Nonalcoholic fatty liver disease (NAFLD): A new risk factor for adverse cardiovascular events in dialysis patients


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**Abstract**

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in Western countries. Today it is believed that NAFLD is a hepatic manifestation of metabolic syndrome, and thus it is closely related to the cardiovascular morbidity and mortality. Cardiovascular diseases (CVD) are the leading cause of morbidity and mortality in patients with end-stage-renal disease (ESRD). NAFLD and ESRD share some important cardiometabolic risk factors and possible common pathophysiological mechanisms, and are linked to an increased risk of incident CVD events. We hypothesize that the coexistence of these two conditions could lead to much faster progress of the aterogenic process. Furthermore, patients with ESRD who suffer from NAFLD have a much higher risk for the development of adverse CVD events. Given the high prevalence of NAFLD, and its tight association with other manifestations of the metabolic syndrome and thus cardiovascular complications, it is important to recognize and aggressively treat this condition in ESRD patients. To evaluate this hypothesis, we propose the use of non-invasive methods such as transient elastography (TE) (Fibroscan-CAP) for the detection and quantification of liver steatosis and fibrosis, as well as an abdominal ultrasound for detecting liver steatosis. We focus on their correlation with carotid intima-media thickness (IMT) and plaque as surrogate measures of increased cardiovascular risk in HD patients in order to investigate the association of NAFLD and increase risk of adverse CVD events. This evaluation will prove useful in assessing the risk in HD patients with NAFLD for increase CVD mortality.

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**Introduction**

Chronic kidney disease (CKD) is a worldwide health problem and according to recent data from the United States population-based third national health and nutrition examination survey (NHANES III) the prevalence of CKD in the United States is approximately 13% [1]. In Europe, the prevalence of CKD is very similar to that in the United States. Furthermore, according to recent data, over 1.1 million patients are estimated to have end stage renal disease (ESRD) worldwide, with an addition of a 7% increase annually. Today, it is well known that cardiovascular diseases (CVD) are the leading cause of morbidity and mortality in CKD patients and that they are responsible for almost 40% of hospitalizations and 50% of deaths in these patients. Less than a half of CKD patients develop end-stage-renal disease (ESRD) and most of them die from arteriosclerotic CVD before they develop ESRD and need for renal replacement therapy [2–6]. In patients who undergo dialysis treatment there are multiple well established risk factors that contribute to the development of CVD. They are commonly divided into three groups. The first group includes traditional risk factors such as hypertension, diabetes, dyslipidemia, smoking, being overweight and hyperhomocysteinemia. In the second group there are some risk factors that are specific to CKD which include hemodynamic overload, anemia, calcium-phosphate disorders, electrolyte imbalance, chronic inflammation, oxidative stress, uraemic state and hypercatabolism. Finally, there are some risk factors that are related to dialysis treatment, such as intra- and inter-dialytic volume changes, fluctuations in blood pressure and serum electrolyte levels, bio-compatibility of membranes and dialysate impurity [2].

