath test, an impairment in the liver function was observed.

In all patients, anamnestic data and complaints were collected, followed by a comprehensive examination encompassing determination of anthropometric parameters, monitoring of clinical symptoms over time, echocardiography, ultrasonography of internal organs, and biochemical blood tests to assess lipid profile, liver function, and ^{13}C-methacetin breath test before and after the initiation of combined therapy.

The diagnosis of stable angina pectoris was confirmed based on the findings of a previously conducted coronary angiography or a positive result from a treadmill exercise test. Diagnosis of fatty liver infiltration involved identifying characteristic features such as diffuse homogeneous increase in liver echogenicity, enlargement of liver size on ultrasound, presence of a distal

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shadowing effect, and an augmented diameter of the portal vein. Assessment of the functional status of hepatocyte microsomal enzyme systems was conducted through the ^{13}C-metacetin breath test. This test involved the ingestion of 75 g of metacetin labeled with the non-radioactive carbon isotope ^{13}C, followed by analysis of breath samples.

All patients received a combined therapy regimen consisting of 20 mg of atorvastatin once daily and UDCA at a dosage of 15 μg/kg/day divided into three doses for a month.

Subsequent assessment of the treatment efficacy in patients with stable angina pectoris and non-alcoholic fatty liver disease was based on the analysis of clinical indicators, biochemical parameters, and the results of the ^{13}C-methacetin breath test.

Totally 20 patients were examined, with men comprising 60% (12 patients) and women 40% (8 patients). The average age was 55.60±2.60 years, and the average duration of the illness was 4.80±0.80 years.

Anthropometric indicators were determined for all patients: BMI of the patients constituted on average 32.78±0.91 kg/m^2, waist circumference 103.28±2.53 cm, hip circumference 101.20±2.08 cm, WC/HC ratio 1.02±0.02 (Table 1).

Table 1

Anthropometric data, age and illness duration of patients who received combined therapy

Indices, units of measurement	Patients receiving combined therapy, n=20
BMI, kg/m^2	31.40±0.69
WC, cm	104.32±1.14
HC, cm	98.27±1.40
WC/HC	1.06±0.01
Age, years	55.60±2.60
Duration of illness, years	4.80±0.79

Note: BMI – body mass index; WC – waist circumference; HC – hip circumference; n – the number of patients in the group

Upon analysis of clinical symptoms in the patients, prevalent cardiovascular complaints included pain behind the sternum or discomfort in the heart area, shortness of breath during physical exertion, palpitations, and leg swelling. Auscultation revealed the accentuation of the II tone over the aorta and murmurs over the carotid arteries, with xanthomas detected in some patients. Additionally, half of the patients were diagnosed with a concurrent condition of stable angina pectoris and arterial hypertension. Following the administration of combined therapy, improvement in overall condition and reduction of clinical symptoms were observed in certain patients (Table 2).

Table 2

The frequency of clinical signs in patients with combined pathology before and after the administration of combined therapy

Clinical signs	Before applying combined therapy n=20		After applying combined therapy n=20	
	abs.	%	abs.	%
pain behind the sternum	14	70.00	13	65.00
palpitations	8	40.00	7	35.00
shortness of breath during physical exertion	9	45.00	8	40.00
leg swelling	11	55.00	7	35.00
accentuation of the II tone over the aorta	8	40.00	8	40.00
murmurs over the carotid arteries	6	30.00	5	25.00
xanthomas	4	20.00	5	25.00

Notes: abs. – absolute number of patients;% – percentage of the total number of patients; n – the number of patients in the group.

Following the implementation of combined therapy, an enhancement in the overall condition of patients was observed. This was evidenced by a reduction in general weakness and fatigue, alleviation of gastrointestinal symptoms, notably the disappearance or attenuation of pain or discomfort in the right hypochondrium, diminished abdominal bloating, nausea, and bitterness in the mouth. However, there was minimal reduction in liver size after one month of treatment (Table 3).

