Assessment of efficiency of fixed combination of simvastatin and ezetemibe in patients with chronic pancreatitis combined with obesity and type 2 diabetes

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Key words: chronic pancreatitis, obesity, type 2 diabetes, dyslipidemia, ezetimibe

Atherosclerasis and metabolic disorders in its presence are known to be essential factors in pathogenesis not only of ischemic heart disease (ICD), but chronic pancreatitis (ChP). Chronical course of oxidative stress, increase of anti-inflammatory cytokines, hyperlipidemia, hypertriglyceridemia, in particular postprandial, are attributed to such factors [1]. High level of triglycerides [TG] promotes the formation of modified low-density lipoproteins (LPLD), rich in triglycerides, and high-density lipoproteins (LPHD), derangement of carbohydrate metabolism and activation of thromboformation [2]. At ChP comorbidity with obesity and DM type 2 insulin resistance (IR), which couses reduction of lipoproteidlipase, promoting hypertriglyceridemia growth of the formation of LPLD and reduction of cholesterin of highdensity lipoproteins is of great importance too [3]. On the other hand, hyperinsulin resistance (HY) and IR stimulate TG synthesis (which is the risk factor of ChP exacerbation) from the liver fructose and decrease phospholipid synthesis due to it LPHD deficit arises and atherogenic lipoproteids of LPLD – small, dense, very low-density lipoproteins (LPVLD), lipoprotein (a) are stored [4].

Data about triglycerides' influence on the development of atherogenic diseases are discrepant, but it is known, that high level of triglycerides and low level of CD LPHD are reliably connected with all cases of ICD and coronary death in patients with DM type 2 [5,6]. This stipulates the need of searching effective methods of treatment, which regulate and correlate dislipidemia (DLP), separate fractions of lipoproteids, displacement of chylomicrons metabolism, improve indices of carbohydrate metabolism, that is, increase sensitivity of tissues to

insulin, decrease prooxidant potential of blood, since these conditions are associated with the development and progression of atherosclerosis.

Such properties has ezetimibe, which is referred to inhibitors of the intestinal microbial protein, transferring triglycerols (MPTTG). Nowadays, it is considered that MPTTG inhibitors obstruct adipose tissue absorption in the intestine and therefore may be taken as a target to correct displacements in lipid metabolism at ChP, obesity, DM and othe conditions, which are accompanied with postprandial hyperchylomicronemia.

Aim of study is to compare efficacy of using fixed combination of simvastation 20mg and ezitimibe 10 mg ("Inedzhi") in comparison with atorvastatin monotherapy 20mg for dislipidemia correction in patients with chronic pancreatitis combined with obesity and diabetes mellitus type 2.

Materials and methods. 40 patients suffering from ChP combined with obesity and DM type 2 aged from 27 till 78, among which there were 25 women (62,5%) and 15 men (37,5%), were includid to the research. Duration of the disease was from 5 to 18 years.

All persons during observation followed hypolipidemic diet and received traditional therapy. For the purpose of DLP correction the patients of group I (20 persons) were administered atorvastatin monotherapy in a dose of 20 mg/day after supper during 8 weeks and fixed combination of simvastatin 20 mg with ezetimibe 10 mg in one tablet usable only once after supper was administreted to the patients of group II (20 persons) during the same period. The patients of groups I and II under study were randomized according to the age sex and duration of the disease.

Clinical investigations were carried out on the basis of gastroenterological department of Oblast Municipal Establishment (OME) "Chernivtsi Regional Clinical hospital" and Chernivtsi regional endocrinological dispensary.

Diagnosis were verified according to the orders of MPH of Ukraine №638 of the 10 th September, 2014 "Unified clinical protocol of primary, secondary (specialized) medical care and medical rehabilitation Chronic pancreatitis" and №1118 of the 21st December, 2012 "Unified clinical protocol of primary,

secondary (specialized) medical care and medical rehabilitation Diabetes Mellitus type 2" on the basis of complex estimation of the patients' complaints, anamnesis data, results of clinical-laboratorial and instrumental investigations. Diagnosis of obesity was made according to International group of WHO as to obesity (IOTF, 1997). Index of body weight (index Ketle) – ratio of body weight expressed in kg to the height in m^2 was used for evaluation of obesity degree.

