Study of Non-alcoholic fatty liver disease among chronic kidney disease patients by Controlled attenuation parameter

Thesis
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List of Abbreviations

ACE	**Angiotensin converting enzyme inhibitors**
ACR	**Albumin-to-creatinine ratio**
AGE	**Advanced glycation endproducts**
ALT	**Alanine aminotransferase**
ARBs	**Angiotensin receptor blockers**
AST	**Aspartate aminotransferase**
BMI	**Body Mass Index**
BUN	**Blood urea nitrogen**
CAP	**Controlled attenuation parameter**
CKD	**Chronic kidney disease**
CRP	**C-reactive protein**
EASL	**European Association for the Study of the Liver**
ESRD	**End-stage renal disease**
EWAS	**Exome-wide association studies**
FBG	**Fasting blood glucose**
FGF	**Fibroblast growth factor**
GFR	**Glomerular filtration rate**
GLP	**Glucagon-like peptide**
GWAS	**Genome-wide association studies**
HbA1c	**Hemoglobin A1C**
HCC	**Hepatocellular carcinoma**
HDL	**High density lipoprotein cholesterol**
IL-6	**Interleukin-6**
KDIGO	**The Kidney Disease Improving Global Outcomes**
LDL	**Low density Lipoprotein cholesterol**
MBD	**Mineral bone disease**
MDRD	**Modification of Diet in Renal Disease**

NAFLD	**Non-alcoholic fatty liver disease**
NASH	**Non -alcoholic steatohepatitis**
NIDDK	**National Institute of Diabetes & Digestive & Kidney Disease**
OCA	**Obeticholic acid**
OSA	**Obstructive sleep apnea**
PCOS	**Polycystic ovarian syndrome**
PNPLA3	**Patatin-like phospholipase domain-containing protein 3**
SAF	**Steatosis, activity and fibrosis**
T2DM	**Type 2 diabetes mellitus**
TE	**Transient elastography**
TZDs	**Thiazolidinediones**

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Abstract

BACKGROUND/AIM Preliminary data suggest an association between chronic kidney disease (CKD) and non-alcoholic fatty liver disease (NAFLD). The aim of this study was evaluate the frequency of NAFLD and its associated risk factors among nondiabetic CKD patients not on dialysis. **METHODS**: A total of 40 subjects were enrolled in the study. Group A (30) Pre dialysis non-diabetic CKD patiens and Group B (10) normal subjects matched for age and sex as a control group. Liver stiffness measurement was used to detect liver fibrosis and CAP (controlled attenuation parameter) was used to detect and quantify liver steatosis (Fibroscan®). NAFLD was defined by CAP values ≥238 dB/m. **RESULTS:** Results of the current study showed that CKD stage III was present in 17 patients (56.7%) and CKD stage IV in 9 patients (30%) and CKD stage V in in 4 patients (13.3%). The total frequency of presence of steatosis (CAP values ≥238 dB/m) whatever degree was significantly higher in CKD group than control; More than (53%) of CKD patients have NAFLD, and (30%) of control group have NAFLD. The severity of liver steatosis was negatively correlated with GFR, Hb and HDL, and positively correlated with Creatinine, BUN, CRP, Cholesterol, TG, LDL, SGPT, SGOT, FBG and HBA1C. There was significant relation between steatosis and CKD etiology. (82.3%) of Patients with hypertension have Steatosis, (33.3%) of Patients with reflux nephropathy have steatosis, (16.7%) of Patients had other causes have steatosis, while patients had renal stones have no steatosis. There was significant positive correlation between fibrosis degree and age of CKD patients and also significant positive correlation between steatosis and fibrosis among CKD patients. The study showed significant positive correlation between SGPT and fibrosis degree. The results suggest a high prevalence of NAFLD in non-diabetic CKD patients. The severity of liver steatosis is negatively correlated with kidney function; there was significant correlation between CKD stage and other risk factors of hepatic steatosis

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease all over the world, with a global prevalence estimated at 25% of the world's population, but with geographical variability; the highest prevalence has been noted amongst western countries ***(Younossi et al., 2016).***

NAFLD is closely associated with obesity, type 2 diabetes, dyslipidemia and other metabolic risk factors, and is commonly regarded as the hepatic component of metabolic syndrome **(*Loomba and Sanyal, 2013).***