Table 3

Characteristics of clinical manifestations of NAFLD in patients with stable angina before and after administration of combined therapy

Clinical signs	Before applying combined therapy n=20		After applying combined therapy n=20	
	abs.	%	abs.	%
general weakness	16	80.00	6	30.00
fatigue	15	75.00	6	30.00
discomfort in the right hypochondrium	17	85.00	7	35.00
pain syndrome	13	65.00	5	25.00
abdominal bloating	18	90.00	6	30.00
nausea	12	60.00	4	20.00
bitterness in the mouth	16	80.00	7	35.00
reduction in liver size	18	90.00	16	80.00

Notes: abs. – absolute number of patients;% – percentage of the total number of patients; n – the number of patients in the group

2. Analysis of indicators of the liver function in patients with combined pathology after administration of combined therapy

The calculation of mathematical coefficients to assess the outcomes of the ^{13}C-methacetin breath test unveiled favorable alterations in liver function among patients with stable angina pectoris and NAFLD following the application of combined therapy comprising atorvastatin and UDCA.

Based on mathematical analysis, prior to the prescribed treatment, the hepatic metabolic rate (MR) stood at 0.59±0.03, indicative of a moderate decline in liver detoxification function with non-cirrhotic alterations, characterized by a mass of functioning hepatocytes ranging from 50% to 100%. This was confirmed by the coefficient of cumulative liver dose at 40 minutes (CD40), which equaled 0.61±0.04. Furthermore, even lower readings were noted in the ^{13}C-methacetin breath test for the cumulative liver dose at 120 minutes (CD120), with a coefficient of 0.49±0.04 prior to commencing combined therapy, signifying a marked reduction in liver detoxification function and a decrease in the mass of functioning hepatocytes to 20-50%.

After the treatment, according to the analysis of mathematical coefficients, the MR increased to 0.79±0.06, and the CD40 increased to 0.80±0.05, which corresponded to the normal detoxification function of the liver. Following the administration of combined therapy, the CD120 also exhibited improvement, evident in its coefficient rising to 0.63±0.04, indicating a moderate decline in liver detoxification function with a level of functioning hepatocytes ranging from 50% to 100% (Table 4).

Table 4

Data of the mathematical calculation of the ^{13}C-methacetin breath test in patients with combined pathology before and after administration of combined therapy

Parameters of ^{13}CMBT	Before combined therapy n=20	After combined therapy n=20	Validity of the difference, p
MR	0.59±0.03	0.79±0.06	<0.01
CD40	0.61±0.04	0.80±0.05	<0.01
CD120	0.49±0.04	0.63±0.04	<0.01

Notes: p<0.05; MR – liver metabolism rate; CD40 – cumulative dose at 40 minutes; CD120 – cumulative dose at 120 minutes; n – number of patients in the group.

An analysis of correlation relationships among indicators of the ^{13}C-methacetin breath test, lipid blood profile, BMI, and levels of liver transaminases in patients with combined pathology prior to the application of combined therapy revealed a direct correlation between MR and CD40 (r=0.75), MR and CD120 (r=0.72), as well as CD40 and CD120 (r=0.62). An inverse correlation was found between the level of TG and HDL (r=-0.72),

while a direct correlation was observed between TC and LDL (r=0.90), as well as between ALT and AST (r=0.59) (Table 5).

Table 5

Significant correlations between the parameters of the ^{13}C-methacetin breath test, the blood lipid spectrum and the level of liver transaminases in patients with combined pathology before the use of combined therapy

I group n=20	Indices	r (by Pearson)
	MR – CD40	0.75*
	MR – CD120	0.72*
	CD40 – CD120	0.62*
	TC – LDL	0.90*
	TG – HDL	-0.72*
	ALT – AST	0.59*

Notes: * – p<0.05; MR – liver metabolism rate; CD40 – cumulative dose at 40 minutes; CD120 – cumulative dose at 120 minutes; TC – total cholesterol; LDL – low-density lipoproteins; HDL – high-density lipoproteins; TG – triglycerides; ALT – alanine aminotransferase; AST – aspartate aminotransferase; n – number of patients in the group.

Similar changes were observed in the study of correlation relationships after the application of combined therapy, where a direct correlation was also found between MR and CD40 (r=0.80), MR and CD120 (r=0.77), CD40 and CD120 (r=0.78). Besides, a positive correlation was also observed between TC and LDL (r=0.94) and between the levels of ALT and AST (r=0.61). An inverse correlation was tracked between TG and HDL (r=-0.54) (Table 6).

