"ROLE OF COMPUTED TOMOGRAPHY IN ESTIMATING THE PREVALENCE OF RENAL ARTERY DISEASE IN PATIENTS OF NON-ALCOHOLIC FATTY LIVER DISEASE: A ONE YEAR HOSPITAL BASED PROSPECTIVE COMPARATIVE STUDY"

BY

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Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"ROLE OF COMPUTED TOMOGRAPHY IN ESTIMATING THE PREVALENCE OF RENAL ARTERY DISEASE IN PATIENTS OF NON- ALCOHOLIC FATTY LIVER DISEASE: A ONE YEAR HOSPITAL BASED PROSPECTIVE COMPARATIVE STUDY"** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee.

(Dr. Smita Sonoli)
Member Secretary
JNMC Institutional Ethics Committee
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For **(Dr. Harsha Hegde)**
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LIST OF ABBREVIATIONS

NAFLD	**Non-Alcoholic Fatty Liver Disease**
NASH	**Non-Alcoholic Steatohepatitis**
CT	**Computed tomography**
CKD	**Chronic kidney disease**
ESKD	**End-stage kidney disease**
IR	**Insulin Resistance**
FFAs	**Free Fatty Acids**
GFR	**Glomerulation Filtration Rate**
FSGS	**Focal segmental glomerulosclerosis**
CVD	**Cardiovascular Disease**
USG	**Ultrasound**

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is a disorder categorized by extreme fat accumulation in the form of triglycerides (steatosis) in liver has been associated various other disorders, including renal abnormalities specially with respect to the renal artery dimension, but this association has not been studied by much scholars.

Objectives: To establish a relationship between non-alcoholic fatty liver disease (NAFLD) with renal artery narrowing in patients coming to the Radiology department of KLE's Dr. Prabhakar Kore Hospital, Belagavi on the basis on CT.

Methodology: A prospective comparative study was conducted from January 2023 to December 2023 at KLE's Dr. Prabhakar Kore Hospital. 30 patients in control and 34 in case group including either gender, aged more than 18 years. Control group had all the individuals of either gender aged above 18 years, with no history of non-alcoholic-fatty-liver disease (NAFLD) on examination. Case group, we had included the patients diagnosed with NAFLD. All the patients subjected for abdomen and pelvis CT. Renal artery diameters were measured using a 128-slice CT scanner. Statistical analysis was performed using SPSS software.

Results: The mean age of controls was 40.86 ± 13.72 years, and NAFLD cases were 49.44 ± 12.41 years, showing a significant difference ($p < 0.05$). We observed significant increase in the incidence of smokers and obese patients in case group but there was no significant difference in renal artery diameter. There is strong significant positive association between Smoking (0.028), Obesity (0.018) hypertension and diabetes (0.086 & 0.068) with the NAFLD. NAFLD cases demonstrated a statistically significant difference in both right (controls: 5.49 ± 0.508 mm, cases: 4.57 ± 0.641 mm) and left renal artery diameters (controls: 5.717 ± 0.5 mm, cases: 4.68 ± 0.616 mm) compared to controls ($p < 0.001$).

Conclusion: NAFLD has significant negative correlation with renal artery dimensions, there is need for further clinical studies with bigger study population in this regard to better understand the same

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a disorder categorized by extreme fat accumulation in the form of triglycerides (steatosis) in liver especially when it surpasses its weight by 5-10%. Subgroups of NAFLD patients also display injury to liver cell and inflammation in addition to unwarranted fat known as steatohepatitis and is referred as Non-Alcoholic Steatohepatitis (NASH). NAFLD is a liver injury that happens in the nonattendance of alcohol abuse and embraces an array of histological anomalies.

Though many conditions such as alcohol abuse, hepatitis C viral infection (HCV), drug toxicity, starvation would lead to fatty infiltration of the hepatic cells, non-alcoholic fatty liver disease is the term reserved mainly for the liver manifestation with respect to metabolic syndrome. Aspects that are accountable for rapid growth in prevalence of this condition includes increase in obesity, sedentary lifestyle, diabetes, and inapt use of drugs. Although this is one of the common conditions, yet under-diagnosed/recognised with less known facts about its pathogenesis, treatment and natural history[1].

Metabolic abnormalities such as obesity and the rise of non-alcoholic fatty liver disease (NAFLD) are closely intertwined. A significant majority (74-90%) of patients undergoing liver biopsy exhibit liver changes due to the accumulation of triglycerides. In obese patients undergoing surgical intervention ie., bariatric surgery, NAFLD is found to be highly prevalent (89%). For those with class III obesity, the likelihood of developing steatohepatitis increases, with approximately 15% to 20% of these patients being diagnosed with NASH [2].

NAFLD pervasiveness has been bigger in many western and Asian countries. Complete countless estimations, it has stood recommended that upto 30 percents of grown-ups may have NAFLD in the United States of America (USA). Prevalence figures of non alcoholic fatty liver disease rely much on the population being studied and diagnostic criteria used. Recent study from Japan, involving healthy middle-aged individuals, non alcoholic fatty liver was found to be 20% using Ultrasononography diagnosis, which is similar to the Italian study with twenty percent prevalence.

In other countries, prevalence of non alcoholic fatty liver disease in general population as defined in USA varies from 9 to 29% in Asia, 16% in Mexico, 30% in Israel and 23% in Italy[3]. A number of other studies have communicated a higher prevalence of NAFLD disease among people with T2DM on comparison with non-diabetics which were found to be ranging from 40% to 69.5%[3].

Even on considering the NAFLD prevalence among Asia Pacific population, it is seen widely prevalent and found to be increasing geometrically and is governed by a majority of risk factors for NAFLD which includes type II diabetes, central obesity, metabolic syndrome and dyslipidemia. Indian epidemiological studies suggest the NAFLD prevalence in general population to be around 9% to 32% with higher prevalence in those suffering from diabetes and also obesity[4].(Duseja, 2010).

Non-alcoholic fatty liver disease is often diagnosed after routine lab investigations or an imaging study is done for some other purposes. Transient elastography (TE) is a diagnostic tool which has been designed and developed to measure liver stiffness via ultrasound. Presence and severity of fat deposition can be measured using non contrast Computed tomography (CT) which is quite helpful in

NAFLD evaluation. However, the most accurate and sensitive imaging technique is Magnetic resonance imaging (MRI).

Non-alcoholic fatty liver disease (NAFLD) is a clinico-pathological entity that encompasses simple hepatic steatosis, necroinflammation with varying stages of fibrosis known as non-alcoholic steatohepatitis (NASH), and cirrhosis. NAFLD may be a new, and added risk factor for extrahepatic diseases such as cardiovascular disease (CVD), chronic kidney disease, colorectal cancer. Chronic kidney disease (CKD) is associated with a variety of distinct disease processes that permanently change the function and structure of the kidney across months or years. Chronic kidney disease (CKD) is becoming more common, posing a substantial global burden[5,6].

Chronic kidney disease (CKD) is defined as a glomerular filtration defect or proteinuria that lasts longer than three months. In most instances, CKD leads to end-stage kidney disease (ESKD), necessitating kidney transplantation[7]. Through typical alterations, including glomerular sclerosis, tubular atrophy, and tubular interstitial fibrosis, kidney biopsy specimens can demonstrate a clear indication of CKD.

Chronic diseases have turned to be a major public health problem. Chronic diseases are a leading root of morbidity and mortality in India and other low and middle income countries. Chronic diseases also known as Non-communicable diseases (NCDs), have a propensity to be of long duration and are the result of a combination of genetic, physiological, environmental and behavioral factors and account for about 60% of all deaths worldwide.

A quick global survey conducted by the World Health Organization (WHO) to assess Non-Communicable Diseases (NCDs) management during COVID 19 found

NCD services has huge impact especially in low-and middle-income countries (WHO, 2020). Chronic diseases have contributed to about 68% of the total deaths in 2012, nearly three quarters of which 28 million have been reported from the low and middle income countries.

As per the World Health Organization (WHO), enhanced control of infectious diseases, rapid urbanization and aging population will amplify probable chronic deaths to about 52 million by 2030 (Global status report – WHO, 2014).

CKD may be regarded as one of the clinical model of accelerated vascular disease and premature ageing and the risk-factor profile changes during the progression from mild- moderate CKD to End Stage Kidney Disease (ESKD). CKD has become a worldwide public health problem, both for the number of patients and cost of treatment involved.

The association between NAFLD and renal disease has received little attention. In the review of recent literature, oxidative and systemic metabolisms are compatible with renal dysfunction. The kidney is a highly vulnerable organ damaged by reactive oxygen species, likely due to the abundance of long chain poly unsaturated fatty acids in the composition of renal lipids and systemic oxidative species can result in peroxidation of lipid that may have an effect in calcium oxalate stone formation[8].

Further data suggest that fatty liver may result in changes, leading to an increased incidence of renal dysfunction[9]. Hence, a study was designed to establish a relationship between non-alcoholic fatty liver diseases with renal artery disease on the basis of CT.

OBJECTIVE

To establish a relationship between non-alcoholic fatty liver disease (NAFLD) with renal artery narrowing in patients coming to the Radiology department of KLE's Dr.Prabhakar Kore Hospital, Belagavi on the basis on CT.

REVIEW OF LITERATURE

NON-ALCOHOLIC FATTY LIVER DISEASE [NAFLD]

Non-alcoholic fatty liver disease [NAFLD] is regarded as a hepatic manifestation of diabetes mellitus and metabolic syndrome. Various co morbidities are commonly presented with NAFLD such as type 2 diabetes, impaired glucose tolerance, obesity, hyperlipidemia and hypertension. This further leads to increase risk of cardiovascular disease and can add to the advancement of liver injury[10]. Hence improving the insulin resistance may give rise as a new therapeutical approach to NAFLD.

Liver anatomy and physiology

With secretions coming from the hepatic cells both inside and externally, the liver is the largest gland in the human body. After passing through the bile capillaries, the bile ducts gather the bile, which is its external secretion. This accumulation forms two sizable channels, which eventually unite to form the hepatic duct. The bile is transported by the cystic duct to the gall bladder, from where it is emptied into the duodenum by the bile duct to aid in digestion.

After being absorbed by the gut, carbohydrates and nitrogenous material are processed by internal secretions and transported to the liver by the portal vein. Once in the liver, carbohydrates are stored as glycogen and then released as sugars into the bloodstream.

Liver is situated in the upper right quadrant of the abdominal cavity, resided in, the greater part of the epigastrium which is almost the whole of the right hypochondrium, and not especially broadening into its left side as long as the mammillary line.

In males, the liver weighs between 1.4 and 1.6 kg, but in females, it weighs between 1.2 and 1.4 kg. It makes up around 1/18th of the body weight in the fetus and one-third of the body weight in the adult, respectively, however it is comparatively larger in the fetus than in the adult. It can reach a maximum transverse length of 20–22.5 centimeters.

The largest anterior to posterior dimension at the top end of the right kidney is 10–12.5 centimeters, whereas the vertical measurement is around 15–17.5 cm, near the right surface. The measurement taken earlier in reverse is halved to approximately 7.5 cm in front of the spinal column. It is very vascular, soft, firm, and friable. It has a 1.05 specific gravity and a dark reddish brown color.

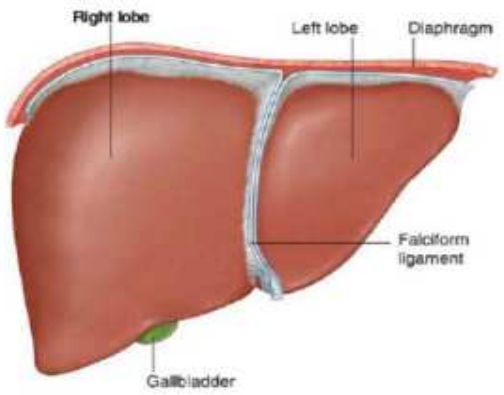


Figure 1 : Anatomy of liver[11]

The liver is divided into two lobes, a right and left lobe. The right lobe and the left lobe are sharply separated by the falciform ligament, with the left lobe being smaller. To the extent that the fifth intercostal space is concerned, the upper surface of the liver is well-positioned. The superior, posterior, anterior, and right surfaces are intricately linked to the anterior part of the abdominal wall and diaphragm, and they are all continuous with one another. In general, the liver has inferior, superior, and posterior surfaces.

The superior and inferior surfaces are separated in front by a distinct, sharp border, with the remaining edges being rounded. The superior surface of the diaphragm links to the anterior abdominal wall through a falciform peritoneum, and the falciform ligament resembles a curving cord similar to the severed umbilical vein.

The 5 fossae of the inferior and posterior surfaces are divided and arranged in the form of the letter H.

