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Interplay between Liver, Kidney, and Heart in Metabolic Regulation and Cardioprotection: Mechanisms and Implications for Therapeutic Strategies

Tom Akello Abbo

Department of Pharmacology, Kampala International University Uganda

ABSTRACT

The intricate interplay between the liver, kidney, and heart in metabolic regulation and cardioprotection is a topic of growing interest, particularly in the context of rising cardiovascular disease prevalence. This paper explores the dynamic interactions among these organs, highlighting their roles in energy metabolism, inflammation, and cardiovascular health. We discuss the mechanisms through which liver and kidney function impact cardioprotective properties, including the regulation of glucose and lipid metabolism, inflammation modulation, and remote conditioning effects. Furthermore, we examine the implications of liver-kidney-heart cross-talk for therapeutic strategies targeting cardiometabolic disorders. Understanding these complex interactions is essential for the development of innovative treatments to mitigate the burden of cardiovascular disease.

Keywords: Liver, Kidney, Heart, Cardioprotection and Therapy

INTRODUCTION

The heart interacts with other metabolic organs, like the liver and kidney, to optimize energy metabolism in order to meet the demands of increasing cardiac workload; evolving fuel requirements between fed and fasted periods conserved between mice and man [1-5]. In response to increasing cardiac workloads or β-adrenergic stimulation, the heart has the capacity to increase its oxidation of not only glucose (i.e., the main source of energy in the normal fed condition) but also fatty acids (in the normal fasted condition), both of which are stored in highly abundant quantities in adipocytes, as long-chain triglycerides [6-8]. In response to an activation of the γ-adrenergic system, adipose tissue can also hydrolyze intracellular triglycerides, releasing free fatty acids (FFAs) (plentiful in the fasted state) and glycerol [9-11]. Induction of cytosolic malate production in the stunned heart, from enhanced glycolytic-derived pyruvate, could supply a shunt for substrate malonyl CoA synthesis at the carboxylase enzymatic step, enabled from malate-pyruvate recycling; the cytosolic reduction of oxaloacetate to malate in the presence of an excess NADH for the shuttling of reducing potential from the cytosol to the mitochondria [12-15]. Diverging from the classical dogma of fuel partitioning where increased glucose oxidation is thought to be cardioprotective, it was observed that chronic stimulation of cardiac glucose utilization (by deletion of heart-specific histone deacetylase 2) could augment injury, in part by reducing oxidation of the essential endogenous protective substrate oleate [16-18]. The prevalence of cardiovascular disease continues to rise in Western societies, making the incidence and management of these pathologies an important public health issue. Indeed, myocardial infarction is still the leading cause of death in the free world [19-22]. Increases in the patient prevalence of obesity, metabolic syndrome, and type-2 diabetes (T2D) have exacerbated the rise in cardiovascular disease, and almost 30% of the general population is now considered obese, increasing the likelihood of further diabetic and non-diabetic cardiovascular disease events [23-25]. Therefore, understanding metabolic pathways and their organ-specific responses to cardioprotective interventions is critical toward creating innovative therapeutic strategies, especially given the recent failure of industry-sponsored clinical trials examining DPP-4 inhibitors and GLP-1 in the T2D population.

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METHODS

This review synthesizes current literature on the interplay between liver, kidney, and heart function in metabolic regulation and cardioprotection. Relevant studies investigating the molecular mechanisms, physiological pathways, and clinical implications of organ-organ interactions were identified through comprehensive literature searches. The findings were critically analyzed to elucidate the intricate relationships among these organs and their roles in cardiovascular health.

Liver Function and Cardioprotective Properties

Interestingly, exploring these adverse relationships between liver function and CVD has opened the door to a much more fascinating story [26-27]. Subsequent to the recognition of CRP as a biomarker of CVD, we have seen greater recognition of the major role of the liver in regulating both hepatic and adipose tissue insulin resistance and glucose metabolism [28-30]. A now common understanding is that insulin resistance is a major contributor to the progression from obesity to type 2 diabetes to diabetes-associated CVD. Hyperinsulinemia downregulates transcription of insulin receptor substrate (IRS-1) via activation of sterol regulatory element-binding protein (SREBP1) that inhibits glucose-6-phosphatase gene transcription that subsequently and transiently secondarily increases glucose disposal, triglyceride synthesis, and fatty acid esterification; the first form of hepatic IR that is silent, reversible, and leads to hyperglycemia when β-cell insulin secretion fails to overcome it. Cardiovascular disease (CVD) has been recognized as one of the top causes of death in the last century worldwide. Inflammation has gained recognition as one of the key pathological factors involved in the development and prognosis of CVD, along with the traditional risk factors. CVD is often associated with increased biomarkers of inflammation including C-reactive protein (CRP) and interleukin-6, both of which are derived from the liver. Interestingly, CRP has been harmful to cardiac myocytes via activation of the IGF-1R/PI3K/Akt pathway that reduces glucose oxidation and ATP generation [31-35]. The liver is vital in the acute phase response; hallmark proteins such as CRP, serum amyloid A, haptoglobin, and α1-protease inhibitor are all produced in response to pro-inflammatory cytokines (TNF-α, IL1, IL6). For example, CRP is strongly linked to both incident and recurrent CVD and it has been suggested that CRP acts as both a biomarker and mediator of CVD, predominantly implicated through the acute phase response [36-37].