Table 6

Following the implementation of combined therapy, significant correlations emerged among parameters of the ^{13}C-methacetin breath test, blood lipid profile, and liver transaminase levels in patients with comorbidities

I group n=20	Indices	r (by Pearson)
	MR – CD40	0.80*
	MR – CD120	0.77*
	CD40 – CD120	0.78*
	TC – LDL	0.94*
	HDL – TG	-0.54*
	ALT – AST	0.61*

Notes: * – p<0.05; MR – liver metabolic rate; CD40 – cumulative dose per 40 minutes; CD120 – cumulative dose per 120 minutes; TC – total cholesterol; LDL – low-density lipoproteins; HDL – high-density lipoproteins; ALT – alanine aminotransferase; AST – aspartate aminotransferase; TG – triglycerides; n – the number of patients in the group.

3. Prognosticating alterations in liver function indicators among patients with combined pathology following combined therapy

The subsequent phase of the research focused on prognosticating changes in liver function indicators (metabolic rate, cumulative doses at 40 and 120 minutes), as well as ALT and AST levels, in patients with combined pathology after receiving statin therapy combined with UDCA.

To solve this problem, the multiple regression method was applied, which was used for each individual indicator.

According to literature data and personal observations, 15 factors were selected that could affect the analyzed indicators after taking UDCA. Using these indicators, a method was subsequently employed to incorporate reliable factors into the prognostic model for the studied parameters. This model aims to predict the combined effect of these factors on the outcome.

This study concluded that it is feasible to forecast MR following combined therapy using equation (1), wherein all factor characteristics are provided prior to the commencement of combined therapy:

$$MR\ (\%^{13}C/h) = 45.433 + 0.002*A + 1.442*B - 4.353*C - 1.052*D - 0.436*E \quad (1)$$

where: A – MR ($\%^{13}C/h$),

B – CD40 ($\%^{13}C$),

C – LDL, mmol/l,

D – TG, mmol/l,

E – BMI

It has been established that having information about the five above-mentioned indicators before the commencement of complex therapy, we can prognosticate MR after its course. Among them, two factors (MR and CD40) have a directly proportional effect on MR, and three factors have an inversely proportional effect (LDL, TG, BMI).

For a better understanding, a clinical example is presented: patient K. (before complex therapy had the following indicators: MR – 14.30%$^{13}C/h$; CD40 – 8.60%^{13}C; LDL – 3.92mmol/l; TG – 1.53mmol/ l; BMI – 37.9. Substituting the given data into the equation (1), we get:

$$MR = 45.433 + 0.002*14.30 + 1.442*8.60 - 4.353*3.92 - 1.052 * 1.53 - 0.436*37.9 = 22.7\%^{13}C/h$$

This patient was prescribed atorvastatin and UDCA, and the post-treatment MR level was 23.0 ($\%^{13}C/h$), which differed by 0.3 ($\%^{13}C/h$) or 1.3% from our predicted index, thus confirming predictive value of our model.

The resulting model (1) is defined by the following parameters: its Fisher criterion is 6.05 at $p = 0.004$. The multiple correlation coefficient value of 0.62 suggests that 38% of the prediction of MR following complex therapy is influenced by other features not encompassed in the regression model.

Prediction of CD40 (%^{13}C) after combined therapy is possible with the help of equation (2), in which all factor characteristics are also given prior this treatment:

40 min = 26.907+ 0.476*A -0.042*B +0.005*C -
-3.896*D -1.294 *E-0.028*F -5.293*G +
+ 1.498*H-0.024*I (2)

where: A – CD40 (%^{13}C)
B – TC, mmol/l
C – HDL, mmol/l
D – LDL, mmol/l
E – TG, mmol/l
F – ALT, mmol/l
G – AST, mmol/l
H – gender (males – 1, females – 2)
I – BMI

With data on the aforementioned nine indicators before treatment, we can predict the CD40 value after treatment. Among them, six factors exhibit an inverse relationship with C40 (TC, LDL, TG, ALT, AST, BMI), while two factors have a direct relationship (CD40 and HDL); the patient's gender is also factored into the equation.

