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RESEARCH ARTICLE

NONALCOHOLIC FATTY LIVER DISEASE AND CHRONIC KIDNEY DISEASE IN PATIENTS WITH CHRONIC HEART FAILURE

Drapkina, O., *Zyatenkova, E. and Ivashkin, V.

The First Moscow Medical University named by I.M. Sechenov,
Clinic of the Propedeutics of the Internal Diseases, Moscow, Russian Federation

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ABSTRACT

Currently, the routine clinical practice does not include the measurement of glomerular filtration rate (GFR) in patients with the absence of risk factors for Chronic Kidney Disease (CKD). However, recent studies have shown that in patients with nonalcoholic fatty liver disease (NAFLD) it is necessary to estimate GFR, even in the absence of classic risk factors for CKD. Early detection of kidney damage in patients with CHF and NAFLD will help to titrate the correct dose of drugs, avoiding chemical overdose.

Materials and Methods: The study included 77 patients with CHF. In all patients, the diagnosis of heart failure was confirmed by measuring the quality NT-pro BNP. The severity of the clinical manifestations of heart failure and the functional status of patients were assessed. All patients underwent clinical and biochemical blood tests, ECG, ultrasound of the liver. Size of the heart chambers, wall thickness of the myocardium and epicardial fat were evaluated by the echocardiography. In all patients GFR, CKD-EPI were calculated, staging of CKD was performed, Fatty Liver Index and NAFLD fibrosis score evaluated.

Results: More than half (68%) of the patients with CHF had C 2 stage of CKD, 6% of patients had a C1 stage; 13% - C 3a, 9% - C 3b, 4% - C4 stage CKD. The average value of GFR was 65,4 ± 14,4 ml / min / 1.73 m2. Statistical analysis revealed that with the increase of HF functional class stage of CKD also increase ($p = 0,0027$). The severity of CKD increases with the level of plasma glucose ($p = 0.0022$). In addition, it was found that the stage of CKD correlate with increase in the size of the right atrium ($p = 0.044$). In assessing the biological age of the vessel wall with the help of apparatus "Angioscan" it was revealed that the larger stage of CKD, the higher biological age of the vessel wall in patients with chronic heart failure ($p = 0.0027$). It was also found that the more severe damage to the kidneys in patients with CHF, the higher level of fibrosis marker PIIINP infarction ($p = 0.047$). According to FLI, 40% of patients are likely to have hepatic steatosis, in 34% of patients the data for the presence of hepatic steatosis is not obtained, 26% of patients took an intermediate value. According to the NFS, 26% of patients had a high likelihood of liver fibrosis, 9% of patients did not have, 65% of patients are in the "gray zone". The analysis of the correlations revealed that with increasing values of NFS reduced GFR increases CKD stage ($p = 0.049$).

Conclusions: Patients with heart failure and concomitant diseases of the liver and kidneys are in need of more intensive treatment with compulsory inclusion of drugs which reduce the process of fibrosis and remodeling of the vascular wall and have protective properties in relation to the liver and kidneys.

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INTRODUCTION

Chronic kidney disease (CKD) is a serious public health problem, both in foreign countries and in the Russian Federation.

Corresponding author: Zyatenkova, E.
The First Moscow Medical University named by I.M. Sechenov, Clinic of the propedeutics of the Internal diseases, Moscow, Russian Federation.

It is well known that cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with CKD. More than 50% of patients die from cardiovascular disease before they develop end-stage renal disease (Renal function and prediction of cardiovascular risk, 2008). The main reasons leading to the development of CKD are diabetes mellitus 2 type (DM), hypertension (HTN) and atherosclerotic vessels ordinances. The same reasons lead to the development of chronic heart failure (CHF).