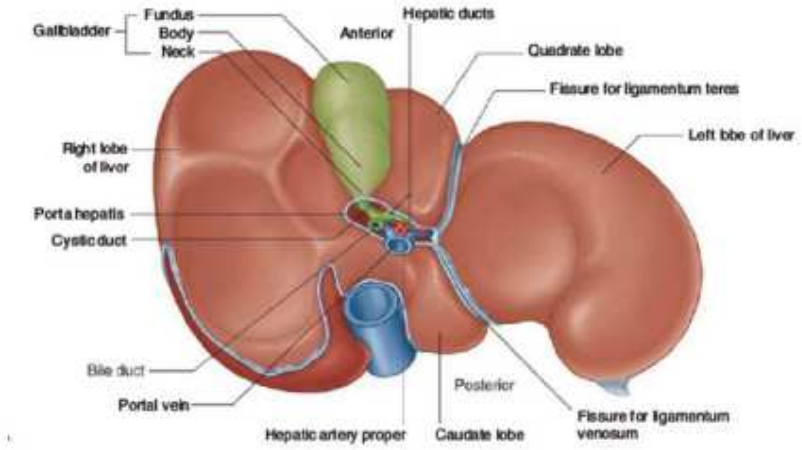


Figure 2 : Surfaces of liver[11]

The division of the liver into right and left lobes is by left limb of the H on these surfaces, known as the left sagittal fossa. This consists of 2 parts, i.e., the fossa for the ductus venosus behind and the fossae for the umbilical vein in front.

Caudate process separates the two fossa of the right limb of the H, behind by the fossa for the inferior vena cava and in front by the fossa for the gall-bladder. The bar that joins the H's two limbs is called the ports transverse fissure; the quadrate lobe is in front of it and the caudate lobe is behind it.

The hepatic vein, the hepatic artery and the portal vein are the blood vessels connected to the liver. The portal vein and hepatic artery are supplemented by several nerves, ascending to the porta, between the layers of the lesser omentum. Blood from

the liver is carried away by the hepatic veins. The nerves originating from liver i.e., the left vagus and sympathetic nerve, enter the porta and go along with the vessels and ducts into the interlobular spaces[11].

Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease [NAFLD] is a liver disease due to insulin resistance associated with metabolic stress and genetic susceptibility having common pathological features to alcoholic liver disease in absenteeism of significant alcohol consumption or other causes of liver disease[12]. To define non alcoholic fatty liver disease it requires -

(a) evidence of abnormal fatty infiltration, diagnosed either by histology or radiological imaging techniques.

(b) No other causes for hepatic fat build-up such as alcohol abuse, hereditary disorders and use of steatogenic medication.

In majority of patients, NAFLD is associated with obesity, diabetes and dyslipidemia. Histologically, non-alcoholic fatty liver disease is classified into

a) Non-alcoholic steatohepatitis (NASH)

b) Non alcoholic fatty liver (NAFL).

Non alcoholic fatty liver (NAFL) is defined as fat accumulation in liver with no evidence of hepatocellular injury or inflammation. Non alcoholic steatohepatitis (NASH) is defined as the presence of fat accumulation and inflammation with hepatic cell injury with or without fibrosis[13]. The spectrum of non-alcoholic fatty liver disease is from abnormal fat build up to nonalcoholic steatohepatitis (NASH) and ultimately might lead to hepatocellular carcinoma and cirrhosis[14].

Epidemiology

The worldwide prevalence of NAFLD vary between 6% to 33% with a 20% median in the general population, based on different diagnostic modalities. However the projected prevalence of non-alcoholic steatohepatitis (NASH) is lower, varying from three to five percent. NASH related cirrhosis prevalence in general population is unknown[15].

Demographics

Age, sex and ethnicity have been associated with a differential prevalence for NAFLD. Several studies have shown that the prevalence of NAFLD increases with age[16,17] In older patients with NAFLD the disease might progress to advanced fibrosis[18] Many recent studies have reported that male sex as a risk factor for fatty liver disease.

Incidence of NAFLD[19]

A recent meta-analysis by Riazi et al[20]. estimated the incidence of NAFLD at 46.9 cases per 1,000 person-years. The incidence of NAFLD was higher in males (70.8 cases per 1,000 person-years) than in females (26.9 cases per 1,000 person-years, $P<0.0001$). However, all included studies were conducted in Asia; hence it is unclear whether these data are generalizable to other parts of the world.

A previous meta-analysis focused on NAFLD in Asia reported an incidence of 50.9 per 1,000 person-years, with the highest incidence of 63 per 1,000 person-years in mainland China and the lowest incidence of 29 per 1,000 person-years in Japan[21]. The NAFLD incidence in South Korea was around 45 cases per 1,000 person-years[22].

Taken together, the estimates for NAFLD incidence in Asia remain consistent across several meta-analyses.

Prevalence of NAFLD

Riazi et al[20]. pooled data from 72 studies (1,030,160 individuals) and estimated that the global prevalence of NAFLD in adults was 32% . The prevalence was higher in males than females (40% vs. 26%, P<0.0001). The prevalence of NAFLD increased from 26% in studies from 2005 or earlier to 38% in studies from 2016 or beyond. However, data from this study by Riazi et al[20] requires cautious interpretation, as data were available from only 17 countries, hence it is unclear if the estimates from this study are a true reflection of 'global' prevalence. The relative lack of studies emphasizes the need to improve data collection from regions such as Africa, Oceania, and South America, where data was lacking. Le et al[23]. also pooled data from 245 studies (2,699,627 individuals) and estimated the global prevalence of NAFLD at 29.8%, which is consistent with Riazi's findings. Likewise, in this study, there was limited or no data from Africa, Oceania, and North and South America.

Aetiology

Accumulation of fat in liver is due to involvement of various factors such as underlying genetic and acquired factors[24]. Fatty liver disease could be:

1. Primarily when there is no underlying cause to explain fat accumulation that too without large amount of alcohol intake.

2. Underlying cause is required to be addressed, as the management is different from that of the primary type.

3. Other common causes include- alcohol abuse, viral infections such as HCV and hepatitis HBV. Other causes which are less common are protein calorie malnutrition,

rapid weight reduction, lipodystrophy, parenteral nutrition, HIV infection, gastric by-pass surgery, inflammatory bowel disease, dysβ-lipoproteinemia, bacterial overgrowth with small bowel diverticulosis.

Micro-vesicular fat buildup where mitochondrial dysfunction plays a major role might be due acute fatty liver in preganancy and Rye syndrome. Drugs such as antimicrobials (zidovudine and tetracycline), synthetic estrogens, tamoxifen, steroids, methotrexate, fialuridine, valproic acid, amiodarone, cocaine, didanosine, and petrochemicals may also lead to NAFLD[25].

Pathogenesis of NAFLD

NAFLD pathophysiology has not yet been completely understood, in recent years much growth has been seen in understanding the pathological process of progression from abnormal fat accumulation to more advanced liver fibrosis. The knowledge is based on the current understanding of NAFLD pathogenesis[26]

1. **The Two Hit Hypothesis**

Initially the proposed theory for NASH pathogenesis was based on a "two hit hypothesis". Accumulation of fat in the form of triglycerides was described as 'first hit', increasing sensitivity of hepatic injury was mediated by 'second hits', not limited to oxidative stress, mitochondrial dysfunction and inflammatory adipokines/cytokines. This combination consecutively leads to fibrosis and/or steatohepatitis. The role of free fatty acids (FFA) is being increasingly recognized in directly promoting hepatic injury leading to modification of this theory. Increased inflow of free fatty acids to the liver has been observed in obesity and insulin resistance.

These free fatty acids are either esterified with glycerol or undergo β-oxidation to form triglycerides, preceding to hepatic steatosis. Enough evidence has been gathered on free fatty acids showing its direct involvement in causing toxicity by increasing the oxidative stress and by initiation of inflammatory pathways.

Hence the accumulation of triglycerides in liver might be a protective mechanism to prevent the toxic effects of unesterified free fatty acids. Hepatic cell death in healthy liver initiates replication of mature hepatocytes, however the central feature of non-alcoholic fatty liver disease pathogenesis i.e., oxidative stress, inhibits this replication resulting in fibrosis/cirrhosis which is considered as 'third hit' of NAFLD[27].

2. Insulin Resistance (IR)

Many of the abnormalities reported in NAFLD contribute to IR by interfering with the insulin signaling cascade. These include FFAs, nuclear factor kappa B (NF-κB), tumor necrosis factor-alpha (TNF-α), cytochrome CYP2E1, jun N-terminal kinase 1 (JNK1), ceramide and SOCS (suppressors of cytokine signalling)[28].

Lipolysis of adipose tissue is suppressed by the potent action of insulin, however, in non-alcoholic fatty liver disease, where insulin resistance is predominant; this suppression is inhibited resulting in an increased outflow of the free fatty acids from the adipose tissue. Hyperinsulinaemia is linked with insulin resistance which leads to inhibition of β-oxidation of FFA for promoting hepatic lipid accumulation and for the up-regulation of a key 32 transcriptional regulator gene that is sterol regulatory element binding protein-1c (SREBP-1c)[29].

3. Genetic Factors

It is suggested that there is a crucial relationship between environmental factors and genetic predisposition in pathogenesis of NAFLD. This is highlighted using the fact that steatosis is common in patients among insulin resistance and obesity but only a minor proportion of it progress to non-alcoholic fatty liver disease and cirrhosis. Gene polymorphisms is related to oxidative stress, insulin resistance, lipid metabolism, cytokines/adipokines and fibrogenesis can alone or in combination increases the susceptibility to developing nonalcoholic fatty liver disease.

Many studies have acknowledged SNP's (single nucleotide polymorphisms) influencing development of fibrosis in other hepatic diseases, particularly chronic hepatitis C. However, studies in non-alcoholic fatty liver disease have so far showed polymorphisms in transforming growth factor β1 (TGF-β1) genes and the angiotensinogen genes in obese patients associated with advanced liver fibrosis. Additionally, single nucleotide polymorphisms in the angiotensin 2 type one receptor which is associated with an increased risk of non-alcoholic fatty liver and related fibrosis. Still more studies are required for identification of exact role of proposed genes[26,30].

4. Lipid Accumulation

NAFLD is characterised by the triglyceride accumulation, built up from the esterification of glycerol and FFA within the hepatic cells. To demonstrate relative contribution of lipid accrual in NAFLD patients, a study was done using multiple-stable-isotope methodology. The results concluded that around sixty percent of triglyceride content in the liver is derived from inflow of free fatty acids and from adipose tissue while 26% from de novo lipogenesis (DNL), and 15% from diet. This

is in contrast to healthy individuals in whom de novo lipogenesis contributes less than five percent of hepatic triglyceride formation[31]. Unusual changes of microsomal transfer protien/apolipoprotein B synthesis and its secretion is proposed as potential mechanism responsible for non alcoholic fatty liver disease pathogenesis leading to a reduced capacity for lipid export.[32]

5. Inflammatory Mediators

The manifestation of steatosis and chronic liver inflammation are strongly associated with an effect that is partly mediated by initiation of the Iκκ-β/NF-κB signalling pathway. In hepatic cell the Iκκ-β/NF-κB pathway can be directly activated by free fatty acids, offering an additional mechanism by which central obesity with subsequent increase in hepatic free fatty acids supply, can add to inflammation. Serum and hepatic levels of tissue necrosis factor alpha are increased in patients with non alcoholic steatohepatitis correlating with histological severity. Additionally to its proinflammatory effects, tissue necrosis factor alpha also promotes insulin resistance[33]. Role of mitochondrial dysfunction and oxidative stress is well established in non alcoholic steatohepatitis patients-correlating with advanced disease and with a higher degree of oxidative stress. In normal liver beta-oxidation takes place in the mitochondria, but in non alcoholic fatty liver disease context this process can be overwhelming as a result of increasing load of free fatty acids, giving rise to reactive oxygen species (ROS)[34]

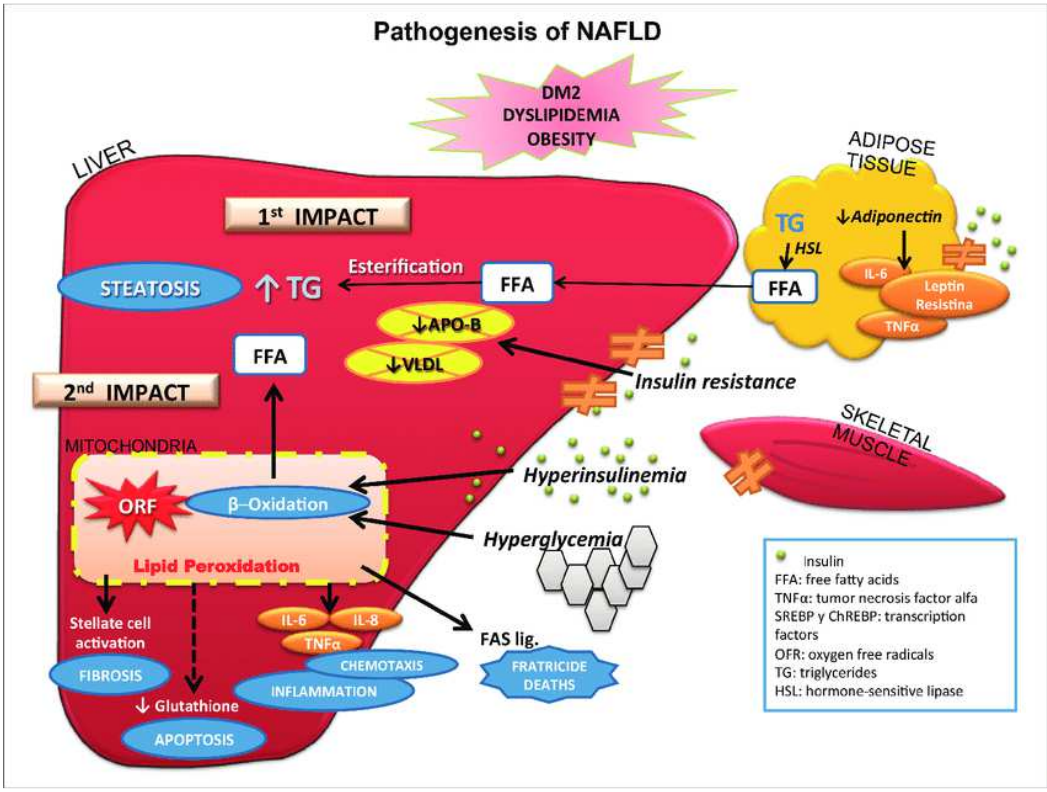


Figure 3: Below image illustrates all pathologies of NAFLD[35]

RENAL ARTERY DISEASE

Kidney disease is considered as a global public health problem which affects more than 750 million people worldwide -GBD Daly‘s and Hale Collaborators, 2016. The burden of kidney disease varies across the world, with its detection and treatment. Although the magnitude and impact of kidney disease are better defined in developed countries, promising evidence suggests that developing countries have a similar or even greater kidney disease burden[36]. In the midst of increasing life expectancy and prevalence of diseases, India has seen a noteworthy rise in occurrence of CKD and it is currently one of the frequently occurring non-communicable diseases in India. CKD is growing globally and it presents challenges for the health systems[37]. There are several studies that suggest that the risk for death which is increased independently

among individuals who have less severe impairment of kidney function and are not dependent on dialysis, compared to those who have preserved kidney function[38,39].

