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Non alcoholic fatty liver disease and Chronic kidney Disease- pathophysiological connecting link

Abstract

Prevalence of Chronic liver disease due to Non alcoholic fatty liver disease (NAFLD) spectrum is increasing worldwide. Patients with type 2 diabetes, metabolic syndrome and obesity are more prone for NAFLD. Recent studies and systematic reviews have shown increased risk of chronic kidney disease (CKD) in patients of NAFLD. NAFLD and CKD share many common overlapping factors like obesity, insulin resistance, and hypertension and as such precise causal pathophysiological relation is difficult to establish between two entities.

Recent animal and other experimental studies have shown that various inflammatory mediators released from adipose tissues and the "cross talk" between adipose tissues, liver and kidney are responsible for potential pathogenetic mechanisms which connects NAFLD and CKD. Presently, there is insufficient data to precisely link the causal-association relationship between these two entities and it's quite difficult to determine exact pathogenetic pathways linking these two diseases because of multiple inter related and common factors.

Keywords: non alcoholic fatty liver disease, chronic kidney disease, adipose tissue

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Abbreviations: NAFLD, non alcoholic fatty liver disease; CKD, chronic kidney disease; CLD, chronic liver disease; IR, insulin resistance; MHO, metabolically healthy obesity; FFA, free fatty acids; TNF, tumor necrosis factor; RAAS, Renin-angiotensin-aldosterone system

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of deranged liver enzymes and prevalence of chronic liver disease (CLD) due to NAFLD spectrum is increasing across the world.[1] NAFLD is defined as the accumulation of fat (>5%) in liver cells in the absence of excessive alcohol intake or other causes of liver disease including autoimmune, drug-induced, or viral hepatitis.[2] NAFLD affects approximately 30% of the Western population, particularly patients with metabolic syndrome, obesity, and type II diabetes are more often affected, however, disease might manifests in patients with lower BMI and is also known to occur in patients without having insulin resistance (IR).[3] NAFLD is also demonstrated in metabolically healthy obesity (MHO) and metabolically abnormal but normal weight (MANW) patients.[4] NAFLD is associated with increased risk of type 2 diabetes, cardiovascular disease,[5] hepatocellular carcinoma[3] and with increased incidence and prevalence of chronic kidney disease (CKD).[6,7]

Epidemiological link between NAFLD and CKD

Prevalence of NAFLD and NAFLD with renal insufficiency (NAFLD-RI) has increased over the past 2 decades. A systematic review and meta analysis of thirty three studies with 63, 902 participants showed that NAFLD was associated with an increased risk of prevalent (odds ratio [OR] 2.12, 95% CI 1.69-2.66) and incident (hazard ratio [HR] 1.79, 95% CI 1.65-1.95) CKD.[8] Many other cross sectional and case control studies have shown link between NAFLD and CKD with variable prevalence.[9–14] Wide variation in prevalence of these studies are because of use of different definitions of CKD, variable ethnicity, age, risk factors, and selection bias. Also major limitations in these studies were use of ultrasound for diagnosis of NAFLD. Prevalence of NAFLD is approximately 30–40% in men and 15–20% in woman and is much higher in people with T2DM and obesity.[15] It's difficult to establish pathophysiological causal relation between NAFLD and CKD because of many overlapping risk factors including hypertension, obesity, dyslipidemia, and insulin resistance.[16]

Pathophysiological link between NAFLD and CKD- What's new?

The pathophysiological mechanisms that are responsible for linking NAFLD and CKD are quite complex are still under study. Common overlapping risk factors such as obesity, insulin resistance, dyslipideimia and hypertension are involved in the development and progression of both NAFLD and CKD and as such precise causal pathophysiological relation is difficult to establish between two entities.

Potential mechanisms

Adipose tissue, liver and kidneys "crosstalk" with each other and various inflammatory mediators released from complex interactive pathways are involved in pathogenesis of NAFLD and CKD. Inflamed adipose tissue and liver activates various pathways and factors e.g. nuclear factor-kB (NF-kB) pathway and nuclear erythroid related factor-2 (Nrf2). This results in local and systemic release of various cytokines, reactive oxygen species (ROS), fibrogenetic, procoagulant and growth factors. Also there is activation of Renin-angiotensin system (RAS) which mediates efferent arteriole constriction and glomerulosclerosis in kidneys. Abundance and activation of these pro inflammatory mediators not only impairs insulin signaling pathways leading to insulin resistance (IR) but also injures liver and kidneys; thus linking liver steatosis/fibrosis with glomerulosclerosis.

Role of adipose tissue

dipose tissue is inflamed in obese individuals with metabolic syndrome.[17,18] Metabolic functions of adipose tissues are altered in insulin resistant obese individuals. Inflamed adipocytes release free fatty acids, inflammatory molecules, and various factors that lead to obesity associated complications. Adipose tissue gets inflamed in conditions of high calorie intake and obesity and is the initial site where liver kidney interaction originates. In inflamed adipose tissue a pro inflammatory cascade is initiated which is characterized by infiltration of macrophages, release of free fatty acids (FFA), pro inflammatory cytokines e.g. interleukin (IL)-6, tumor necrosis factor (TNF)-alpha etc.[19,20] These inflammatory mediators then activates nuclear factor-kB (NF-kB) pathway and c-Jun N-terminal kinase (JNK) pathway via toll like receptors.[21] Activated NF-κB leads to increased transcription of several pro-inflammatory genes which in turn regulates expression of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), and adiponectin. These inflammatory molecules then augment local and systemic chronic inflammation, impairs insulin signalling and leads to insulin resistance, liver steatosis and chronic kidney disease.[22] In the presence of these inflammatory mediators, liver is both the contributor and target of inflammatory changes. Systemic release of above mediators activates several other pathways and factors including activation of coagulation pathway, renin angiotensin system, increased oxidative stress and generation of reactive oxygen species. Liver and kidney interact with each other through these molecules and pathways leading to dysfunction of either organ.