Obesity, disorders of carbohydrate and lipid metabolism as a part of the metabolic syndrome (MS) accelerate the development and progression of CKD and CHF. In recent years, another MS is a recognized component of non-alcoholic fatty liver disease (NAFLD). NAFLD encompasses the spectrum of states from hepatic steatosis to cirrhosis and hepatocellular carcinoma. Recent studies support the hypothesis that NAFLD leads to a higher risk of cardiovascular disease independently of other prognostic risk factors. There is also evidence confirming the possibility that NAFLD and atherosclerosis share common molecular mechanisms.

NAFLD affects the prognosis of not only CVD, but also CKD. The study of Italian scientists G.Targher and his co-authors in 2010 demonstrated the link between histologically proven NAFLD and CKD, independent of traditional risk factors, insulin resistance (IR) and the components of MS (Targher *et al.,* 2010). In another study (1361 patients) conducted by Hwang and his co-authors it has been shown that patients with NAFLD (proved by ultrasound) had a significantly higher prevalence of microalbuminuria than patients without NAFLD (Hwang *et al*., 2010). Similar results were obtained in several other studies (Mikolasevic *et al.,* 2013) and (Mikolasevic *et al.,* 2014). These data led to raising the issue that NAFLD may be a new and additional risk factor for the development and progression of CKD.

The mechanism by which the risk of NAFLD and CKD progression increases is still not clear. The liver is the main organ manufacture of various classical biomarkers of inflammation, proinflammatory cytokines and endothelial dysfunction. Insulin resistance and metabolic syndrome lead to increased secretion of these proteins. Animal experiments show that cytokine imbalance is also involved in the pathogenesis of CKD (Targher *et al.,* 2011). Thus, the synthesis of different promoters of inflammation, such as a tumor necrosis factor α, transforming growth factor ß, reactive oxygen species, plasminogen activator inhibitor-1, C-reactive protein and interleukin-6 may be the link between NAFLD and CKD. NAFLD also exacerbates the already existing hepatic and systemic IR, which promotes atherogenic dyslipidemia, which plays an important role in the development and progression of CKD.

Another cause of CKD in the NAFLD may be the reduction in the level of adiponectin, which has anti-inflammatory, anti-atherogenic properties, the protein also reduces IR. This observation is confirmed in the review Joachim H. Ix in 2010 [Joachim and Sharma, 2010]. Free fatty acids, IR and NAFLD lead to elevated levels of fetuin-A, which in turn inhibits the transcription of adiponectin. The lack of adiponectin is associated with reduced activity of AMP-activated protein kinase (AMPK), which causes damage to hepatocytes and podocytes, launch of inflammatory and profibrotic cascades that lead to the fibrosis of the liver and kidneys. One cannot forget about the renin-angiotensin-aldosterone system (RAAS), which plays an important role in the development of systemic fibrosis. RAAS activation that is associated with CVD, entails not only cardiac complications and changes, but also affects the liver and kidneys.

According to the recommendations of the "gold standard" CKD is a count of glomerular filtration rate (GFR) calculated using the formula CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), which takes into account race, sex, age, serum creatinine (Renal function and prediction of cardiovascular risk, 2008). The best diagnostic method to confirm NAFLD is considered to be liver biopsy. The risk of complications and the cost of the study limit the use of biopsy in the general practice. According to the practical recommendations of the American College of Gastroenterology, the American Association for the Study of Liver Diseases, the American Gastroenterological Association for the diagnosis of non-alcoholic fatty liver disease, liver biopsy should be performed in patients at high risk of steatosis to steatohepatitis transformation and progressive fibrosis. The recommendations stated that instrumental methods of research, such as ultrasound, spiral CT, MRI, are not completely reliable methods of diagnosis of NAFLD (Naga Chalasani *et al.,* 2012). So today there is an active search for non-invasive methods for the diagnosis of NAFLD and evaluation of the degree of steatosis and fibrosis of the liver.