However, rigorously conducted studies have found that slight or no significant rise is the cause or cardiovascular mortality in the setting of mild to moderate chronic kidney disease[40,41]. Even though the precise pathophysiology is not lucid, and mild forms of CKD are known to be associated with morbidity and mortality along with societal and individual impacts which are exceptionally practiced in disadvantaged communities[42]

Regardless of medical assessment, renal dysfunction is defined as the occurrence of renal injury (albuminuria) or impaired kidney functioning designated by increased glomerular filtration rate (eGFR) up to 60 mL/min per 173 m^2 for at least 3 months, according to Kidney Disease Improving Global Outcomes (KDIGO). According to the severity of kidney damage, KDIGO21 categorizes it into five phases based on glomerular filtration rate [Fig 4]

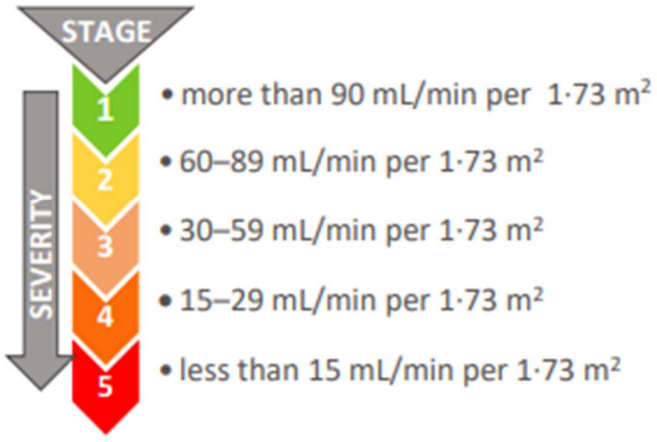


Figure 4: Phases of renal dysfunction based on GFR

Considering GFR is a prevalent indicator of kidney functioning and albuminuria as a sign of glomerular injury, GFR and albuminuria are used to categorize CKD. Both have been demonstrated to be accurate indicators of CKD results. The following standards define chronic kidney disease:

- Duration >3 months based on documentation or inference
- GFR <60 mL/min per 1-73m^2
- Increased glomerular permeability, urine ACR > 30mg/g*

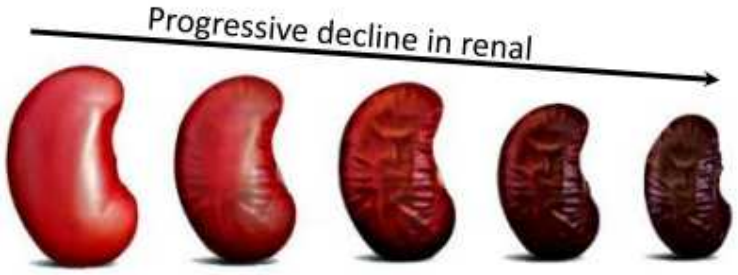


Figure 5: Progression of kidney fibrosis leading to end stage kidney disease

Epidemiology and Prevalence

In conjunction with, and irrespective of, reduced GFR and the risk factors for cardiovascular disease, several demographic research has discovered progressive associations between rising albuminuria, their mortality, and its kidney functioning. Proteinuria plays an essential role in the pathophysiology of the illness developed, according to observations from potential therapeutic research[43,44].

The prevalence of CKD is reported in an increasing number of studies worldwide, which has made it possible to aggregate their findings and to derive information about global CKD prevalence. Study results assessing the prevalence and burden of CKD in 2010 concluded that among 33 population-based representative

studies around the world, reported an age-standardized global prevalence of CKD staging from 1–5 in individuals ≥20 years of 10.4% among men and 11.8% among women. Study reported important differences by geographic region classified by income level, with CKD age-standardized prevalence of 8.6% and 9.6% in men and women, in high-income countries, and 10.6% and 12.5% in men and women, respectively, in low and middle-income countries. The age-standardized global prevalence of CKD stages 3–5 in adults ≥20 years in the same study was 4.7% in men and 5.8% in women.

A recent study conducted a comprehensive systematic review and meta-analysis among 100 studies comprising 6,908,440 patients, and reported a global prevalence of 13.4% for CKD stages 1–5 and 10.6% for CKD staging 3–5. The prevalence of the individual in CKD stages was 3.5% (stage 1), 3.9% (stage 2), 7.6% (stage 3), 0.4% (stage 4), and 0.1% (stage 5). On this basis the results of studies examining the global prevalence of CKD, the current total number of individuals affected by CKD stages 1–5 worldwide was estimated to be 843.6 million.[45]

Mechanisms/pathophysiology

Nephron loss

In humans, nephrons are formed between 13 to 36 weeks of pregnancy, with an average of 950,000 nephrons per kidney (ranging from 200,000 to >2.5 million)[46]. Ever since this time, no additional nephrons can be produced. To satisfy growing kidney requirements, the existing nephrons continue growing over development. In addition, GFR diminishes with aging. However, nephrons can cope with transitory rise in filtration fraction by escalating eGFR temporarily with no transformation and continuous rise in body mass during pregnancy or obesity which encourages nephron

hypertrophy mainly consisting of enhanced components of the glomerular tuft, Bowman's capsule, and the proximal tub. Nephron loss, such as damage or transplantation of one of the kidneys, can cause the residual nephrons to become hypertrophic. Moreover, severe kidney damage or conjunction of damage and age related nephron reductions increases GFR (single-nephron) and removal of remaining nephrons, particularly in those with low nephron reserve and obesity[47]

Nephron hypertrophy

Increased GFR (single-nephron) and glomerular hypertension over glomerular filtration barrier and implying glomerular hyperfiltration cause residual nephron hypertrophy. Rise in glomerular filtration and hypertension causes the production of TGFβ (transforming growth factor β) and EGF (epithelial growth factor) receptors[48,49] , that encourage hypertrophy of nephrons and lower glomerular hypertension by raising the filtering surface. Furthermore, despite losing half of their nephrons, kidney donors can retain a 'normal' kidney function thanks to elevated GFR (single nephron) and remnant nephron hypertrophy. Once kidney donors are appropriately screened for healthy nephron supply, the lack of obesity, diabetic diseases, and additional types of nephritic damage, kidney transplantation does not always result in CKD[50]. Hyperfiltration-induced elevations in the glomerular area, on either hand, can be hazardous in some cases[51,52]. Increased applied load on podocytes causes podocyte separation, focal segmental glomerulosclerosis (FSGS), global glomerulosclerosis, and eventual nephron atrophy; a feedback loop diminishes nephron amount and expands the glomerular filtration barrier[53-55].

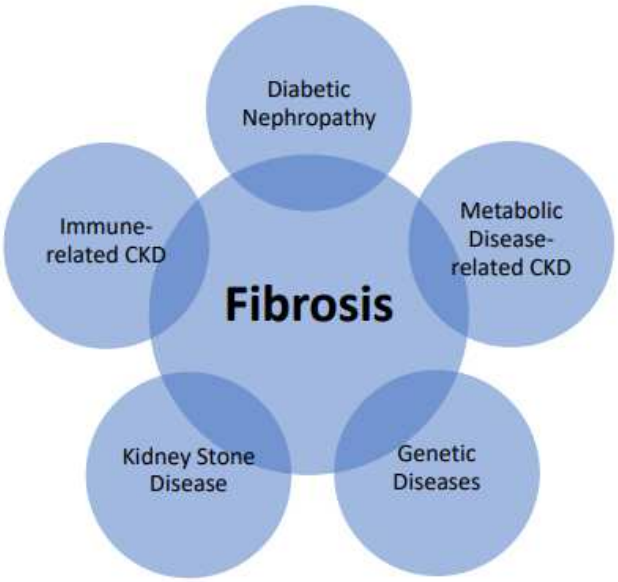
Impaired glomerular filtration.

Angiotensin II secretion and the mTOR pathway sustain continuous hypertrophic podocytes and increased glomerular filtration, eventually exacerbating podocyte depletion and albuminuria. Angiotensin II hormone regulates vasculature constriction and aldosterone release of component in the renin-angiotensin system (RAS). Therefore, the sodium retention and a rise in blood pressure. Aldosterone, in effect, inhibits glomerular barrier filtering performance, perhaps by reducing the production of nephrin[56]. Angiotensin II may potentially play a role in dysfunctional reaction of progenitor parietal epithelial cells along with Bowman's capsule, which results in FSGS lesions rather than the replacement of missing podocytes. Proteinuria, a hallmark of nephron injury and a predictor of advancement of chronic kidney disease (eGFR drop of >5ml/min/1.73m2 per year), is a clinical manifestation of this intrinsic reshaping the glomerulus[57,58] .

Fibrosis.

Interstitial fibrosis is generic wound healing process caused by nephron depletion. Proximal tubular epithelial cells are activated by invading immune cells, albuminuria, and, in diabetes, glucosuria, leading to the release of proinflammatory and profibrotic substances that induce inflammatory responses and interstitial fibrosis[61]. Interstitial fibrosis appears to promote additional nephron damage by promoting kidney ischemia[59], although scar production may physically stabilize the residual nephrons in various organs[60].

Figure 6: Etiologies of fibrosis



Intracellular acidosis, Anaerobic metabolism, and endoplasmic reticulum stress are involved in the elevated tubular transport capacity of remaining nephrons, which induce secondary tubular cell damage[61].

ASSOCIATION OF NON-ALCOHOLIC FATTY LIVER DISEASE [NAFLD] WITH CHRONIC KIDNEY DISEASE [CKD]

Non-alcoholic fatty liver disease (NAFLD) is a clinic-pathological entity that encompasses simple hepatic steatosis, necroinflammation with varying stages of fibrosis known as non-alcoholic steatohepatitis (NASH), and cirrhosis. NAFLD may be new, and added risk factor for extrahepatic diseases like CVD, chronic kidney disease, colorectal cancer, endocrinopathies including type 2 diabetes mellitus [T2DM] and thyroid dysfunction, and osteoporosis.

Majority of studies reported that NAFLD is independently associated with CKD even after adjusting for traditional risk factors like age, sex, BMI, hypertension,

diabetes (and duration), smoking, and hyperlipidemia[62]. The presence and severity of NAFLD are associated with an increased risk and severity of CKD[63].

CKD is associated with increased risk of end-stage renal (kidney) disease and of cardiovascular disease. Life-threatening complications are preventable through early identification and treatment of CKD. Early recognition of CKD has the potential to reduce health-related burden, and search is on for new modifiable risk factors for CKD. One possible new risk factor is non-alcoholic fatty liver disease, which, like CKD is becoming increasingly common[64]

Early recognition and its treatment is aimed at reducing the renal disease progression and CVD complications may limit its health-related burden[65]. Patients with stage 3 CKD benefit from early referral strategies[66]. Despite these premises, CKD often goes unrecognized: in the Third National Health and Nutrition Survey (NHANES III), and among all individuals with stage 3 CKD, the awareness was only 8.2%[67].

The high morbidity, mortality, and health care costs with CKD has led investigators to seek novel modifiable risk factors. Non-alcoholic fatty liver disease is a hepatic manifestation of the metabolic syndrome that affects 30% of the general adult population and 60%–70% of diabetic and obese patients[68].