Recently non-alcoholic fatty liver disease (NAFLD) has been recognized as a new risk factor for development of atherosclerosis in the general population. The term NAFLD is used to cover a spectrum of diseases that are characterized predominantly by macrovesicular steatosis of the liver and occur in people who do not consume large amounts of alcohol. Today, there is growing evidence that NAFLD is strongly associated with cardiovascular diseases. Furthermore, many authors have expressed their opinion that NAFLD represents a liver manifestation of metabolic syndrome (MS)–disease which is related to diabetes mellitus type 2, insulin
resistance, central obesity, hyperlipidemia and hypertension [7]. Approximately 90% of patients with NAFLD have more than one component of metabolic syndrome and 35–75% meet all of the diagnostic criteria. Non-alcoholic fatty liver disease is one of the most common forms of liver disease in Western countries, but the true prevalence of NAFLD remains unknown. Depending on the used diagnostic criteria the prevalence of NAFLD ranges from 10% to 24% in the general population. The prevalence of NAFLD increases with age, from less than 20% in people under the age of 20 to more than 40% in over 60s. Also, NAFLD has been reported in children, with a prevalence of 2.6%, which may rise to anywhere in the range of 10–80% in obese children [8–10]. The clinical spectrum of NAFLD ranges from simple steatosis to non-alcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma. Simple steatosis is the mildest form of NAFLD while the next more severe form of NAFLD is NASH, or fatty liver with inflammation and evidence of hepatocellular damage, with or without fibrosis. In 20–25% of cases NASH may progress to advanced stages of hepatic fibrosis and cirrhosis. In some cases of NAFLD related cirrhosis the hepatocellular carcinoma will develop. Giving the fact that NAFLD is usually an asymptomatic disorder, it is often unrecognized in everyday clinical practice. Namely, most patients with NAFLD have no symptoms, and aminotransferase levels which are used as a marker of liver damage are within normal values in almost half of all patients. In approaching patients with NAFLD there are many non-invasive procedures that have been intensively investigated for detecting hepatic steatosis and fibrosis. To-day contrast ultrasonography and magnetic resonance spectroscopy, as well as ultrasonographic elastography (Fibroscan®) have shown promising results. However, a liver biopsy still remains the gold standard for definitive diagnosis. But, it samples only 1/50,000th of the liver and is prone to significant sampling error. It's an invasive procedure which can have serious complications and cannot be performed in patients with impaired hemostasis. Today, there are still no clear recommendations on whether or not liver biopsy is required to confirm a diagnosis of NAFLD. [11–14]. Recently a novel parameter has been developed, i.e. the controlled attenuation parameter (CAP); one that can be quantified using transient elastography (TE) (Fibroscan®) and which is able to efficiently separate different grades of severity of steatosis. CAP is based on the properties of ultrasonic signals acquired by the Fibroscan®. This diagnostic tool allows us to simultaneously measure liver stiffness and CAP in the same liver volume. The volume used for the measurement by the Fibroscan® is 200 times larger than the one used for a liver biopsy specimen. Therefore the Fibroscan® is used more and more in clinical practice [15].

As mentioned above, research in recent years, has led to the recognition of the importance of NAFLD and its relationship with MS. This has led to a growing interest in the potential prognostic value of NAFLD for adverse CVD outcome. The possible link between NAFLD and CKD has also attracted research interest. Preliminary data suggest an association between CKD and NAFLD: the prevalence of CKD was significantly higher in patients with NAFLD/NASH compared to those patients without NAFLD/NASH. Furthermore, a recent study documented moderately decreased eGFR and high frequency of microalbuminuria in patients with biopsy proven NASH; the severity of liver damage was associated with lower eGFR [16,3,17]. Therefore, it is logical to expect that ESRD patients that are on maintained haemodialysis would also have a high incidence of NAFLD/NASH that could contribute to further cardiovascular mortality in these patients. Furthermore, we propose that all the patients who undergo dialysis treatment should be screened for NAFLD/NASH in order to identify the high risk for the development of CVD in these patients.

**Hypothesis**

The main risk factors responsible for the development of NAFLD/NASH (mainly diabetes mellitus, hypertension and dyslipidemia) are highly present in dialysis patients. Today NAFLD/NASH represents a liver manifestation of MS and it increases the risk of coronary heart disease and cardiovascular complications in general population. We hypothesized that patients undergoing dialysis treatment have a high prevalence of NAFLD due to a high prevalence of above mentioned components of MS in dialysis patients. Furthermore, we hypothesize that NAFLD/NASH is a new important risk factor that contributes in the development of CVD in dialysis patients. Our hypothesis is that ESRD patients with NAFLD have a higher risk of suffering or even dying from CVD than those ESRD patients without NAFLD. The possible underlying mechanism is sub-chronic liver inflammation in NAFLD/NASH patients that leads and contributes to dyslipidemia, inflammation, enhanced oxidative stress and endothelial dysfunction. All of these can consequently result in accelerated atherosclerosis and further cardiovascular and kidney damage progression. According to this, we hypothesize that the presence of NAFLD/NASH in dialysis patients could be a strong predictor of adverse CVD events in this population of patients. Our hypothesis is supported by recent investigations as mentioned above. Namely, preliminary data suggest an association between CKD and NAFLD: the prevalence of CKD was significantly higher in patients with NAFLD/NASH compared to patients without NAFLD/NASH. Furthermore, a recent study documented moderately decreased eGFR and high frequency of microalbuminuria in patients with biopsy proven NASH; the severity of liver damage was associated with lower eGFR [16,3,17]. Therefore, it is logical to expect that ESRD patients that are on maintained haemodialysis would also have a high incidence of NAFLD/NASH that could contribute to further cardiovascular mortality in these patients. Furthermore, we propose that all the patients who undergo dialysis treatment should be screened for NAFLD/NASH in order to identify the high risk for the development of CVD in these patients.