The above recommendations are encouraged to use NAFLD fibrosis score (NFS) to identify a group of patients at high risk of transformation of non-alcoholic liver disease to fibrosis and / or cirrhosis. The presence of metabolic syndrome and counting NFS can be a decisive factor for the formation of a group of patients at high risk of transformation of NAFLD in steatohepatitis and progressive fibrosis of the liver. It is calculated by the formula (Angulo *et al.,* 2007):

- 1,675 + 0,037 x A + 0,094 x BMI + AST/ALT – 0,013 x PL – 0,66 x Al

A–age, year; BMI - body mass index kg/m$^{2;}$ AST – Aspartate aminotransferase, IU/L; ALT– Alanine aminotransferase, IU/L; PL – Platelets, 10^9/l; Al – Albumin, g/l

< -1.455: predictor of absence of significant fibrosis (F0-F2 fibrosis)

≤ -1.455 to ≤ 0.675: indeterminate score

> 0.675: predictor of presence of significant fibrosis (F3-F4 fibrosis)

The value of the use of NFS is shown in a meta-analysis of 13 studies involving 3064 patients. So the value of <1.455 (90% sensitivity and 60% specificity) indicates the absence of significant fibrosis, with the value of> 0.676 (67% sensitivity and 97% specificity), the likelihood of liver fibrosis is very high (Angulo *et al.,* 2007). Another surrogate marker for NAFLD is the Fatty Liver Index. The value of this test has been shown in the RISC Study. The study included 1307 patients under 60 without diabetes with a high cardiovascular risk. The results of the study claimed that FLI was connected with IR, TIM, with an increased risk of coronary heart disease (Gastaldelli *et al.,* 2009). Also the predictive value of FLI was demonstrated in two other large studies. The 9-year follow-up of French scientists over 3811 patients found that the high value of FLI served as an independent predictor of diabetes (Balkau *et al.,* 2010). The 15- year study Cremona with 2074

patients showed that the high value of FLI is associated with a high risk of mortality both from cardiovascular problems and from liver disease (Calori *et al.,* 2011). Fatty Liver Index (FLI) is calculated by the formula (Calori *et al.,* 2011):

e0,953 x loge (TG) + 0,139xBMI + 0,718 x loge (GGT) + 0,053 x WC - 15,745 /1+(e0,953 x loge (TG) + 0,139 x BMI + 0,718 x loge (GGT) + 0,053 x WC - 15,745)x100

TG- triglycerides, g/l; BMI - body mass index kg/$m^{2;}$ GGT-gamma-glutamyl-transferase, IU/L; WC - waist circumference, sm; With the value of more than 30 the likelihood of steatosis is high, at the value of less than 30 it is low. The FLI ranges from 0 to 100 and in the population of Bedogni *et al*. FLI <30 ruled out and a FLI 60 ruled in fatty liver with a good diagnostic accuracy (AUROC = 0.85; 95% CI 0.81–0.88). Thus, the presence of NAFLD patients with cardiovascular diseases, not only leads to a deterioration of the forecast of CVD, but also to the development and progression of CKD. All this was the reason for the study of the kidneys in patients with CHF and NAFLD in our work.

MATERIALS AND METHODS

The study included 77 patients with CHF. In all patients the diagnosis of heart failure was confirmed by quality measuring NT-proBNP (> 125 pg / ml) by means of an express test (Getein Biotechnology, China). The severity of the clinical manifestations of heart failure by means of an evaluation scale of clinical condition in CHF, functional status of the patient were assessed using a six-minute walk test.

All patients underwent clinical and biochemical blood tests, an electrocardiogram. The size of the heart chambers, wall thickness of the myocardium and epicardial fat by echocardiography were estimated on the apparatus Siemens Sequoia 512 with a sector probe 3V2Cs. All the patients underwent the calculation of GFR CKD-EPI and staging of CKD, Fatty Liver Index, NAFLD Fibrosis Score. In these patients we measured markers of collagen synthesis-N-terminal propeptide of collagen type III (PIIINP) to assess the process of fibrosis and the contribution of this process to the development of heart failure by means of immunoassay («USCN Life Science», China).