Renin angiotensin aldosterone system

Renin-angiotensin-aldosterone system (RAAS) is an important system in maintaining homeostasis and plays major role in the pathogenesis of many cardiometabolic disorders like diabetic kidney disease, cardiorenal syndrome, heart failure etc. NAFLD is basically a metabolic disorder and RAAS plays a key role in IR, fibrosis and is common to pathogenesis of both NAFLD and CKD. Angiotensin II (Ang II) is the biologically active product of RAAS which acts on AT1 and the AT2 receptors (AT1R and AT2R). Physiological effects of Ang II are mediated via AT1 receptor and include blood pressure regulation, salt and water retention, sympathetic nervous system stimulation, growth and proliferation of vascular smooth muscles, extracellular matrix formation and fibrosis. NAFLD patients have significantly increased levels of Ang II, and the elevated Ang II level is an independent risk factor of NAFLD.[23] Apart from the circulating RAAS, local RAAS have been identified in adipose tissues. In adipose tissues, AngII induces generation of ROS, stimulates the production of growth factors including transforming growth factor (TGF)-β1, promotes cell growth, proliferation and apoptosis and regulates the production of pro-inflammatory cytokines, including tumor necrosis factor α (TNF α), interleukin-6 (IL-6) and the expression of the transcription factor nuclear factor kappa B. The local and systemic RAAS complement each other and impairs insulin signaling resulting in insulin resistance which plays a central role in the pathophysiology of NAFLD.[24] Inflammation of adipose tissue is the initial step in the sequence of events that leads to systemic inflammation, fibrogenesis and systemic insulin resistance. The exact mechanisms by which chronic inflammation and RAAS activation can damage the kidney are not well delineated. Studies has shown that in the kidney, RAS activation plays a key role in determining renal ectopic lipid deposition which is known to cause oxidative stress and inflammation through hemodynamic effects of glomerular efferent arteriole vasoconstriction leading to glomerulosclerosis.[25]

Oxidative stress linking NAFLD and CKD

Obesity is associated with increased oxidative phosphorylation in mitochondria and nicotinamide adenine dinucleotide phosphate oxidases (NOX) production which leads to generation of reactive oxygen species leading to insulin resistance. Generation of ROS impairs insulin signaling pathways, activates pro inflammatory mediators and dysregulation of adipocyte metabolism leading to insulin resistance. In obesity, mitochondria are loaded with free fatty acid (FFA) flux and incomplete betaoxidation of these excessive FFA leads to accumulation of long chain fatty acids which further aggravates inflammation and alter insulin signaling. The imbalance between overproduction of ROS and diminished oxidant capacity leads to excess oxidative stress. Nuclear erythroid related factor-2 (Nrf2) is a transcription factor highly expressed in the liver and kidney which regulates genes encoding for antioxidant molecules.[26] Beneficial effect of activation of NRf2 in NAFLD by many agents like osteocalcin,[27] scutellarin- a flavonoid glycoside,[28] apigenin,[29] has been studied with favorable results in various studies.[30] In NAFLD, due to excessive oxidative stress and reactive oxygen species, antioxidant capacity of Nrf2 is impaired with loss of its cytoprotective ability and various agents capable of inducing Nrf2 are currently under study to prevent and treat NAFLD.[31]

Impaired energy homeostasis

In obese individuals with high calorie intake, adipocytes are loaded with excess lipid which causes disturbed energy homeostasis. Fetuin A is a glycoprotein hepatokine which plays an important role in insulin resistance and metabolism in liver and metabolically active organs. Levels of Fetuin A are increased in obesity and are associated with increased insulin resistance, metabolic syndrome, liver steatosis and worsening of pro inflammatory state. A study from Korea concluded that high levels of Fetuin A not only predicts metabolic health but also associated with arterial stiffness and derangement of metabolism independent of body mass index.[4] Fetuin A plays important role in impairment of SIR T1 (sirtuin1)-AMPK (5'-AMP activated protein kinase) axis. Fetuin A suppresses tumor necrotic factor α (TNF α) and prevents activation of Caspase 1, SIR T1 cleavage and AMPK activation causing augmentation of inflammation.[32] Increased levels of Fetuin A are linked to decreased levels of adiponectin and suppression of AMPK. Adiponectin, adipose-specific adipokine is a multifunctional cytokine that has a role in regulating inflammation. Adiponectin levels are inversely propotional to the amount of fat cells and low levels coincides with high levels of Fetuin A. Fetuin A inhibits adiponectin through Wnt3a-PPARγ (Peroxisomal proliferator-activated receptor-γ) signaling pathway.[33] PPAR-γ is a transcription factor which regulates adiponectin gene expression and thus plays key role in energy homeostasis in adipose tissue. Animal study demonstrated that Rosiglitazone, a PPAR-γ agonist attenuates liver steatosis in ethanol fed mice by increasing adiponectin level.[34] Reduced levels of adiponectin inhibits AMPK activation and other downstream signaling molecules, leading to inflammatory and profibrotic cascades culminating in insulin resistance and organ damage. In obesity and IR, CKD at early stages develops in parallel with atherosclerotic process of the carotid arteries, which correlates with attenuation of organ-protecting properties of adiponectin.[35]

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Conclusion

Current data suggests that NAFLD and CKD are metabolic disorders which have common risk factors and both diseases share common pathophysiological pathways although it is currently quite difficult to determine exact pathogenetic pathways linking these two diseases because of multiple inter related and common factors.

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Conflicts of interest

The authors declare that they have no conflicts of interest to disclose.

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