Non-alcoholic fatty liver disease (NAFLD) is defined by the presence of excessive hepatic steatosis (5% or more) without a history of excessive alcohol use in the absence of other liver disease causes ***(Spengler and Loomba, 2015).***

It is a heterogeneous disease, manifesting a spectrum of phenotypes, ranging from simple steatosis, which is traditionally considered relatively benign, to the more aggressive non-alcoholic steatohepatitis (NASH) which is found in 10 to 25% of the cases. Up to one-third of the patients with NASH may progress onwards to liver cirrhosis and other liver-related complications, such as hepatocellular carcinoma (HCC) ***(*Lonardo *et al., 2017).*** In particular, significant fibrosis at the time of diagnosis is the most essential histological feature associated with mortality in NASH ***(Ekstedt et al., 2015).***

Liver biopsy is still the gold standard for diagnosing NAFLD and early liver fibrosis presence. However, histologic lesions are not evenly distributed throughout the liver ***(Lee et al., 2016).***

Recently, Controlled attenuation parameter (CAP) has been introduced as a simple method to assess hepatic steatosis. CAP is a novel physical parameter based on the properties of ultrasonic signals acquired by the Fibroscan® device (EchoSens, Paris, France). CAP measures ultrasound attenuation at the central frequency of the Vibration-controlled transient elastography (VCTE) at M or regular probe (***de Lédinghen et al., 2012).*** CAP was also recorded as an accurate factor which estimates hepatic steatosis ***(Kwok et al., 2015).***

Chronic kidney disease (CKD) is a worldwide health problem with a high economic expense to health care foundations and is an independent hazard factor for cardiovascular illness. All CKD stages are associated with elevated risks of cardiovascular morbidity, poor quality of life and premature mortality, CKD has a high global prevalence with an international occurrence approximately 11 to 13% of adult population ***(Hill et al., 2016).***

Chronic kidney disease (CKD) was defined by persistent urine abnormalities, structural abnormalities or impaired excretory renal function suggestive of a loss of functional nephrons. The majority of patients with CKD are at risk of accelerated cardiovascular disease and death ***(Romagnani et al., 2017)***.

Growing evidence suggested that NAFLD may be linked to an increased risk for (CKD) development and progression. Growing evidence suggests that the metabolic syndrome is an important factor in the pathogenesis of CKD. Several reports had investigated the association of CKD and NAFLD Given the fact that about 90% of patients with NAFLD have more than one component of metabolic syndrome and 45–75% meets the diagnostic criteria. It is not surprising that NAFLD patients will have also lowered renal function ***(Orlić et al., 2014)***.

In fact NAFLD patients have significantly higher levels of various plasma pro-inflammatory cytokines and pro-coagulations factors. Therefore, subchronic liver inflammation in NAFLD/NASH patients leads and contributes to atherogenic dyslipidemia, state of chronic inflammation, enhanced oxidative stress, and endothelial dysfunction. Experimental evidence supposed that NAFLD itself can trigger systemic and hepatic insulin resistance, causes atherogenic dyslipidaemia, and releases a variety of pro-fibrogenic, pro-inflammatory, pro-coagulant and pro-oxidant mediators which may have role in the development and progression of CKD ***(Targher et al., 2014).***

Aim of the Work

To evaluate the frequency of Non-alcoholic fatty liver disease (NAFLD) and its associated risk factors among non-diabetic chronic kidney disease (CKD) patients not on dialysis.

Non-alcoholic fatty liver disease (NAFLD)

Definition

Nonalcoholic fatty liver disease (NAFLD) is becoming the most common chronic liver disease. It is defined as at least 5% steatosis observed in the hepatocytes on either histology or by imaging methods such as proton density fat fraction (PDFF) with the absence of drug abuse and excess alcohol intake ***(Yu et al., 2018).***

Epidemiology

The global prevalence of NAFLD is estimated to be around 25%. In a recent meta-analysis, NAFLD was found to be most prevalent in the Middle East 31%, followed by South America 30%. NAFLD was also found to be least prevalent in Africa 13%. Comparatively, the prevalence of NAFLD in Asia, Europe, and North America was found to be 27%, 23%, and 24% respectively ***(Iqbal et al., 2019)***.