Content of total cholesterol (TChL), TG, HD LPHD, HD LPLD in the blood serum by means of enzymatic method using diagnostic standards of sets of PZ Cormay S.A. firm (Poland) was determined in all patients included in the research.

Atherogenesity index (AI) according to A.M. Klimov's formula was calculated for mare precise representation of favourable and unfovourable combination of lipidogram indices concerning the risk of atherosclerosis development [7].

AI = TChL – LPHD / LPHD

Where AI – atherogenesity index,

Where TChL – index of total cholesterol in the blood (mmol/l),

LPHD – index as to the data of the flood analysis (mmol/l).

The above mentioned indices of lipid metabolism were determined in patients before administration of hipolipidemic therapy and after 8 weeks of treatment. Achievements of purpose – oriented lipid levels in patients were checked as to recommendations of the European Society of Cardiologists (ESC, 2011) [8] and Management in treatment of dislipidemia ADA and ACC (2008) for the patients of high cardiometabolic risk [9].

Biochemical studies of the blood with determination of the content of urea, creatinin, urinary acid, activity of hepatic transaminase (aspartat – and alaninaminotransferase (AsAT, AlAT), creatine phosphokinase (CPhK), by standard generally known methods were carried out in order to estimate hypolipidemic therapy sofety in dynamics of taking care of a patient [10].

Life quality of a patient was appreciated as well (according to the data of questionnaire SF-36): general health state and mental health of the patients suffering from ChP at DM type 2 and obesity.

Statistical processing of the data obtained was carried out on personal computer by means of applied program Statistica for Windows version 8.0 (StatSoft inc., USA). Mean arithmetical Value (M), its mistake (m), criterium Student (t), possibility (p) with provision of probability not less than 95% were taken into consideration.

Results of research. Indices of the life quality became better: (in 18 (90%) of persons of group II and in 14 (70%) group I). Manifestations of pain, dyspeptic syndromes in 19 (95%) persons of group II and 10 (50%) of group I became minimal.

Before treatment TChl level of plasma in the patients of group I constituted 5,85±0,3 mmol/l, in 8 weeks – 4,8±0,26 mmol/l ($p<0,05$). The level of TG plasma in these patients before treatment constituted 3,03±0,47 mmol/l, in 8 weeks – 2,48±0,47 mmol/l ($p<0,05$). LPLD level constituted 3, 34±0,24 mmol/l before treatment, in 8 weeks – 2,68±0,23 mmol/l ($p<0,05$). The level of LPHD before treatment was 0,78±0,09 mmol/l, in 8 weeks – 0,99±0,1 mmol/l ($p<0,05$). AI before treatment constituted 7,12±1,03 abs. un., in 8 weeks – 4,22±0,67 abs. un. $p<0,05$ (fig.1).