**Evaluation of the hypothesis**

Recently, we have evaluated frequency of NAFLD in ESRD patients on maintained haemodialysis (unpublished data). To this end we used transient elastography (Fibroscan®-CAP). In this cross-section analysis we have found that NAFLD was present in 29 of 60 HD patients (48.3%). The number of hospitalizations and duration of hospitalizations due to adverse CVD events was significantly higher in this group of patients. The severity of liver steatosis was correlated with cerebral infarction ($r = 0.319; p = 0.017$) and ischemic heart disease with acute myocardial infarction ($r = 0.435; p = 0.005$). For further perspective and testing of our hypothesis, in vivo test, including transient elastography (TE) (Fibroscan®-CAP) will be used as non-invasive method to detect and quantify liver steatosis and fibrosis. Liver stiffness will be used to assess liver fibrosis and controlled attenuation parameter (CAP) to detect and quantify liver steatosis by using TE. Also, for detecting liver steatosis we will use an abdominal ultrasound. By anamnesis, clinical and laboratory evaluation, we will exclude pos-
sible other causes of chronic liver disease such as viral hepatitis (hepatitis B and C viral markers), autoimmune and cholestatic liver disease, or use of potentially hepatotoxic medications (e.g. corticosteroids, high-dose estrogen, methotrexate or amiodarone within 6 months of enrollment). In addition, the patients with a history of current or past excessive alcohol drinking (more than 20 g alcohol per day) will be excluded from the study. In all patients we will evaluate and all clinical and laboratory parameters related to hae-modialysis treatment.

The second approach to testing our hypothesis is to investigate the association of NAFLD with carotid intima-media thickness (IMT) and plaque as surrogate measures of increased cardiovascular risk in HD patients. Furthermore, included patients will be monitored during a 24 months period for the number of hospitalizations due to adverse CVD events and the number of hospitalizations for other indications (infection and bleeding), taking into account the cause of hospitalization and its duration. The following disorders will be taken into account as adverse cardiovascular events: cerebral infarction, ischemic heart disease with acute myocardial infarction, and ischemic heart disease without acute myocardial infarction. This data, as well as the above mentioned IMT and plaque measurement, will be correlated with the presence of liver fibrosis/steatosis measured by Fibroscan®-CAP as well as by abdominal ultrasound findings.

Consequences of the hypothesis and discussion

The importance of the liver in the regulation of metabolism has been recognized for over a century and a half, but fatty liver has for a long time been considered a trivial finding. So, today the current importance of NAFLD and its link to MS has encouraged an interest in its possible role in the development of atherosclerosis in recent years. Namely, according to literature, there is a strong association between liver histology in NAFLD patients and greater carotid intima-media thickness and plaque and lower endothelial flow-mediated vasodilatation (as a marker of subclinical atherosclerosis). Furthermore, NAFLD histology predicts carotid intima-media thickness independently of traditional risk factors, insulin resistance and features of MS [9]. Fracanzani et al. [20] showed that steatosis is highly associated to intima-media thickness and to an increased risk of atherosclerosis in subjects with metabolic syndrome. A study from Taiwan revealed that those subjects whose ultrasound scans were comparable with hepatic steatosis had a higher prevalence of ischemic heart disease, irrespective of obesity and other factors [9]. An autopsy study of 742 children found that the prevalence of coronary heart disease is twofold higher in those with NAFLD [21]. Furthermore, a study by Targher et al. [22] has shown that NAFLD is not merely a marker of CVD, but it may actually be actively involved in its pathogenesis. All of these studies confirm the hypothesis that NAFLD-patients have a higher risk of suffering from CVD.

On the other hand, it’s been well established that the life span of patients receiving dialysis is cut short mainly as a consequence of premature cardiovascular death [1,2]. Nonalcoholic fatty liver disease and CKD share some common features such as diabetes mellitus type 2, hypertension and metabolic syndrome while the two most common etiological factors for the development of ESRD are diabetes mellitus type 2 and nephroangiosclerosis. Both diseases are also linked with an increased risk for the development of CVD [19]. Therefore it is not surprising that these two disorders are closely associated one with the other. As mentioned above, in recent years, several studies, as well as our own, have shown that NAFLD is associated with a significant decrease in glomerular filtration rate and an increase in albuminuria and the incidence of CKD [22–25]. Although, the association between HD patients, NAFLD and CVD has still not been investigated, and there is no epidemiological data about this relationship, it is reasonable to expect that patients with CKD stage V, that are on maintained HD, will also have a high or maybe higher incidence of NAFLD than those patients that have CKD stage III and IV.