NAFLD encompasses a histological spectrum that ranges from simple steatosis to non-alcoholic steatohepatitis (NASH), with or without advanced fibrosis. NAFLD confers an increased risk of cirrhosis, largely limited to NASH, and CVD, independently of metabolic syndrome and traditional risk factors through mechanisms which remain unclear[69].

Growing experimental and epidemiological evidence suggests that NAFLD and CKD share a common pathogenic mechanisms and interactions[70]. Evidence for

link between NAFLD and CKD is uncertain due to small study populations and borderline association between NAFLD and traditional risk factors for CKD in the literature published. A meta-analysis on the association of NAFLD and CKD has not been conducted till date.

In cross-sectional studies, the prevalence of CKD was 20– 55% in patients with NAFLD compared to patients without NAFLD which was 5–30% with a persistent association even after adjustment for DM and other common risk factors[71]. In a meta-analysis study conducted in 13 longitudinal studies, risk of incident CKD was 80% greater in NAFLD (HR: 1.79, CI: 1.65–1.95) independent of overlapping cardio-metabolic risk factors[63]. Similarly, in a meta-analysis of 9 observational cohort studies, presence of NAFLD was associated with a 40% increased risk of CKD stage ≥3 (HR: 1.37, CI: 1.20–1.53)[72].

Importantly, more advanced NAFLD has even greater impact on incident CKD findings. In comparison to NAFL, NASH is been associated with an increased prevalence (OR: 2.53, CI: 1.58–4.05) and incidence (HR: 2.12, CI: 1.42–3.17). Histological components that define NASH is portal inflammation score ≥3 which is associated with significant increase in the risk of renal outcomes (HR: 6.58, p=0.001) when it is adjusted for age, sex, insulin resistance (IR), and hypertension (HTN)[73]. In comparing biopsy proven NASH with control non-NAFLD individuals matched for age, sex, and body mass index, there is a significantly increased prevalence of CKD and albuminuria[74]

Among patients with NASH, incident risk of CKD increases further with greater stages of CKD (OR: 2.49 CI: 1.21–5.13 in stage 3b, 3.45 CI: 1.15–10.39 in stage 4, 3.87 CI: 1.1–13.58 in stage 5). In a posthoc analysis from a trial which studied impact of lifestyle changes on biopsy-proven NASH said that histological

resolution of NASH had an improvement in kidney function (GFR 2.32 vs −1.04 mL/min/ 1.73 m2 , p=0.04) irrespective of weight loss. In comparison to lower stage of fibrosis, NASH with advanced fibrosis is associated with higher risk of incident for CKD (HR: 3.29, CI: 2.3–4.71) that is progressively increased with higher stages of CKD (OR: 7.48 CI: 2.95–18.97 in stage 3b, 7.66 CI: 2.72–21.56 in stage 4, 12.67 CI: 4.49–35.76 in stage 5)

Fibrosis staging in NASH has a graded association with decreasing GFR which is independent of age, body mass index, IR, and components of the metabolic syndrome. Improvement of a single fibrosis stage in NASH leads to improvement in kidney function (GFR +7.6 vs −1.98 mL/min/1.73 m2, p< 0.01) irrespective of weight loss[75].

The Link between NAFLD and CKD: Common Risk Factors and Shared Mechanisms

NAFLD is a multiorgan disease and is strongly associated with type 2 DM, CVD, and CKD. A causal relationship between NAFLD and CKD is difficult to prove due to their risk factors including IR, DM, HTN, dyslipidemia, and obesity. Numerous shared risks and pathogenetic mechanisms carry out similar processes of injury with interplay between the organs (Figure 7)

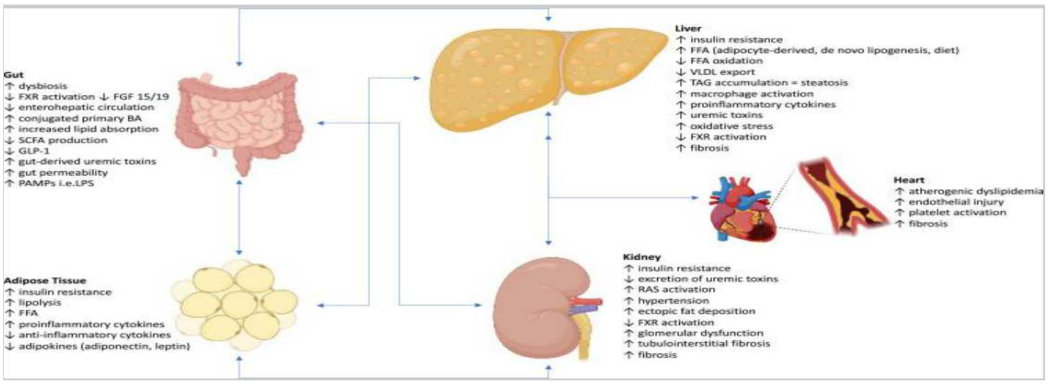


Figure 7: Role of a Gut-AT-Liver-Kidney Axis Leading to NAFLD and CKD

IMAGING TECHNIQUES TO EVALUATE NON-ALCOHOLIC FATTY LIVER DISEASE AND CKD

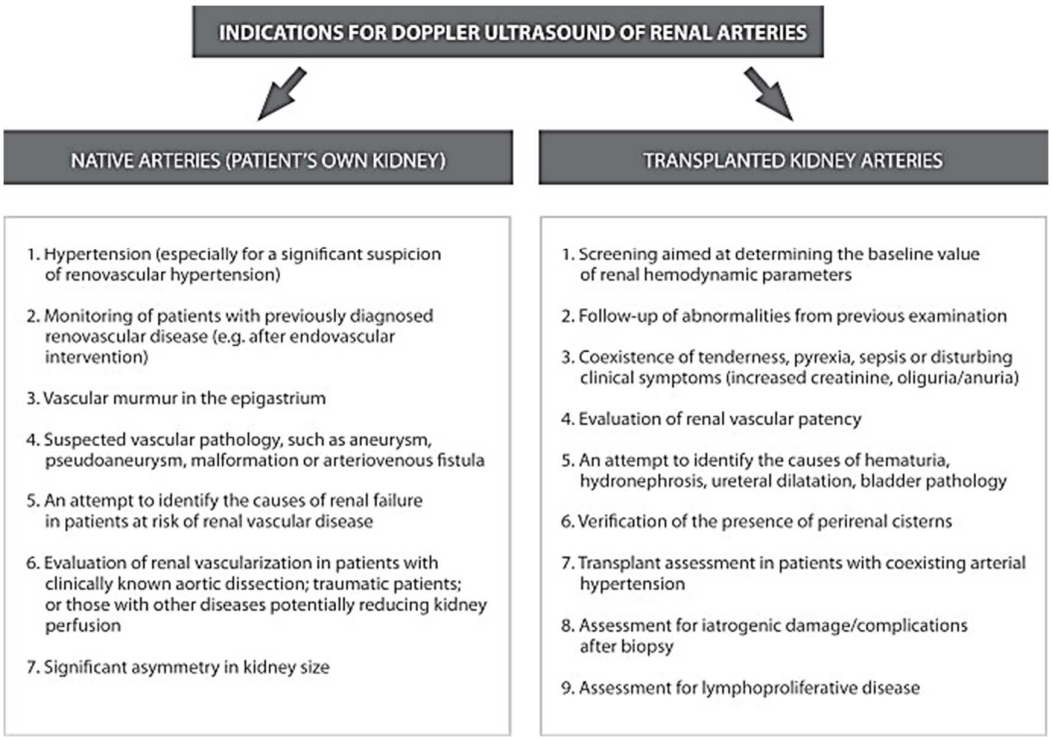
There is a substantial motivation for the development of non-invasive approaches for the management of NAFLD and imaging techniques that quantify hepatic steatosis or liver stiffness[75] [Brunt EM, 1999], and to assess other potential quantitative imaging biomarkers. Recent progress in modern imaging techniques over the past 2 decades in non-invasive imaging techniques can help to detect and quantify hepatic steatosis and are increasingly chosen in clinical settings[76].

Focus on non-invasive imaging techniques such as ultrasound (USG), computed tomography (CT), and magnetic resonance imaging (MRI) for the diagnosis and staging of NAFLD, provides an overview of the concepts, diagnostic performance, and advantages and limitations of each approach. Hence, we are focusing on the CT for diagnosis and to estimate the prevalence of CKD in NAFLD. CT is a generally used imaging technique for the abdominal exam that can objectively quantify liver fat content. X-ray absorption of the fatty tissue is less than that of normal hepatic tissue, resulting in a decrease in attenuation as fat concentration increases.

USG OF RENAL ARTERY

Machine for USG intended for renal artery examination should be equipped with duplex functionality for evaluating the colour coded blood flow which would be preferably an additional option in order to visualizing low-velocity blood flow as well as recording the spectrum of blood flow. As the renals and related arteries are deep located, a typical convex transducer which is having the frequency of 2–5 MHz (most commonly 3.5 MHz) must be used in most cases. In well-prepared, lean patients,

blood flow assessment might be performed using 6 to 12 MHz multi-frequency linear transducer which allows more accurate hemodynamic measurements and the most favorable Doppler insonation angle[77].



Also, arterial flow study, the doppler USG is indicated in the above conditions and the normal values of the same are as follows,

Normal values of arterial parameters[78]:

- PSV in the trunk of about 100 cm/s
- RAR (renal aortic ratio, the ratio of maximum blood flow velocity in the renal artery to the maximum velocity in the aorta) of about 0.8–1.0
- AI (acceleration index, the rate of acceleration specifying the slope of the curve expressed in m/s2) ≥3 m/s^2
- AT (acceleration time, the time counted in seconds since the beginning of the systolic phase to reaching the maximum velocity in the mid-systolic phase) ≤0.07 s
- PI (pulsatility index) 0.78–1.33
- RI (resistance index) about 0.5–0.8

Renal RI (RRI), introduced by Pourcelot et al[87] is defined as a: ratio of the difference between maximum and minimum end-diastolic flow velocity to maximum flow velocity derived from the Doppler spectrum of intrarenal either segmental or interlobar arteries. Normal RI values in adults are in the range of 0.47–0.70 with a difference between two kidneys of <5–8 %. Resistive index measured in intrarenal segmental arteries is a well-known marker of renal vascular and interstitial damage, corresponding to an increased total cardiovascular risk.

In chronic kidney disease, the RRI observed by articles have been varied widely but the cut off of >/=6.5 mentioned it as indicator of severe interstitial fibrosis (>20 %), severe arteriosclerosis and decline of renal function.

Limitations[78]:.

- Anatomy and congenital defects – mobile kidney, multiple renal arteries, horseshoe kidney
- Severe condition of the patient – lack of respiratory cooperation as they might not be able to at supine position and also the change in respiratory pattern could affect the view
- Difficult scanning conditions – large number of intestinal gases or obesity

LIVER ON CONVENTIONAL UNENHANCED CT

Normal liver parenchyma is about 60 HU in unenhanced CT, and it hyperattenuates to the spleen[79], while steatosis is approximately at 40 HU, the liver tissue hypoattenuates to the fat-free spleen[80]. The sensitivity and specificity of unenhanced CT for low-grade steatosis (cut-off values, 10–20%) are 57% and 88%, respectively. For high-grade steatosis (cut-off values, 25%), the sensitivity and specificity increase to 72% and 95%, respectively[81]. A HU threshold of 48 in unenhanced CT acquired at 120 kVp has been strongly specific (100%) for high-grade steatosis (~30%), with a positive predictive value of 100% and negative predictive value of 94%, with a sensitivity of 54%. Unenhanced CT is usually preferable for predicting pathologic liver fat content as assessed by histopathology because iodine-based contrast agents increase hepatic attenuation, preventing precise quantification of liver fat content[82].

However, the absolute attenuation value of liver parenchyma on an unenhanced CT scan can be affected by beam hardening effects in patient with a large body habitus and CT acquisition parameters including kVp and vender-specific filters and reconstruction algorithms[83]. Therefore, instead of using absolute attenuation value

of liver parenchyma on unenhanced CT scan (CTL), attenuation differences between the liver and spleen on unenhanced CT using the spleen as an internal control has been thought to be a more adequate quantitative parameter to evaluate hepatic steatosis[84] Clinical CT provides a significant potential for detecting incidental steatosis and may aid in clarifying the standard course of NAFLD[85].

RENAL ARTERY ON CT

The renal artery on computed tomography (CT) imaging is typically visualized as a pair of major blood vessels emanating bilaterally from the lateral aspects of the abdominal aorta, just inferior to the superior mesenteric artery. Utilizing contrast-enhanced CT angiography, the renal arteries are clearly delineated, appearing as high-attenuation structures that course laterally and posteriorly towards the kidneys. This imaging modality allows for detailed assessment of the vascular anatomy, enabling the identification and characterization of pathological conditions such as renal artery stenosis, aneurysms, occlusions, and fibromuscular dysplasia. Moreover, CT imaging is instrumental in preoperative planning and post-interventional evaluation of renal vascular procedures..