RESULTS

All patients had clinical signs and symptoms of CHF. Of the 77 patients 25 (32%) were male. The mean age was 63, 9 ± 10,3 years. BMI 29, 0 ± 5, 80 kg / m2. Among all patients 8 patients (10%) had evidence of CHF stage I; 46 (60%) patients had - II A stage; 19 (25%) patients had - II B and 4 (5%) of patients had stage III CHF. After evaluation of the severity of CHF by clinical state scale, among all patients, 12 had FC I, (15%); 43 patients had (56%); II FC, 16 (21%) patients had III FC; 6 (8%) patients had IV FC. Average for clinical state scale among all patients was 5 (50% CI 4-7). According to the ultrasound examination of the liver 64% of patients had hepatic steatosis. All the patients underwent liver steatosis count index (FLI) by the formula shown earlier. If the value of FLI ≥ 60 chance of steatosis> 78% (Calori *et al.,* 2011).

When calculating FLI, 26 (34%) patients had no steatosis; 31 (40%) patients had steatosis; 20 (26%) patients took between (Figure 1).

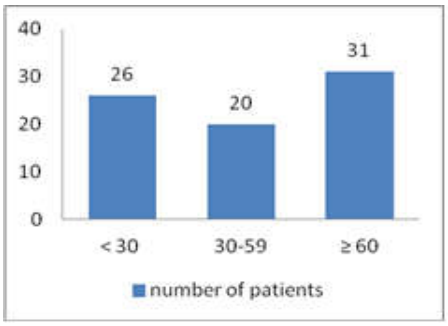

Figure 1. The distribution of patients with CHF, depending on the value of FLI

Also, the index is calculated in all patients of liver fibrosis (NAFLD Fibrosis Score). 7 (9%) patients had no liver fibrosis, 19 (26%) patients had significant liver fibrosis, 51 (65%) patients were in the "gray zone" (Figure 2).

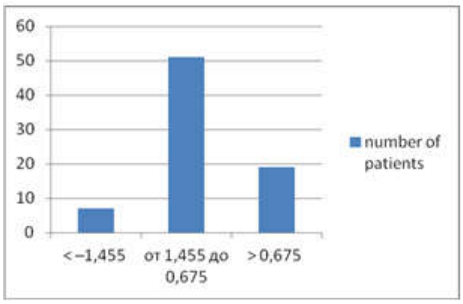

Figure 2. The distribution of patients with CHF, depending on the value of NFS

In assessing the level of the average value of PIIINP it was 2, 8 ± 1, 5 μg/l. Patients were distributed at the stage of CKD as follows: 5 (6%) of patients had stage C 1; 52 (68%) of patients had stage C 2; 10 (13%) of patients had stage C 3a; 7 (9%) of patients had stage C 3b; 3(4%) of patients had stage C 4. There were no patients with the end-stage (C5) (Figure 3). The average value of GFR 65,4 ± 14,4 ml / min / 1.73 m2. We studied the characteristics of the patients, depending on the condition of renal excretory function.

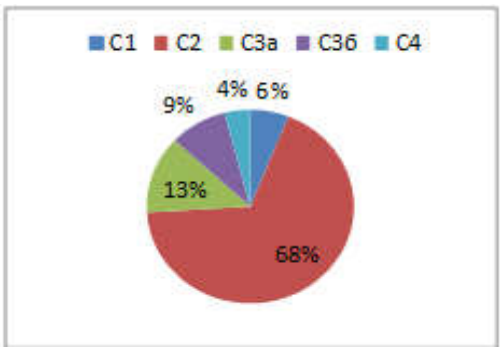

Figure 3. The distribution of patients with CHF, depending on the stage of CKD

It was found that FC evaluation scale of clinical condition in CHF increases CKD stage (p = 0, 0027) (Figure 4).