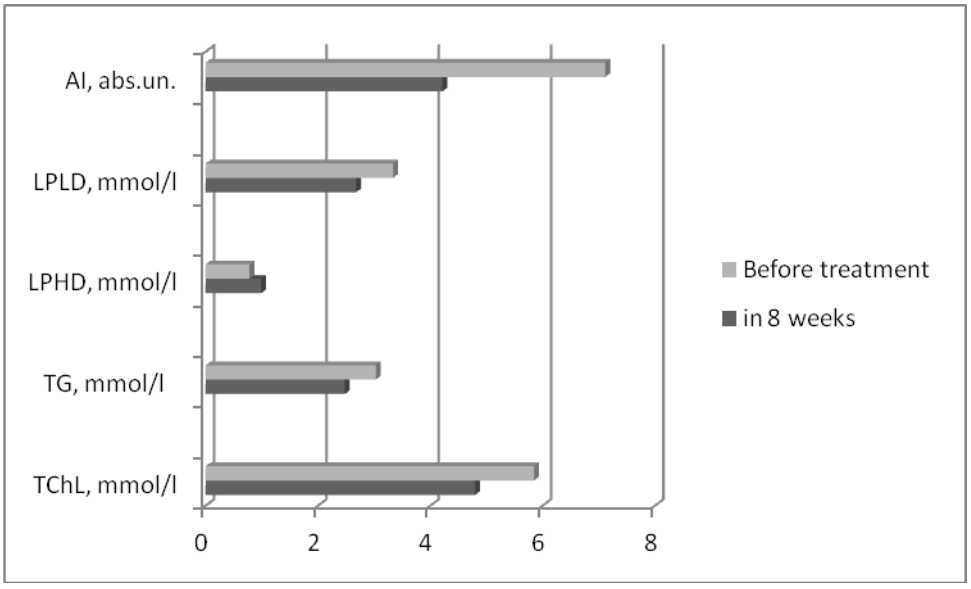

Fig. 1. Changes of lipid metabolism indices in the examined patients under the influence of atorvastatin.

Such changes of lipidogram indices were revealed in the patients of group II: TChL plasma before treatment constituted 6,55±0,24 mmol/l, in 8 weeks – 3,87±0,47 mmol/l ($p<0,05$). TG level of plasma in these patients before treatment was 3,22±0,38 mmol/l, in 8 weeks – 2,37± 0,25 ($p<0,05$). LPLD level before the treatment constituted 4,54±0,16 mmol/l, in 8 weeks – 1,67±0,36 mmol/l ($p<0,05$). LPHD before treatment constituted 0,87±0,19 mmol/l, in 8 weeks – 1,31±0,15 mmol/l ($p<0,05$). AI before therapy was 10,4±4,22 abs.un. in 8 weeks – 2,01±0,32 abs.un. $p<0,05$ (fig. 2).

Changes of lipid metabolism indices in the examined patients under the influence of simvastatin and ezetimibe treatment are shown in fig.2

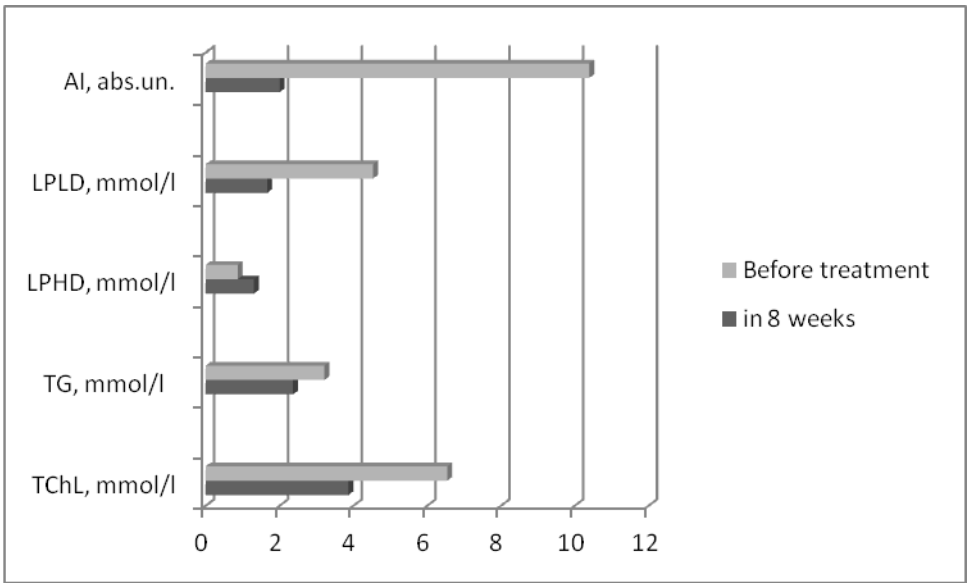

Fig. 2. Changes of lipid metabolism indices in the examined patients under the influence of simvastatin and ezetimibe treatment.

Indices of lipidograms in case of inclusion of ezetimibe into the course of treatment significantly improved in comparison with the group of patients, where the treatment was carried out using atorvastatin monotherapy. TChL level in connection with the treatment decreased 48% ($p<0,05$), in comparison with 18% at

monotherapy, LPLD – 37% ($p<0,05$) and 20%, TG – 26% and 18% respectively ($p<0,05$). LPHD index increased 34% in patients of groupe II ($p<0,05$) and 22% in patients of groupe I.