COMPARATIVE STUDIES

Study done by Hamdy in 2013[89], found that NAFLD is good predictor of cardiovascular diseases and renal diseases. A study done by Leonard Kaps, Christian Labenz et al (2020, Germany)[90] found NAFLD constitutes independent risk factor for CKD. Patients living with NAFLD should be monitored for change in kidney function, facilitating therapeutic measures for kidney disease at an early stage.

Seungho Ryu, Yoosoo Chang, Dong-Il Kim, Won Sool Kim, Byung-Seong Suh (2007, Korea)[91] found that the serum GGT may be an early predictor for the development of CKD, independent of baseline confounding factors and the subsequent development of hypertension. Amanda Cheung and Aijaz Ahmed (2021, USA)[92] found that there is strong evidence for the increased prevalence and incidence of CKD in NAFLD, including severity in NASH and advanced fibrosis. NAFLD and CKD have similar impact on outcomes, mostly on cardiovascular morbidity and mortality. Hence, early recognition and screening for CKD in NAFLD patients is important to allow for earlier implementation of relevant strategies.

Hossam El-Din A. Mahmoud, Wael A. Yousry, Shereen A. Saleh, Mohamed El Badry, Ahmed Hussein, Mostafa Hassan Ali et al (2020, Egypt)[93] found that RRI was significantly higher in NASH patients with fibrosis (mean = 0.74) than NASH patients without fibrosis (mean = 0.65) and patients with simple steatosis (mean = 0.63). It was the lowest in normal controls (mean = 0.61). G. Targher, L. Bertolini, M. Chonchol, S. Rodella, G. Zoppini, G[94]. Lippi et al (2010, Italy) found that the age- and sex-adjusted prevalence of diabetic retinopathy (53.2 vs 19.8%) and CKD (37.8 vs 9.9%) was markedly higher in patients with NAFLD than in those without ($p < 0.0001$).

Maria Mohiuddin[95] and colleagues conducted a study to determine the reference range of renal artery measurements by using multidetector CT angiography and also to find the association of renal artery measurements with respect to artery side, age and gender. They concluded that the mean diameter and mean length were found significant between right and left side of main renal artery and between males and females.

MATERIALS AND METHODS

Patients above the age of 18 years coming to the Department of Radiology of KLEs Dr. Prabhakar Kore Hospital, to get the CT abdomen scan done during the 1-year period from January 2023 to December 2023.

Study Design: Prospective comparative study

Study Period: January 2023 to December 2023

Sample Size: The formula used for sample size calculation is,

$$n = \frac{2\left(Z_{\alpha/2} + Z_{\beta}\right)^2}{d^2}$$

$$where, d = \left(\frac{|\mu_1 - \mu_2|}{\sigma}\right)$$

where, µ1 is mean of the first group, µ2 is mean of the second group, σ^2 is the common error variance, $Z_{\alpha/2}$value is 1.96 for 95% confidence level and Z_{β} value is 0.8416 for 80% power. Considering between group (with and without NAFLD) effect size for renal artery diameter to be 0.8, at 5% level of significance, and 85% power, the sample size is obtained to be 30 subjects for each group.

Total sample size required is 30 x 2 = 60 subjects.

As sample size increases, the accuracy increases.

Sampling technique: Convenient sampling.

Inclusion Criteria: Patients of age 18 years and older

All the individuals of either gender aged above 18 years, on the basis of clinical history and CT examination who did not have features of non-alcoholic-fatty-liver disease (NAFLD) were kept in the control group and the patients who had features of NAFLD were included in the case/test group.

Exclusion Criteria:

- Known history of liver disease such as viral, genetic, autoimmune, and drug induced liver disease
- Patients with positive test for Hepatitis B antigen or Hepatitis C antibody
- Patients with a history of alcohol intake or cancer
- Patients with previous history of overt proteinuria
- Patients receiving medical treatment for current kidney disease

Study protocol:

Institutional ethical clearance was obtained. Study population were included based on the above inclusion and exclusion criteria. Detailed protocol, the need for CT, guidelines and detailed procedure of CT was explained to all the patients. Written informed consent was taken. Demographic data, past medical, surgical, personal, and present medical history were noted. Patients had undergone routine blood investigations but those were not recorded by us as we focused only on CT findings and the comparative changes. CT was conducted using 128 slice Computed Tomography machine manufactured by GE Healthcare. Standard abdomen scan protocol was maintained. The observed findings were noted.

Their scans had been evaluated for NAFLD and renal artery disease, and the findings were noted and analyzed on SPSS.

STATISTICAL METHODS USED

Data was analysed using SPSS software version 21 and Excel. Categorical variables were given in the form of frequency table. Continuous variables were given in Mean ± SD/ Median (Min, Max) form. Categorical variables are analysed by Chi square test. Ordinal data was analysed by Independent t test and Mann Whitney U test. Normality was analysed by Shapiro wilk test. P-value less than or equal to 0.05 indicates statistical significance.

RESULTS

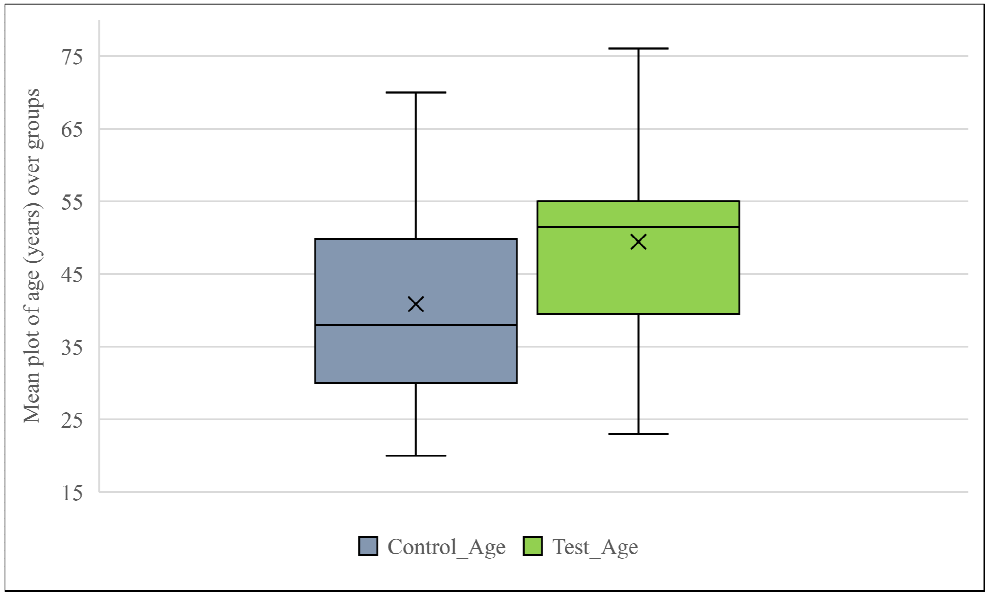
Data contains information of total 64 subjects who were divided in two groups, Control were subjects without NAFLD and Test were subjects with NAFLD. Control group had 30 subjects and Test group had 34 subjects. The mean age was 40.86 ± 13.72 of controls and 49.44 ± 12.41 of test. The following tables give the summary of data.

Table 1: Distribution of subjects according to different variables over groups

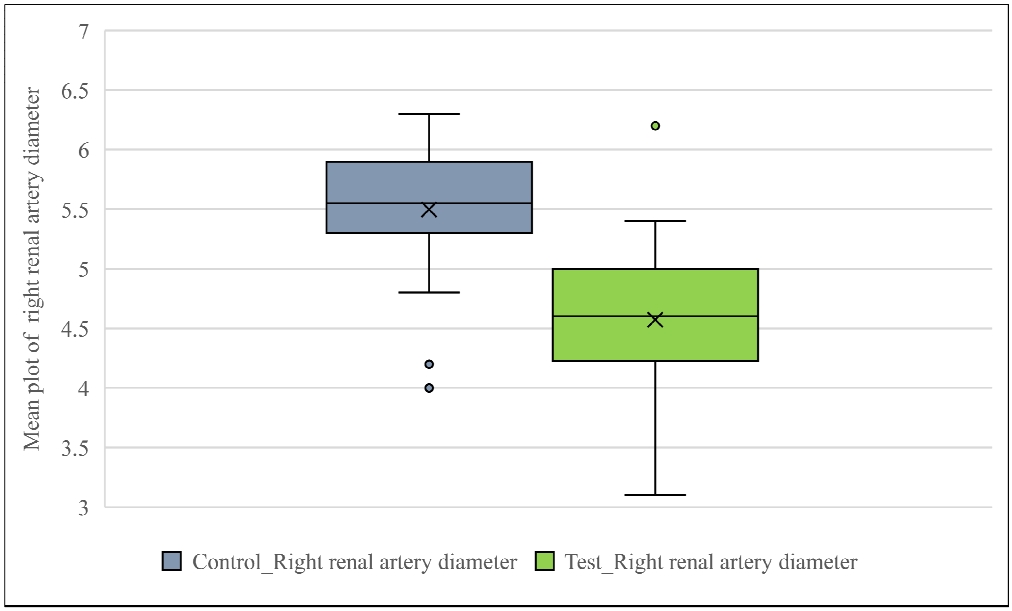
Variable	Sub Category	Groups		p-value
		Control	Test	
Age (years)	Mean ± SD Median (Min, Max)	40.86 ± 13.72 38 (20, 70)	49.44 ± 12.41 51.5 (23, 76)	**0.010*^{t}**
Right renal artery diameter	Mean ± SD Median (Min, Max)	5.49 ± 0.508 5.55 (4, 6.3)	4.57 ± 0.641 4.6 (3.1, 6.2)	**<0.001*^{MW}**
Left renal artery diameter	Mean ± SD Median (Min, Max)	5.717 ± 0.5 5.9 (4.1, 6.4)	4.68 ± 0.616 4.65 (3.2, 6.5)	**<0.001*^{MW}**

*Abbreviation: t- independent t test, MW- Mann Whitney U test, *- indicates statistical significance*

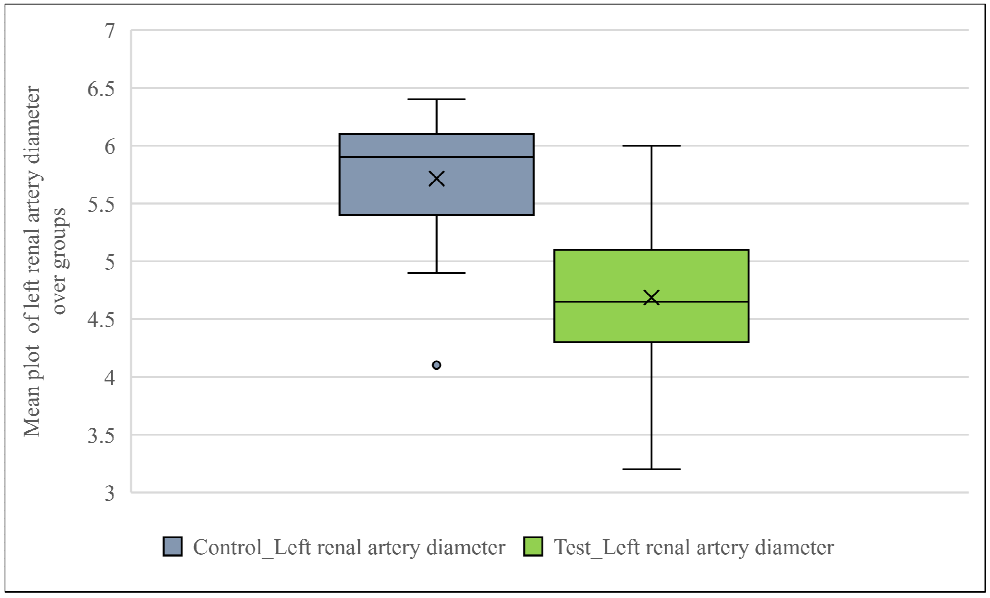
From independent t test, it can be observed that there is significant difference in the means of age over groups. From Mann Whitney U test, it can be observed that there is significant difference in the means of Right artery diameter and Left artery diameter over groups.



Graph 1: Mean plot of Age (years) over groups.



Graph 2: Mean plot of Right renal artery diameter over groups.