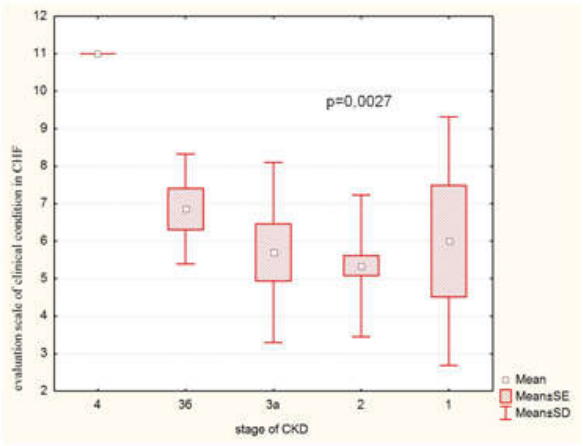

Figure 4. Value for FC evaluation scale of clinical condition in CHF depending on the stage of CKD

Also it was revealed that the severity of CKD increases with the level of glucose (p = 0.0022). The analysis of the correlations revealed that with the increase of NFS values GFR reduces increasing CKD stage (p = 0.049) (Figure 5). Furthermore, it was found that at the stage of CKD patients noted an increase in the size of the right atrium (p = 0.044) (Figure 6). In addition to these instrumental methods of examination, all patients were assessed for the biological age of the vessel wall with the help of apparatus "Angioscan." It was found that the larger stage of CKD, the higher the biological age of the vessel wall in patients with chronic heart failure (p = 0.0027) (Figure 7).

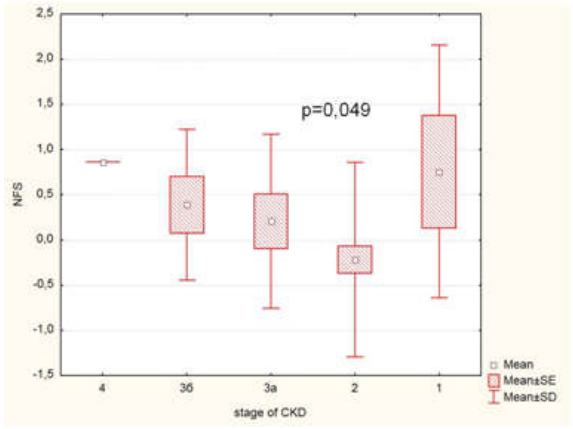

Figure 5. NFS value depending on the stage of CKD

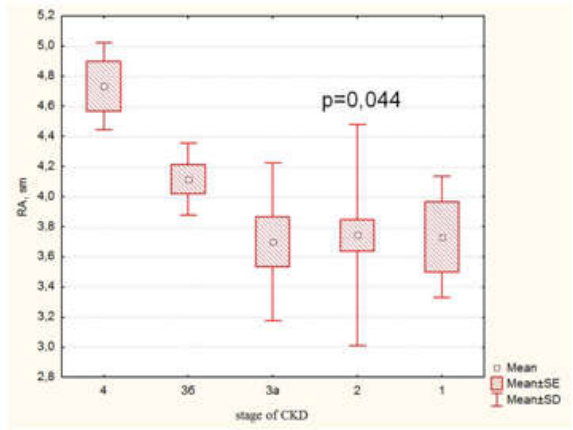

Figure 6. Changing the size of the right atrium, depending on the stage of CKD

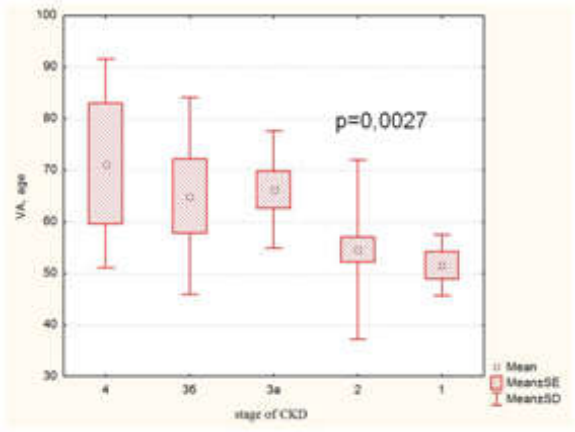

Figure 7. The value of the biological age of the vessel wall, depending on the stage of CKD