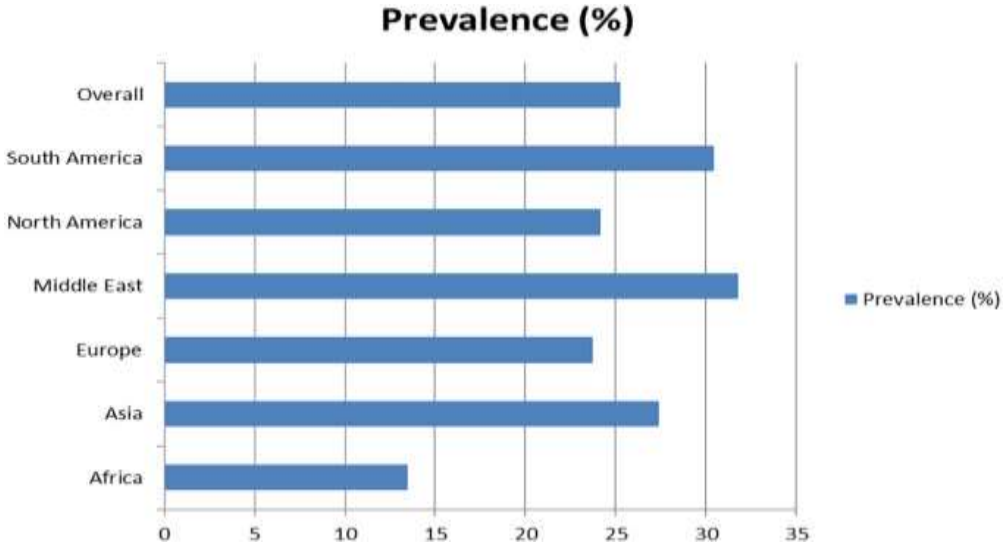

Figure (1): Prevalence of NAFLD in different regions ***(Iqbal et al., 2019).***

The increasing incidence of NAFLD has been associated with the global obesity epidemic and its metabolic complications, including diabetes, hypertension, and dyslipidemia ***(Iqbal et al., 2019).***

The prevalence of NAFLD and NASH varies in individuals with different ethnicities. Hispanics exhibit the greatest prevalence of NAFLD, which is then followed by Caucasians ***(Younossi et al., 2016)***.

Natural history

NAFLD represents a wide spectrum of clinical entities from asymptomatic hepatic steatosis to more advanced liver disease with hepatic failure or hepatocellular carcinoma (HCC) ***(Fazel et al., 2016)***.

The benign form of NAFLD named NAFL (non-alcoholic fatty liver), progresses to NASH (non-alcoholic steatohepatitis) with or without fibrosis. Subsequently, NASH causes cirrhosis and eventually hepatocellular carcinoma (HCC). NASH may progress to HCC without cirrhosis (Figure 2) ***(Cobbina and Akhlaghi, 2017)***.

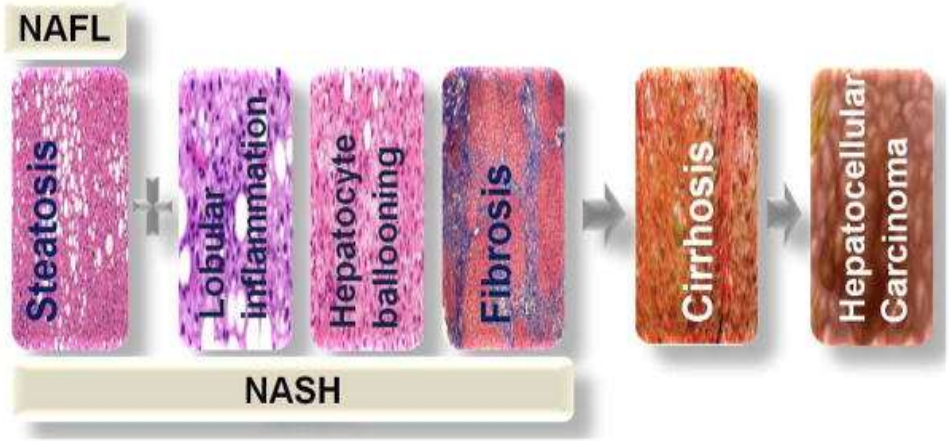

Figure (2): The progressive stages of NAFLD ***(Cobbina and Akhlaghi, 2017).***