Clinical example: the male patient K. had the following parameters before therapy: CD40 – 9.20 (%^{13}C), TC – 6.11 mmol/l, HDL – 1.18 mmol/l, LDL – 4.03 mmol/l, TG – 1.98 mmol/l, ALT – 0.66 mmol/l, AST – 0.48 mmol/l, BMI – 28.1. Substituting the given data into equation (2), the result was 11.03 (%^{13}C). The patient was prescribed UDCA together with atorvastatin, and the CD40 level after treatment was 11.30 (%^{13}C), which differed by 0.27 (%^{13}C) or 2.3% from our predicted value, thus proving the good prognostic value of our model.

The CD40 prediction model (2) derived from the data is described by the following parameters: its Fisher criterion is 7.02 at p = 0.003. The multiple correlation coefficient value of 0.86 suggests that 14% of the prediction of CD40 after combined therapy is influenced by other features not encompassed in the regression model.

This research also shows the possibility of predicting the value of CD120 (%^{13}C) after treatment with atorvastatin and UDCA using equation (3), in which all factor characteristics are also given prior receiving complex therapy:

CD120 = 28.605+ 0.532*A – 0.837*B -15.496*C – 0.703*D (3)

where: A – CD120 (%^{13}C)
B – TG, mmol/l
C – AST, mmol/l
D – portal vein diameter (mm)

In this scenario, the CD120 indicator after intake of atorvastatin and UDCA is directly related to the corresponding pre-treatment indicator and inversely related to the levels of TG, AST, and the portal vein diameter.

The prognostic significance of the established model is illustrated in the following clinical example: Patient M. exhibited the following indicators prior to combined treatment: CD120 14.90 (%^{13}C), TG 3.46 mmol/l, AST 0.32 mmol/l, portal vein diameter 15.0 mm. By substituting these values into equation (3), the result is 18.13 (%^{13}C).

The patient was prescribed UDCA in combination with atorvastatin. Following the comprehensive treatment, the CD120 level measured 17.90 (%^{13}C), deviating by 0.23 (%^{13}C) or 1.3% from our projected value, further validating the prognostic efficacy of the developed model.

The derived CD120 prediction model (3) is characterized by the following parameters: its Fisher criterion is 5.82 at p = 0.005. The multiple correlation coefficient value of 0.61 suggests that 39% of the prediction of CD120 following combined therapy is influenced by other features not encompassed in the regression model.

Models for predicting ALT and AST in patients after complex treatment have also been developed. The regression model for ALT prediction (4) is represented by the following formula:

$$ALT = 0.645-0.022*A + 0.112*B – 0.086*C – 0.010*D + \\ +0.002*E \quad +0.005*F \qquad (4)$$

where: A – HDL, mmol/l

B – ALT, mmol/l

C – gender (males – 1, females – 2)

D – BMI

E – portal vein diameter (mm)

F – age, years

It has been discovered that the level of ALT is influenced by patients' gender, increasing with age, ALT level, and diameter of the portal vein. Simultaneously, the analyzed indicator is inversely related to HDL and BMI.

Clinical example: a male patient, aged 55. Prior to the comprehensive treatment, the following indicators were recorded: HDL 1.18 mmol/l, ALT 0.66 mmol/l, BMI 28.1 kg/m^2, portal vein diameter 10.00 mm. By substituting these values into equation (4), a predicted ALT value of 0.62 mmol/l was obtained, perfectly aligning with the indicator after administration of comprehensive treatment.

The derived model (4) is defined by the following parameters: its Fisher criterion is 4.01 at p = 0.017. The multiple correlation coefficient value of 0.65 suggests that 35% of the prediction of ALT after combined therapy is influenced by other features not encompassed in the regression model.

As for AST, the regression model for forecasting this indicator (5) is computed within the equation:

$$AST = -0.029 + 0.031*A + 0.097*B + 0.109*C + 0.006*D \quad (5)$$

where: A – TG, mmol/l,

B – ALT, mmol/l,

C – AST, mmol/l,

D – age, years.

Thus, AST is directly influenced by the levels of TG, ALT, AST, and age.

Clinical example: Patient K., aged 53, prior to combined therapy, presented the following indicators: TG – 1.51 mmol/l, ALT – 0.56 mmol/l, AST – 0.44 mmol/l. Substituting these values into equation (5) yielded a predicted AST value of 0.42 mmol/l, differing by 0.01 mmol/l (or 2.3%) from the actual values after combined therapy.

The obtained model (5) exhibits the following parameters: its Fisher criterion is 4.15 at p = 0.024. The multiple correlation coefficient value of 0.51 suggests that 49% of the prediction of AST after undergoing complex treatment is influenced by other features not included in the regression model.