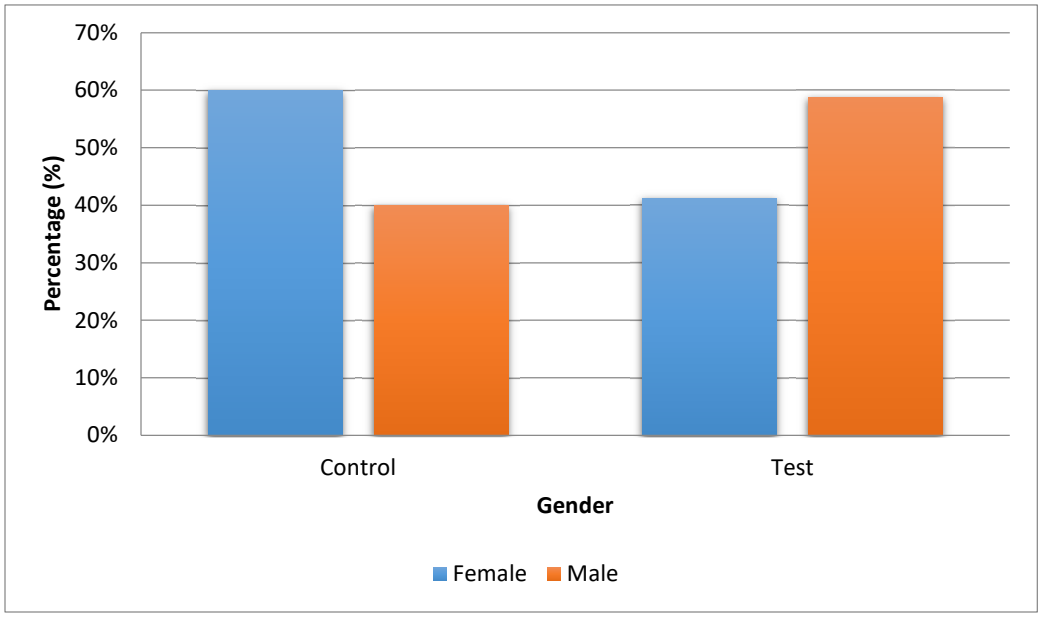


Graph 3: Mean plot of Left renal artery diameter over groups.

Table 2: Distribution of subjects according to gender over groups

Variable	Subcategory	Control	Test
Gender	Female	18 (60%)	14 (41.2%)
	Male	12 (40%)	20 (58.8%)
Total		**30 (100%)**	**34 (100%)**

In control group, there were 18 (60%) female and 12 (40%) male. In test group, there were 14 (41.2%) female and 20 (58.8%) were male.



Graph 4: Distribution of gender over groups

Table 3: Distribution of subjects according to different variables over groups

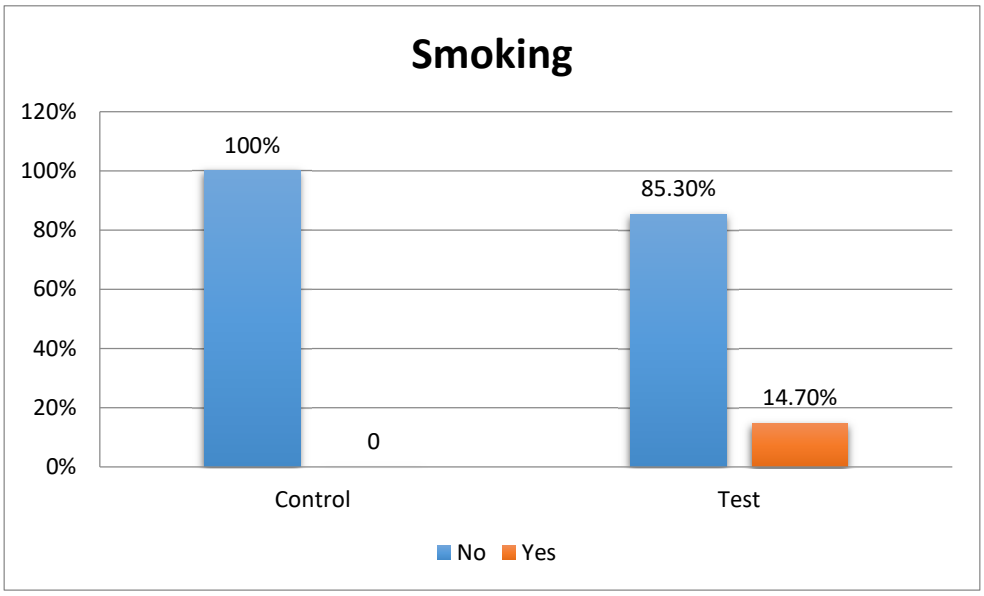
Variables	Sub Category	Groups		Total	p-value
		Control	Test		
Smoking	No	30 (100%)	29 (85.3%)	59 (92.7%)	**0.0287*[C]**
	Yes	0	5 (14.7%)	5 (7.3%)	
Right renal artery diameter		5.33 ± 0.41	5.42 ± 1.01	**0.31**	
Left renal artery diameter		5.21±0.9	4.96± 0.3	**0.17**	
Obesity	No	28 (93.3%)	23 (67.6%)	51 (80.5%)	**0.0108*[C]**
	Yes	2 (6.7%)	11 (32.4%)	13 (19.5%)	
Right renal artery diameter		5.11 ± 1.3	5.08 ± 0.7	**0.14**	
Left renal artery diameter		5.05± 0.7	4.86 ±0.39	**0.11**	

*Abbreviation: C- Chi square test, *- indicates statistical significance*

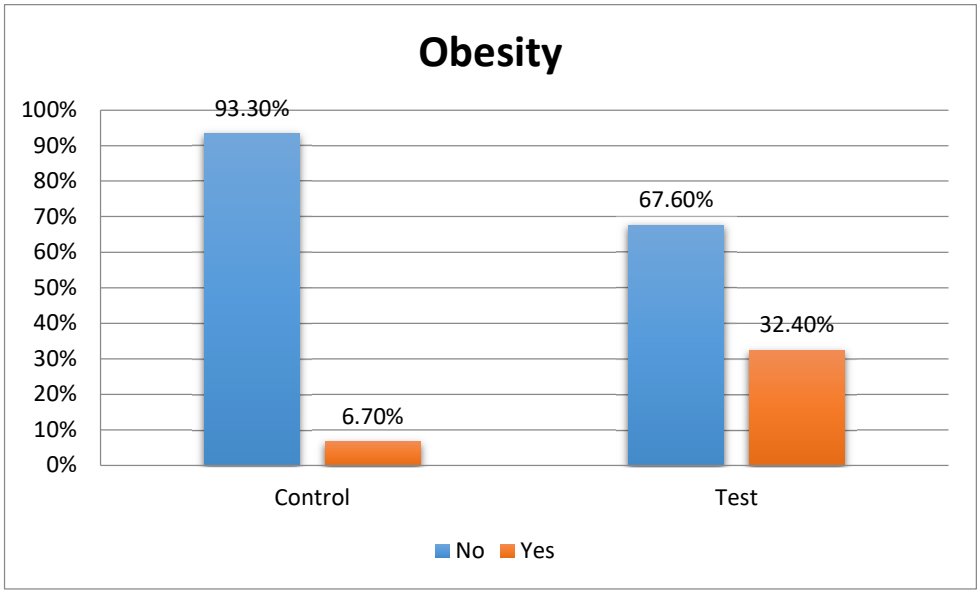
From Chi square test, it can be observed that, there is significant association between Smoking, Obesity and groups. However, no association was observed between other variables over groups.

Table 3A: Co-morbid conditions

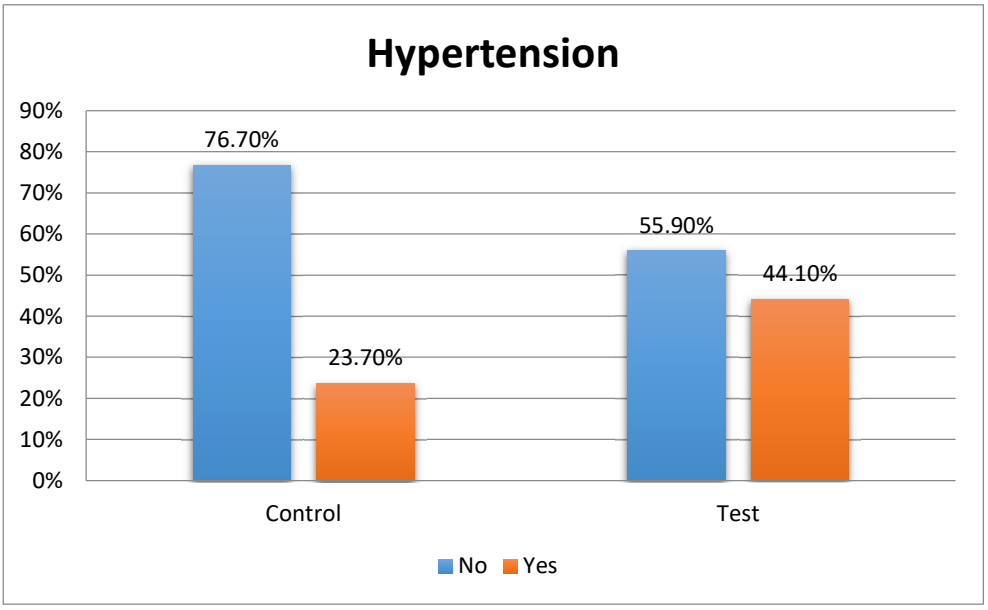
Comorbidity	Sub category	Control	Test	Total	P value
Hypertension	No	23 (76.7%)	19 (55.9%)	42 (66.2%)	0.0806[C]
	Yes	7 (23.7%)	15 (44.1%)	21 (33.8%)	
Diabetes Mellitus	No	23 (76.7%)	18 (53%)	41 (64.8%)	0.068[C]
	Yes	7 (23.7%)	16 (47%)	23 (35.3%)	



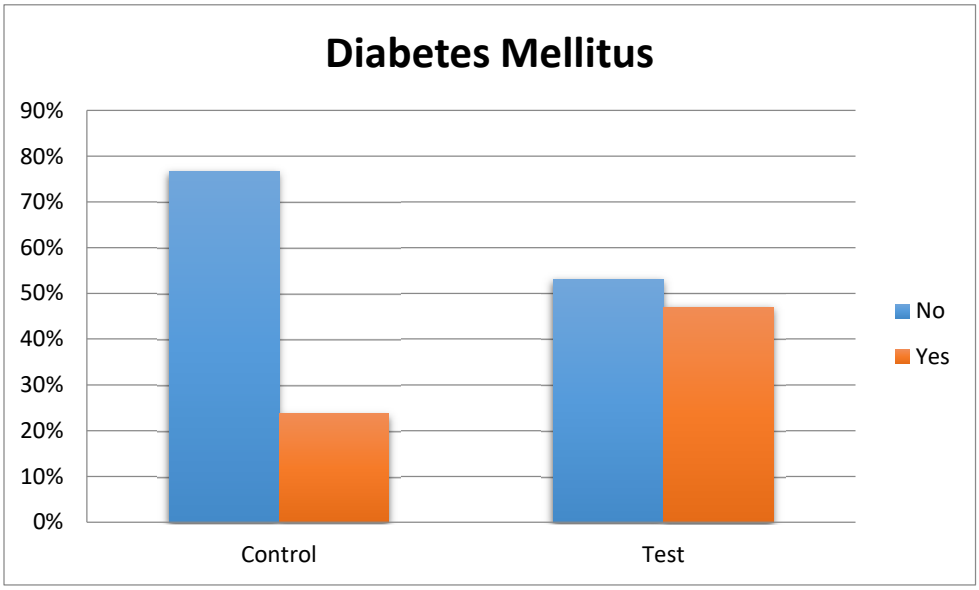
Graph 5: Distribution of subjects based on Smoking over groups.



Graph 6: Distribution of subjects based on Obesity over groups.



Graph 7: Distribution of subjects based on Hypertension over groups.



Graph 8: Distribution of subjects based on Diabetes Mellitus over groups.

DISCUSSION

As per the mined evidences, we found that there is significant association of NAFLD through numerous disease/disorders on which the many clinical studies have been conducted and published as well. But, one of the associated cases among those, the chronic kidney disease (CKD) which had been proved to be having very significant association, has emerged as crucial one not only due to its prevalence but also the significance.[63,64]

Hence, the early diagnosis of the renal artery association has been one of the most important for the prediction of cases between NAFLD and CKD. Than, the early diagnosis, even the accuracy of assessment with respect to renal function is also critical for nephrologists as well as hepatologists.

There has been usage of several methodologies in the published data for the valuation of renal functioning in cases of NAFLD till date. Various formula for the assessment of Glomerular Filtration Rate (eGFR) and Albumin: Creatinine Ratio (ACR) used are modest, practical, and straightforwardly available means for the given association.[93-95]Hence, we conducted this study to asses for the renal artery changes among NAFLD cases.