Role of Liver in Cardiovascular Health

Hepatic involvement in the development of acute kidney injury is bidirectional. There was a marked correlation between liver and renal injuries. Downregulation of Klotho is a response to the hepatic injury, serving as a mechanism of defense against liver injury, which seems to correlate with kidney damage and reduced function. Albumin can modulate kidney injury through different mechanisms: direct sustenance of the tissue, with anti-inflammatory effects, as well as free and protein-bound toxic radicals that promote apoptosis and cell death [38-41]. The liver, like Klotho, was first discovered as a tissue responsible for removing potassium from the blood, thus protecting the CVS. In vitro, albumin and different forms of albumin protect cardiomyocytes against different drugs, which indicate that the beneficial effects of albumin (or the lack thereof) in the renal or cardiovascular setting are multifaceted and it is difficult to establish a complete mechanistic explanation [42-46]. The interconnectivity between the liver, kidney, and heart represents a complex matrix that involves multiple regulatory factors in the context of cardio-renal syndromes. In health, the liver and the kidney correspond to a positively reinforcing unit and efficiently exchange information as they actually target the same vital function of ensuring whole-body homeostasis. The hepatic influence on the cardiovascular system (CVS) is well known, and it has been reported to be fundamental. An imbalance of hepatic remodeling causes affecting nitric oxide regulation as well as coronary circulatory function. Nitric oxide has been applied as an important signaling molecule in the cardiovascular system as well as in the process of maintaining liver perfusion [47-50].

Mechanisms of Liver's Cardioprotective Effects

The data confirmed the conclusion of according to whom the liver exerts cardioprotective action during hypoxia and ischemia due to the action of HLF produced by it and, therefore, the lack of the heart's native fibrinogen synthesized only in the heart. Apparently, the intimate contact of the liver and heart, typical to their anatomical localization and achieved on top of their functional mobility, helped to understand the effect of the liver on cardiac performance [1-4]. Further studies demonstrated a very important stabilizing effect of albumin in HLF preparations aimed to model the effects of vascular and extravascular liver. Among many possible reasons for such pronounced effects of HLF in the heart, the dominant stabilizing effect of albumin in HLF may critically define its stabilization of the vascular and extravascular structures [5-8]. Several mechanisms of the liver's cardioprotective effects have been discussed, but the main attention was given to the effect of horse liver fibrinogen (HLF). Since 1990, it has been shown many times that HLF possesses a unique property to protect the heart from

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ischemia/reperfusion injury. In experiments with animal models of ischemic contracture of the heart muscle, HLF significantly retarded the development of rigor and increased the threshold of calcium-induced rigor activation [9-12]. Besides the effect on the contractility of the heart, HLF protected the heart muscle against the ultrastructural alterations following the ischemia/reperfusion: the structure of intercalated discs, mitochondria, sarcoplasmic reticulum, and sarcolemma remained preserved. The distinct antihypoxic, antiischemic, and antireperfusion activities of HLF are maintained upon tissue application [13-16].

Kidney Function and Cardioprotective Properties

Recent research finds that kidney function (KF) also extends to other tissues and organs. Two prospective studies found an inverse association between eGFR and CVD, including coronary heart and heart failure, independent of blood pressure levels, with normal kidney function [20-26]. Additionally, it is reported that in a prospective study of 591 diabetes cases that occurred 10 years earlier, large kidney granules, an index marker of diabetes-associated kidney disease sensitive to acute changes in prediabetes obesity, were temporally associated with greater occurrence of LV growth [9]. More recently, we found that the estimated eGFR was inversely linked to left ventricle hypertrophy in this FHS series, except in those without GFR risk factors. It is well-established that the kidneys' primary role is removing waste products from the circulating blood. However, it has become evident that kidney function is intricately linked to other physiological functions, including blood pressure, while kidney dysfunction contributes to various pathologies, including cardiovascular diseases (CVD). The kidneys impact the heart through the renin-angiotensin-aldosterone system (RAAS), blood pressure regulation, and filtering waste such as uric acid and uremic toxins, while kidney dysregulation causes salt and fluid overload, anemia, malnutrition, endothelial dysfunction, sympathetic overcompensation, metabolic acidosis, and the accumulation of fibrotic and inflammatory markers. In the last decade, a focus specifically on renal tissue damage, referred to as cardiorenal syndrome, has arisen as an independent field of interest due to an increasing awareness of the importance of exploiting this understanding to emerge in therapy alternatives to the high mortality associated with cardiorenal diseases [12].