A Microsoft Excel program was developed for the automatic calculation of predicted indicators after combined therapy (Fig. 1).

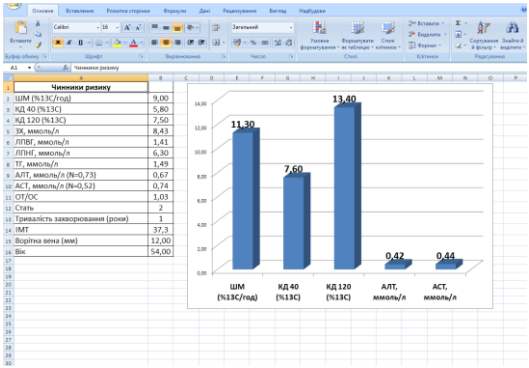

Fig. 1. Screenshot of the automatic program for predicting the analyzed indicators after administering combined therapy consisting of atorvastatin and UDCA

The essence of the development lies in the attending physician inputting information about the risk factors of a patient with stable angina pectoris and NAFLD into a specialized program prior to administering atorvastatin and UDCA. The program then automatically calculates the predicted values of liver metabolism rate, cumulative doses at 40 and 120 minutes, ALT and AST

levels in these patients following combined therapy, based on the developed models.

CONCLUSIONS

The findings of the conducted study demonstrate the established pharmacotherapeutic efficacy of administering combined therapy comprising UDCA and atorvastatin to patients with stable angina pectoris coupled with non-alcoholic fatty liver disease. Analysis of the study results reveals that one month following the implementation of statin therapy in conjunction with UDCA, a favorable impact is observed on patients' overall condition, alleviation of symptoms, improvement of the clinical course of the disease, and normalization of biochemical blood parameters attributable to the reduction of proatherogenic fractions within the lipid spectrum of the blood. Additionally, improvements in liver functional state indicators are noted among patients with the given comorbid pathology.

The analysis of liver detoxification function parameters, based on assessing the results of the ^{13}C-methacetin breath test through mathematical coefficient calculations, validates the positive trend in changes within hepatocyte functional state following combined therapy administered to patients. This is evidenced by an elevation in liver metabolic rate to the levels indicative of normal detoxification function, along with enhancements in cumulative doses at 40 and 120 minutes. Results from the ^{13}C-methacetin breath test indicate a substantial increase in liver metabolic capacity during complex therapy utilization, contrasting with decreased capacity observed in all patients prior to its implementation.

Predicting changes in liver functional state indicators holds significant scientific and practical importance in treating patients with combined pathology undergoing combined therapy. The utilization of an automated program for predicting these analyzed indicators is highly diagnostically valuable for practicing physicians. It empowers cardiologists, gastroenterologists, and family physicians to discern the potential favorable or unfavorable effects of drugs within combined therapy on liver functional state. This enables the selection of the most optimal and safe therapeutic strategies, considering the individual characteristics of each patient.

SUMMARY

One of the risk factors for the development of cardiovascular diseases is non-alcoholic fatty liver disease. NAFLD is associated with dyslipidemia, obesity, metabolic syndrome, and type 2 diabetes. The development of NAFLD is pathogenetically related to the development of coronary heart disease. In patients with stable angina pectoris, the presence of NAFLD significantly increases the manifestations of ischemia, the frequency of

ventricular rhythm disturbances and worsens the indicators of autonomic regulation of cardiac activity. For the treatment of this combined pathology, statin therapy is most often used, which not only reduces the risk of developing adverse cardiovascular events, but also plays a significant role in the prevention and treatment of NAFLD. Ursodeoxycholic acid (UDCA) is administered to patients with steatohepatitis as adjunctive drug therapy to mitigate potential adverse effects of statins on hepatocyte function. However, despite ongoing research efforts, definitive therapeutic criteria have yet to be established, and standardized drug approaches for treating patients with stable angina pectoris alongside concurrent NAFLD remain unapproved.

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Information about the author:
Karpyshyn Natalia Vasylivna,
Candidate of Medical Sciences
Assistant at the Department of Family Medicine
Danylo Halytsky Lviv National Medical University
69, Pekarska str., Lviv, 79010, Ukraine