We included total 64 individuals and divided them in two groups, Control were subjects without NAFLD and test or cases group with NAFLD. Control group had 30 subjects and Test group had 34 subjects. The mean age was 40.86 ± 13.72 of controls and 49.44 ± 12.41 of cases. This difference was statistically significant. We could observe that patients in case group were older than controls. Mohiuddin M et al conducted a study to determine the normal dimensions of renal artery on CT. Multiplanar reconstructed (MPR) and Maximum intensity projection (MIP) images with thin (0.5 mm) and thick (3 mm) slice thicknesses were used to evaluate the renal

arteries. Axial MIP images were generated to visualize renal artery along its route. Renal artery diameter was measured in the proximal segment (1.5 cm from origin) of the renal artery. They observed that the average right and left renal artery length were 44.69 ± 2.48 and 35.10 ± 2.86 mm with the diameters of 6.66 ± 0.39 and 6.79 ± 0.36 mm respectively. These values were comparatively lesser than our study subjects. This had significant difference but with no pathological changes. Added to this, elder patients had observed to be having significant negative correlation with the diameters of both arteries,[95] which was not observed among our cases, which would be due to lesser number of cases more than fifty-five-year-old. In a study conducted by Abd Elrahim E et al, the diameter were significantly higher in males than females with the diameters of left and right renal arteries being 5.482±1.37 versus 5.288±1.09 mm in males and 5.544±1.14 versus 5.188±1.05 mm among females, respectively, though these values were almost same as of our study subjects, we did not find such significant difference. As our study samples was comparatively lesser, through the clinical observations found, which were also not significant, statistical significance also might not have been found.[96] The thickness of arteries among elders might be due to formation of age associated atherosclerosis. Lin Y et al, a new study on epidemiological distribution of NAFLD analysed that 50- to 64-year-old were the commonly affected age group. In the present study, 18 (60%) female and 12 (40%) males were present in control group and 14 (41.2%) female, 20 (58.8%) males in test group.[97] Nagral A et al had reported the prevalence of NAFLD among various countries including India. Based on their statistics, this is almost double among men.[98]

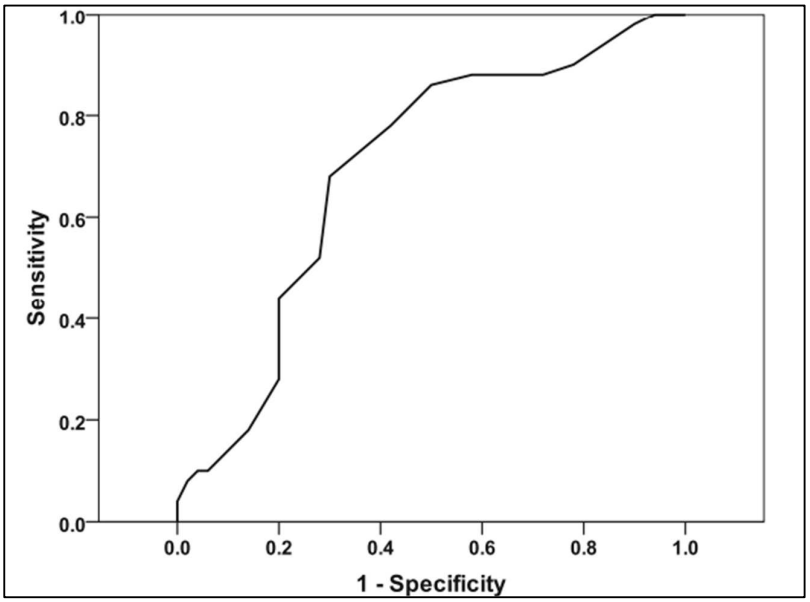
Right renal artery diameter in controls and cases/test group were 5.49 ± 0.508 mm and 4.57 ± 0.641 mm respectively. Left renal artery diameter in controls and cases were 5.717 ± 0.5 and 4.68 ± 0.616 mm respectively, which had significant

reduction in cases than controls. K Yasui et al CKD among NAFLD cases were 14% (24/174) cases this was also a hospital based cross-sectional clinical trial like ours. They had further assessed and interpreted that CKD was 21% among non-alcoholic steatohepatitis (NASH) cases with statistically significant association even with proteinuria.[99] Even in Targher G et al, NASH cases had significantly lesser GFR than non-NASH and NAFLD compared to non-NAFLD.[100]

These and few more evidences who had suggested the strong correlation between CKD and NAFLD are mostly by doing eGFR, urine albumin and A:G.[101]Mahmoud et al is similar to our clinical protocol, who had recruited 150 patients and divided them as 3 different arms: 1. Cases of NASH, 2. simple steatosis and 3. Normal individual volunteers. Complete demography, past and present history, clinical examination, blood tests, abdominal & pelvis ultrasound and RRI measurement was done in them. RRI is the [maximum flow velocity of the blood during systole - minimum flow velocity of blood at the end of diastole over peak systolic velocity]**.** Also, they found that, RRI among hepatic fibrosis was about 0.74 and 0.65 in non-fibrosis cases, with significant gap on statistical means. So, this could be the fate of our patients as well if the analysis was delayed, which would have led to the progression of fibrosis in NAFLD which in turn leading to increased incidences of CKD.[102]

This could be not happening on further explanation based on the findings of scholar, Catalano et al who did not observe that significant difference of RRI between NAFLD compared to healthy volunteers.[101] Also, they did not find a significant difference between NAFLD, RRI and the variation in liver enzymes. Though we had not mentioned the tables, we also could not see any association between the deviation in liver enzymes and the renal artery changes between NAFLD and non-NAFLD.

Below is the ROC curve obtained by Mohmmed et al which is explaining that RRI also could be the sensitive, accurate indicator of CKD in NAFLD patients.[102]



As per our analysis, there is significant positive association between Smoking, Obesity, and the patients in test group. This signified that those with chronic history of smoking, obesity is at higher risk of developing non-alcoholic fatty liver disease and the renal artery changes will be higher among these. For further explanation, peri renal fatty accumulation in NAFLD would also alter the renal physiology, leading to arterial changes in renal arteries.

Meanwhile, we did not see any association among other variables over groups. Though there was comparatively reduced diameter of both right and left renal arteries among the patients between control and test group, in smoking and alcohol usage, this did not have any significant difference. We can substantiate this with the findings by Lin Y et al who had found that though the NAFLD is common among elderly patients, the cases with history of increased BMI have been the risk factor. Also, the metabolic syndrome has been significant factor for both hepatic and renal disorders, of which BMI is one of the components.[97]

To further describe this we can see that even Mahmoud et al had reported the observed positive correlation between BMI and RRI indicating the resistance in arteries being higher in NAFLD cases with renal artery abnormality.[102] Yang M et al would be one of the types of evidence we would like to mention, in which they have described that oxidative stress, pro-inflammatory, profibrotic responses and apoptosis are the major pathology behind NAFLD due to accumulation of fat.[103] This could be the similar cause for renal failure among those patients in future. So, the assessment of any specific pro-inflammatory/ inflammatory marker would have been one of the crucial assessments and correlating that with the renal artery changes might have been provided additional data for the future references. As per our analysis the renal artery diameters of both left and right were comparatively lesser among diabetics and hypertensive patients, there was no significant change as such but Lauder L et al in their analysis of 1000 patients with hypertension, found that not only there was significant reduction in the diameter of the arteries, there were also few cases of renal artery anomalies such as single artery, accessory arteries. The variation in diameter was especially seen among the cases of uncontrolled hypertension.[104]

As there was statistically increased number of individuals in test group were chronic smokers, with hypertension and diabetes, these also could have been the aggravating or might even be the associated factors with NAFLD which have led to decreased renal artery diameter, indicating the poor prognosis with these associated risk factors.

CONCLUSION

The mean age of cases of NAFLD was 49.44 ± 12.41 years being significantly higher than non-NAFLD. The right and left renal artery diameters among controls was 5.49 ± 0.508 mm and 5.717 ± 0.5 mm respectively. Whereas in cases, 4.57 ± 0.641 mm and 4.68 ± 0.616 mm were the diameter of right and left renal artery respectively with the statistically significant difference (<0.001). Whereas we did not find any radiologically significant association correlating with the symptoms of the attended patients. Hence, there is need for further clinical studies with bigger study population in this regard to better understand the same. There is strong significant positive association between Smoking (0.028), Obesity (0.018), hypertension and diabetes (0.086 & 0.068) with the NAFLD.

SUMMARY

- As per the available evidences, Non-alcoholic fatty liver disease (NAFLD) is a disorder categorized by accumulation of fat in the form of triglycerides (steatosis) in liver.
- This has been associated various other disorders such as metabolic syndrome and many other. Few recent evidences have shown renal abnormalities specially with respect to the renal artery dimension being associated with NAFLD but this association has not been studied by much scholars.
- We had taken this study to establish a relationship between non-alcoholic fatty liver disease (NAFLD) with renal artery narrowing in patients coming to the Radiology department of KLE's Dr.Prabhakar Kore Hospital, Belagavi on the basis on CT.
- There were 30 patients in control who were: the individuals of either gender aged above 18 years, with no history of non-alcoholic-fatty-liver disease (NAFLD) on examination. 34 in case: the patients diagnosed with NAFLD. All the patients subjected for abdomen and pelvis CT.
- In this study, the Mean age was 40.86 ± 13.72 years of controls and 49.44 ± 12.41 of test with no significant difference.
- There was strong significant positive association observed between Smoking (0.028), Obesity (0.018), hypertension and diabetes (0.086 & 0.068) with the NAFLD.
- There was significant statistical difference in the diameter of bilateral renal arteries in cases group than control group. For the control group and cases, the diameter of right renal artery was 5.49 ± 0.508 and 4.57 ± 0.641 mm respectively.

Whereas for left renal artery, it was 5.717 ± 0.5 mm in controls and 4.68 ± 0.616 mm in cases with p value of <0.001.

- Hence, we could conclude that NAFLD has significant negative correlation with renal artery dimensions, there is need for further clinical studies with bigger study population in this regard to better understand the same.

LIMITATIONS

LIMITATIONS OF OUR STUDY

Firstly, selection bias as this is an observational study and the selection of the patients is by the investigator on the basis of the presentation of the patient.

Secondly, as this is a single center observational study conducted at our hospital with lesser sample size due to time limit as well as the number of cases with NAFLD admitted during our study period were also lesser, it cannot be generalized to the population. Hence, we stress on the need for clinical studies with more samples.

Moreover, we did not asses for other laboratory parameters including eGFR which could have been one of the most reliable parameters. Also, the studies conducted in this regard have been only on USG and lesser, than the studies regarding the same comparing the outcome on the basis of USG and CT so that we could assess which radiological modality would be accurate in early detection of CKD among NAFLD cases, so, that the precaution and the required management could be done.

STRENGTH OF OUR STUDY

The first ever radiological data analysing for the association of renal artery diameter in NAFLD and comparing it with the control group (non-NAFLD) on the basis of CT. Also, CT is a non-invasive study.

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ANNEXURES – I

INFORMED CONSENT FORM

TITLE: "ROLE OF COMPUTED TOMOGRAPHY IN ESTIMATING THE PREVALENCE OF RENAL ARTERY DISEASE IN PATIENTS OF NON-ALCOHOLIC FATTY LIVER DISEASE: A ONE YEAR HOSPITAL BASED PROSPECTIVE COMPARATIVE STUDY"

Objective: To establish a relationship between non-alcoholic fatty liver disease (NAFLD) with renal artery narrowing in patients coming to the Radiology department of KLE's Dr.Prabhkar Kore Hospital, Belagavi on the basis on CT.

Introduction: Non-alcoholic fatty liver disease (NAFLD) is a clinic-pathological entity that encompasses simple hepatic steatosis, necroinflammation with varying stages of fibrosis known as non-alcoholic steatohepatitis (NASH), and cirrhosis.

NAFLD may be a new, and added risk factor for extrahepatic diseases such as CVD, chronic kidney disease(CKD), colorectal cancer, endocrinopathies (including type 2 diabetes mellitus [T2DM]and thyroid dysfunction), and osteoporosis.

The prevalence of CKD in NAFLD patients ranged from 21% to 54% compared to 3.7%-24.2% in non-NAFLD patients with the highest rates being noted by Targher et al. in an outpatient-based study of 343 type 1 diabetics. Importantly, the majority of these studies reported that NAFLD was independently associated with CKD even after adjusting for traditional risk factors including age, sex, BMI, hypertension, diabetes (and duration), smoking, and hyperlipidemia[1]. The presence and severity of NAFLD are associated with an increased risk and severity of CKD[2].

Assessment of hepatic steatosis using CT is based on the measurement of attenuation value of liver parenchyma, expressed as Hounsfield units (HU). Because attenuation

value of fat, usually about -100 HU, is much lower than that of soft tissue usually about 30-40 HU, attenuation value of liver parenchyma decreases as hepatic steatosis develops and progresses [3].

Explanation of procedure: The patients referred to the Radiology department for the CT abdomen will undergo the scan according to the standard protocol.

Withdrawal from participation in the study: Participation in this study is voluntary. You will be free to decide whether to participate in this study or continue participation once enrolled. In case you decide to withdraw your participation, you are free to do so. However, please convey the decision to the principal investigator.

Possible benefits from participating in the study: You will/will not have nor get any benefits by participating in this study. The data gathered will help the population at large.

Possible risks from participating in the study: There are no risks involved in participating in this study.

Privacy and confidentiality: The information collected from you will be coded, to prevent any person from identifying you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study.

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purposes and or presented to scientific groups. However, your identity will never be revealed.

Questions: In case of any questions with regard to this study, you are free to contact: REG. NO. BS0121007, If you have any question or complaints with regard to your right as study participant you may contact Dr Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

Legal rights: By signing this consent form, we are not waving any of your legal rights.

CONSENT STATEMENT

I am making a voluntary decision to participate in the study "**ROLE OF COMPUTED TOMOGRAPHY IN ESTIMATING THE PREVALENCE OF RENAL ARTERY DISEASE IN PATIENTS OF NON-ALCOHOLIC FATTY LIVER DISEASE: A ONE YEAR HOSPITAL BASED PROSPECTIVE COMPARATIVE STUDY"**. My signature below indicates that I have decided to participate and I have read the information provided above or the information provided above has been read to me in the language that I understand best. I was given the opportunity to ask questions and that they have been answered to my satisfaction.