The presence of insulin resistance is recognized as the pathophysiological hallmark of NAFLD and is believed that it is present in up to 95% of NAFLD patients [7]. Insulin resistance also plays a role in the development of CKD. In patients with CKD the exact mechanism of insulin resistance is not known but it is believed that vitamin D deficiency, obesity, metabolic acidosis, inflammation, and accumulation of “uremic toxins” contribute in the development of insulin resistance [3,19].

Today it is believed that inflammation plays a key role in the initiation and progression of the atherosclerotic process, and according to many authors atherosclerosis has been defined as “an inflammatory disease”. A high percentage of ESRD patients have serological evidence of an activated inflammatory response due to decreased renal clearance of pro-inflammatory cytokines, co-morbidities, the accumulation of advanced glycation end-products, etc. Furthermore, the generation and metabolism of various proinflammatory and anti-inflammatory cytokines is disturbed in ESRD patients. High serum concentrations of proinflammatory mediators in ESRD patients has been associated with atherosclerosis and increased cardiovascular mortality in these patients [2]. On the other hand, the liver is the central organ for the production of various classical biomarkers of inflammation and endothelial dysfunction, the secretion of which partly depends on factors that are up regulated in the presence of insulin resistance and the metabolic syndrome. Today, there is growing evidence suggesting that in patients with NAFLD/NASH there is an increased production and release of various proinflammatory cytokines. These include increased reactive oxygen species, TNF-α, TGF-beta, plasminogen activator inhibitor-1, C-reactive protein (CRP), IL-6 and etc. produced by hepatocytes and nonparenchymal cells, including Kupffer cells and hepatic stellate cells. So, enhanced oxidative stress, inflammation with release of inflammatory cytokines and abnormal lipoprotein metabolism could account for the proatherogenic effect of NAFLD [8,26–33].

Furthermore, in HD patients who develop chronic liver disease (CLD) as a consequence of NAFLD, there is one more risk factor that could contribute to CVD mortality. Namely, there is a widespread opinion that patients with CLD are protected from thromboembolic incidents, largely because of the increased risk of bleeding and altered conventional coagulation tests. However, an increasing number of publications are reporting a rising incidence of thromboembolic incidents in patients with CLD relative to the general population, possibly due to decreased levels of synthesis of protein C, protein S and tissue plasminogen activator. It is important to note that this increased risk cannot be assessed by the usual coagulation test, which is not adequate to evaluate the risk of future thromboembolic incidents [34,35].

According to these observations, HD patients who develop NAFLD/NASH as a consequence of shared etiological factors (the components of metabolic syndrome) probably have a much higher level of oxidative stress, endothelial dysfunction and much faster progression of atherosclerotic process and development of adverse CVD events, compared to patients without NAFLD. We purpose that NAFLD should be considered as a new important risk factor for increased cardiovascular morbidity and mortality in patients undergo dialysis treatment. Also, we purpose that some of non-invasive methods for detecting NAFLD such as transient elastography (Fibroscan-CAP) could be used in this population of patients as a screening method for detecting a high risk patients in order to timely act and prevent adverse CVD. Furthermore, the use of a non-invasive approach for detecting NAFLD in HD patients is...
important due to previous observations which indicated that standard reference values of liver tests cannot be used as markers of liver damage in HD patients. The use of liver biopsy in HD patients is limited due to an increased risk of bleeding in this population of patients [36–38].

We hope that the proposed research will contribute to the greater general knowledge about the association of NAFLD and the increased risk of adverse CVD events in HD patients. The work could help to determine the incidence of NAFLD in HD patients, as well as to determine if HD patients with NAFLD have a higher incidence of CVD disease. The results could consequently help to recognize high risk patients for adverse CVD events that should be aggressively treated in order to reduce their CVD morbidity and mortality. We hope that our proposed research will encourage new investigations on NAFLD in ESRD patients as well as in those having the earliest stage of CKD.

Declaration of funding source

We have no sources of financial support to declare.

Conflict of interest

None.

References