AI decreased 81% ($p<0,05$) in patients when ezetimibe was included to theis treatment and only 41% in the patients who were treated with atorvastatin.

Both eight weeks intake of the fixed combination of simvastatin with ezetimibe and 8 weeks of atorvastatin monotherapy were accompanied with the absence of the negative changes of the laboratory indices including activity of hepatic transaminases (AsAT, AlAT), CPhK, levels of urea, creatinin in the patients suffering from ChP combined with obesity and DM type 2 included to the research. Changes in the coudition of patients (meteorism, intermittent headache), connected with hypolipidemic therapy, were of a temporary character and didn't require refusal of hypolipidemic means.

Discussion. The results of influence of simvastatin treatment in combination with ezetimibe on indices of lipidograms, obtained by us, indicate to greater efficacy of such combination in comparison with atorvastatin monotherapy. It is explained by the fact that ezetimibe inhibits cholesterol suction in the intestine, influencing upon suction of other liposoluble substances, including decrease of the lipid level. Inhibiting suction of cholesterol on the level of villous edge if the intestine (may be, by means of interaction with intestinal microsomal protein, transfer triaglycerols (NPCIL1), ezetimibe reduces cholesterol quantity, which gets into the liver from the remnants of chilomicrons. The liver, in respose to activates LPLD receptors on its surface, that promotes their excretion from the blood.

Abatement of hypotriglyceridemic action of atorvastatin is reliably stipulated by IR presence, existing at DM type 2, since additional TG synthesis by the liver (according to glycerophosphate way) [11, 12] from free fatty acids in combination with an increased glucose level is enhanced.

LPHD level as antiatherogenic factor of blood plasma may not only testify to the evidence of atherosclerosis changes, but underline significance of such

ethiopathogenic link of ChP development, as hypertriglyceridemia, in particular, at lipogenic ChP in this group of patients [13].

Such changes are known to increase the risk of atherosclerosis development and possibility of its aftereffects including the combined clinical course with ChP [14]. Therefore, achievements of the purpose-oriented levels of the given index is desirable for the patients with ChP at obesity and IR and DM type 2. In its turn, more efficient decrease of atherogenesity enables to confirm, that owing to simvastatin treatment in combination with ezetimibe cardiovascular risk is significantly decreased in such patients in comparison with atorvastatin monotherapy.

Conclusions:

1. In patients suffering from chronic pancreatitis, combined with obesity and diabetes mellitus type 2 addition of traditional therapy with simvastatin and ezetimibe promote the improvement of lipidogram indices (reduction of TChL level 48% ($p<0,05$), LPLD – 37% ($p<0,05$), TG – 26%, IA – 81% ($p<0,05$) and increase of LPHD level 34% ($p<0,05$)).
2. Changes of lipid profile indices in patients suffering from chronic pancreatitis, combined with obesity and diabetes mellitus type 2 against a background of atorvastatin monotherapy were less evident TChL decreased 18% ($p<0,05$), LPLD – 20% ($p<0,05$), TG – 18% ($p<0,05$), AG – 41% ($p<0,05$), LPHD index increased 22% ($p<0,05$)).
3. Fixed combination of simvastatine 20mg with ezetimibe 10 mg once a day after supper during 2 months is recommended to be prescribed to the patients suffering from chronic pancreatitis, combined with obesity and diabetes mellitus type 2 in order to improve cholesterol metabolism.

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The article presents a comparative description of the effectiveness of 8-weeks lipid-lowering therapy by fixed combination of simvastatin 20 mg with ezetimibe 10 mg ("Inedzhi") versus monotherapy by atorvastatin 20 mg for the correction of dyslipidemia (DSP) in patients with chronic pancreatitis combined with obesity and type 2 diabetes. It is shown that DSP correction upon inclusion of ezetimibe to a course treatment significantly improved as compared with a group of patients in which treatment by atorvastatin monotherapy was conducted. The level of total cholesterol decreased in connection with the treatment by 48% ($p < 0.05$), LDL — by 37% ($p < 0.05$), TG — by 26% ($p < 0.05$), IA — by 81% ($p < 0.05$). HDL index increased by 34% ($p < 0.05$).