Name of the participant:

Signature or left thumb impression of the participant:

Name of the witness:

Signature or left thumb impression of the witness:

Name of the investigator:

Signature of the investigator:

ANNEXURE II-PROFORMA

TITLE: ***"ROLE OF COMPUTED TOMOGRAPHY IN ESTIMATING THE PREVALENCE OF RENAL ARTERY DISEASE IN PATIENTS OF NON-ALCOHOLIC FATTY LIVER DISEASE: A ONE YEAR HOSPITAL BASED PROSPECTIVE COMPARATIVE STUDY"***

NAME:

AGE & SEX:

CT NO.:

K/C/O LIVER DISEASE	
K/C/O RENAL DISEASE	
HYPERTENSION	
DIABETES	
OBESITY	
SMOKER	

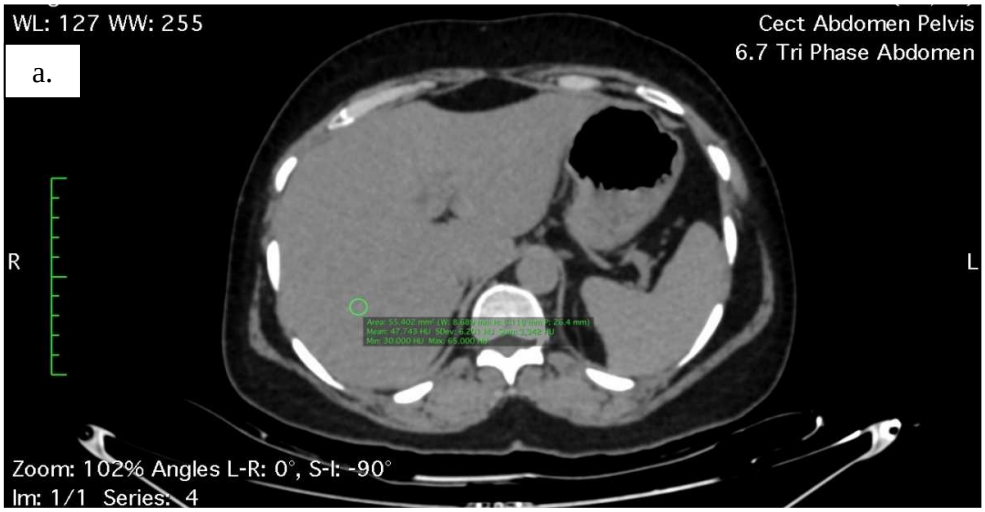
RENAL ARTERY DIAMETER:

RIGHT	
LEFT	

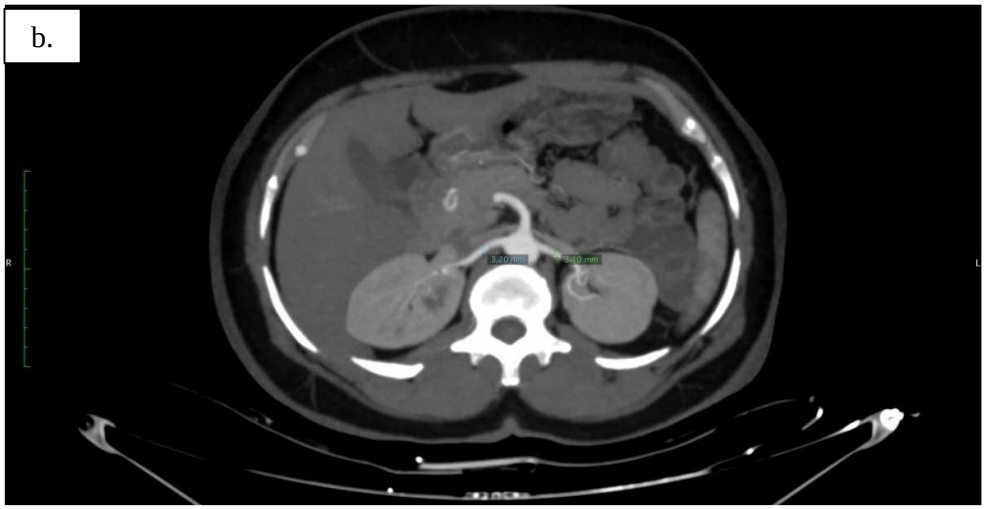
ANNEXURE III: FIGURES

CASE IMAGE 1

Figure 8: A case of a 59 year old female with NAFLD.



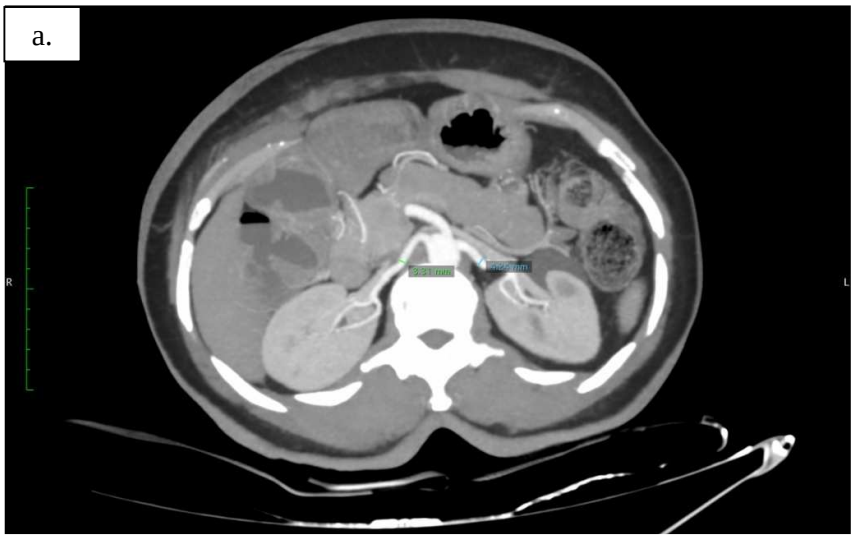
a. Axial unenhanced CT image shows the attenuation values of liver parenchyma as 30.0 HU which is consistent with fatty liver



b. Axial contrast enhanced CT in the arterial phase MIP image of the same patient showing the diameters of right and left renal arteries as 3.2 mm and 3.1 mm respectively

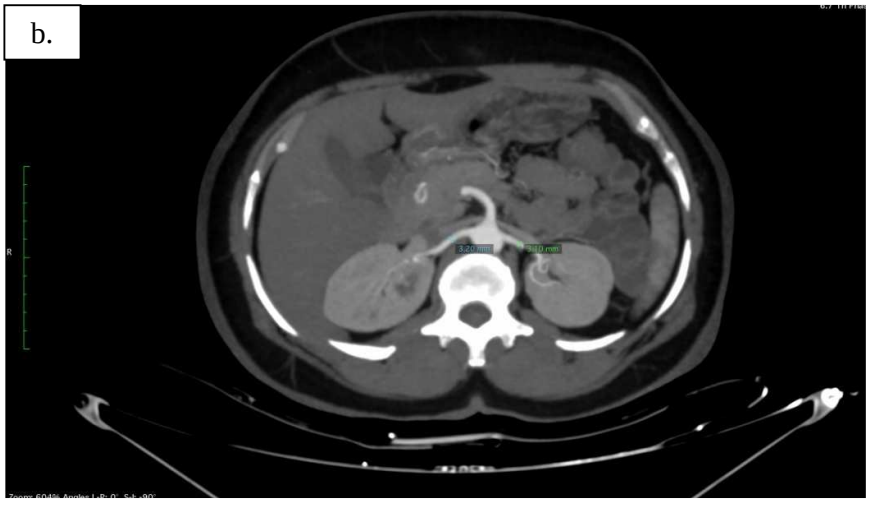
CASE IMAGE 2

Figure 9: A case of NAFLD in a 54 year old male. Axial enhanced CT in the arterial phase MIP image shows the diameters of right and left renal arteries as 3.3 mm and 4.2 mm respectively.



CASE IMAGE 3

Figure 10: Axial enhanced CT MIP image in the arterial phase of a 37 year old male without NAFLD, showing the diameters of right and left renal arteries as 5.9 mm and 6.0 mm respectively.



Master Chart

ANNEXURE – IV

MASTER CHART

CONTROLS

S. No.	Age	Sex	Smoking	Obesity	Hypertension	k/c/o kidney disease	k/c/o liver disease	Diabetes Mellitus	Right renal artery diameter	Left renal artery diameter
1	23	M	No	No	No	No	No	No	6	6.1
2	36	F	No	No	No	No	No	No	4	4.1
3	37	M	No	No	No	No	No	No	5.9	6
4	44	M	No	No	Yes	No	No	No	5.5	5.6
5	45	F	No	Yes	No	No	No	No	5	5.2
6	60	F	No	No	No	No	No	Yes	5.3	5.4
7	20	F	No	No	No	No	No	No	5.6	5.5
8	39	M	No	No	No	No	No	No	5.6	5.9
9	25	M	No	No	No	No	No	No	5.9	6
10	70	F	No	Yes	No	No	No	Yes	4.2	5
11	20	M	No	No	No	No	No	No	5.9	6
12	60	F	No	No	Yes	No	No	Yes	5	5.7
13	48	M	No	No	Yes	No	No	No	4.8	4.9
14	29	M	No	No	No	No	No	No	5.5	5.9
15	52	F	No	No	Yes	No	No	Yes	5.6	6
16	32	F	No	No	No	No	No	No	5.5	6.4
17	35	M	No	No	No	No	No	No	5.8	5.9
18	36	M	No	No	No	No	No	No	5.6	6.1
19	34	M	No	No	No	No	No	No	5.4	5.9
20	58	F	No	No	Yes	No	No	No	5.5	5.4
21	38	F	No	No	No	No	No	No	5.9	6.2
22	38	F	No	No	No	No	No	No	5.9	6.1
23	30	F	No	No	No	No	No	No	5.9	6.1
24	30	F	No	No	No	No	No	No	6	6.1
25	41	F	No	No	No	No	No	No	5.5	5.4
26	49	F	No	No	Yes	No	No	No	5.2	5.5
27	52	M	No	No	No	No	No	Yes	5.4	6.2
28	26	F	No	No	No	No	No	No	6.3	6.1
29	70	F	No	No	Yes	No	No	Yes	5.3	5
30	49	F	No	No	No	No	No	Yes	5.9	5.8

CASES

S. No.	Age	Sex	Smoking	Obesity	Hypertension	k/c/o kidney disease	k/c/o liver disease	Diabetes Mellitus	Right renal artery diameter	Left renal artery diameter
1	55	F	No	No	Yes	No	No	Yes	4.3	4.7
2	37	M	No	Yes	Yes	No	No	No	4	4.2
3	53	F	No	No	Yes	No	No	Yes	4.4	4.6
4	50	M	No	No	Yes	No	No	Yes	4.9	5
5	33	M	Yes	No	No	No	No	No	4.7	5.1
6	62	M	No	No	No	No	No	No	3.8	4
7	33	M	No	No	No	No	No	No	4.7	4.8
8	76	F	No	No	Yes	No	No	No	4.7	4.6
9	44	M	No	No	No	No	No	No	4.3	4.5
10	36	M	No	No	No	No	No	No	4.5	4.7
11	52	F	No	No	Yes	No	No	Yes	4.4	4.8
12	31	M	No	No	No	No	No	No	5	5.4
13	52	F	No	Yes	Yes	No	No	No	4.3	4.7
14	40	M	No	Yes	No	No	No	No	4.6	4.4
15	51	M	No	No	Yes	No	No	Yes	5.4	5.1
16	70	F	No	No	No	No	No	Yes	4	3.5
17	38	M	Yes	No	No	No	No	No	4	5.6
18	23	M	No	No	No	No	No	No	5.2	5.6
19	74	M	Yes	Yes	Yes	No	No	Yes	4.9	4.3
20	67	M	No	Yes	No	No	No	Yes	3.7	4.3
21	48	M	No	No	No	No	No	Yes	4.9	5.6
22	53	M	Yes	Yes	Yes	No	No	Yes	5.2	4.9
23	55	F	No	No	Yes	No	No	Yes	5.2	3.8
24	43	M	No	No	No	No	No	No	4.4	5.3
25	52	F	No	No	Yes	No	No	Yes	5.4	5.2
26	41	F	No	No	No	No	No	No	5.2	4.6
27	51	F	No	Yes	Yes	No	No	Yes	3.8	4.2
28	54	M	No	No	No	No	No	No	6.2	6
29	59	F	No	No	No	No	No	Yes	3.1	3.2
30	54	M	No	No	Yes	No	No	Yes	3.3	4.2
31	45	F	No	Yes	No	No	No	Yes	4.6	4.5
32	35	F	No	Yes	No	No	No	No	5	5.1
33	54	F	No	Yes	Yes	No	No	No	5	4.5
34	60	M	Yes	Yes	No	No	No	No	4.4	4.3