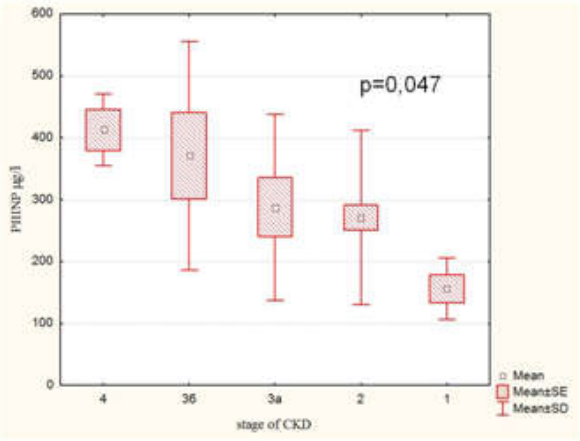

Figure 8. PIIINP value depending on the stage of CKD

It was also found that the more severe the damage to the kidneys in patients with CHF, the higher the level of fibrosis marker PIIINP infarction (p = 0.047) (Figure 8).

DISCUSSION

As it is known, GFR deterioration is a predictor of unfavorable prognosis of CHF. The contribution of kidneys to the development of heart failure is not only in the formation of edema syndrome, but the progression of myocardial dysfunction.

Kidneys, increasing the preload, contribute to LV dilatation, hypertrophy and the development of myocardial fibrosis by activating the RASS. So in our study we showed that with the increase of CKD stage patients have an increase in the size of the right atrium (p = 0.044) (Arimoto *et al.,* 2007; Niizeki *et al.,* 2007). The presence of comorbidity in the form of non-alcoholic liver disease worsens the prognosis and course of chronic heart failure (Drapkina and Drapkina, 2014; Drapkina and Ivashkin, 2014). NAFLD affects the prognosis of not only CVD (Drapkina and Ivashkin, 2011; Ivashkin *et al.,* 2010), but also CKD. The study of Chinese scientists has shown that patients with NAFLD have GFR considerably smaller than patients without NAFLD (Shen *et al.,* 2015). Portuguese scientists in their study found that the presence and severity of

liver inflammation are linearly correlated with low GFR (Machado *et al.,* 2012). So in our study, with an increase in the likelihood of liver fibrosis (NFS) the value of GFR decreases and the CKD stage increases (p = 0.049).

Activation of neurohumoral systems launches fibrogenesis not only in the kidneys, liver and heart, but also in blood vessels (Drapkina and Gegenava, 2013; Drapkina and Dubolazova Yu, 2011; Drapkina *et al.,* 2015; Korneeva *et al.,* 2013). Surragatnym marker for increased rigidity of blood vessels is the biological age of the vessel wall. It is a current integral index, based on the extensibility of the arterial wall, and amplitude characteristics of the reflected wave. Our work revealed that the larger stage of CKD, the higher the biological age of the vessel wall in patients with chronic heart failure (p = 0.0027) and hence greater rigidity of blood vessels, which in its turn leads to the acceleration of the remodeling. In addition, our work estimated the level of N-terminal pro-peptide of type III collagen. PIIINP is a protein that is formed during the synthesis of type III collagen. This token represents the synthesis of collagen, fibrosis processes. It was found that the more severe the damage to the kidneys in patients with CHF, the higher the level of fibrosis marker PIIINP infarction (p = 0.047), indicating that the contribution of renal pathology to the process of fibro genesis.

Thus, patients with NAFLD and chronic heart failure need the evaluation of the glomerular filtration rate. Early detection of kidney damage in patients with CHF and NAFLD will allow administering the correct dose of medicines, avoiding drugs overdose. These patients need more intensive treatment compulsory including drugs, which reduce the process of fibrosis and remodeling of the vascular wall and have protective effects on liver and kidney (Drapkina and Ivashkin, 2011; Drapkina and Ivashkin, 2012).

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