Role of Kidney in Cardiovascular Health

KRT provides higher information than traditional measures of renal function because reduced kidney clearance capacity is indicative of multi-site renal pathologies, including sclerosis of the renal microvasculature, namely arteriosclerosis, atheroma, medial arterial calcification, loss of peritubular capillaries, and frank fibrosis secondary to subtle renal conditions, also affecting the renal microvasculature like glomerulonephritis and uninephrectomy [13]. That is, damage at the blood filtration barrier (glomerulonephritis) or any other site of the nephron involved with blood filtration (tubules and the rectal medulla) domino down to proximal tubular handling and renomedullary circulation by pacemaker cells between the glomeruli in the afferent arterioles [17]. Increased KRT has been associated with a higher amount of grey matter in the brain and higher brain microvasculature density among subjects with incident stroke. In separate reports, the investigators reported KRT predicting the progression of white matter hyperintensities, deep cerebral infarction, and subclinical brain infarction. Kidney clearance capacity of middle and low molecular weight solutes, hereafter referred to as KRT, is the product of the glomerular filtration rate and renal tubular handling effected by the proximal tubule and renomedullary circulation, which are directly or indirectly regulated by the renal microvasculature [19]. Emerging consensus is that KRT provides substantially higher information compared to glomerular filtration rate or albuminuria, which are the two measures recommended as the most valuable for characterizing renal function by the international expert panel KDOQI. KRT is a measure of intrinsic capability and actual performance, while both glomerular filtration rate and albuminuria are measures of performance alone.

Mechanisms of Kidney's Cardioprotective Effects

Furthermore, many studies have uncovered mechanisms by which manipulation of different parts of the CNS or peripheral nervous system has trophic or protective effects on the kidney, leading to the concept that the kidney (or perhaps the cardiovascular system, because of its own ability to modulate nerve function and proximity to central RCC) possesses the neurovascular unit, which is responsible not only for maintaining everyday kidney and heart function but also for initiating a response with direct and remote protective effects in the face of injury [12-18]. These examples of self-survival mode acquisition during intra-renal and extra-renal homeostasis disrupted by ischemia are consistent and demonstrate the remarkable ability of kidney injury to be reduced by seemingly stochastic events [20-25]. The kidney possesses an extraordinary capacity to respond to and mitigate injury. The protection may be remote or local, initiated at the onset of insult or requiring days to develop, and lasting only hours or as long as

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weeks with the response being a reflex adaptation or a programmed event. The current state of evidence indicates that both conventional and atypical RAS operating through intrarenal or extrarenal mechanisms enable the kidney to protect itself from ischemic injury by increasing its resistance to apoptosis, accelerating DNA repair, and reducing inflammation [26-30].

Interplay between Liver and Kidney Function

The best example of the importance of liver function in the setting of critical illness comes from patients with advanced heart failure listed for heart transplantation. It is well known that abnormalities of liver function tests are related to poor outcome in heart failure patients bridged to heart transplantation with mechanical assist devices [31-35]. These investigations are, however, limited by the fact that hepatorenal interactions can be confounded by multiple factors present in critically ill patients beyond the superficial diagnosis of heart failure, and the objectives of these associations are mainly focused on prognostication, not causation. Knowledge of the exact effect of intermediate hepatic metabolism on kidney function over the spectrum of heart failure degrees at different stages of management may help address the hazards of iatrogenics in the already complex course of these patients. Consequently, impairment in kidney function or liver function can substantially limit therapeutic options in heart failure [36-40]. The Kidney Disease: Improving Global Outcomes (KDIGO) work group has introduced the term cardiorenal syndrome (CRS) to describe abnormal kidney function secondary to heart failure. A comprehensive approach to the management of heart failure would include treatments that protect not only the heart but also kidney and liver functions. However, the interplay between kidney, liver, and heart functions in the setting of heart failure is still not well understood. Given the prominent role of the kidney and liver in intermediate metabolism, any interplay between these two organs is likely to be function-dependent. In other words, the nature of interactions depends on the current function of these two organs and its changes over time rather than their gross structure or superficial statistical links [41-45].

Cross-Talk between Liver and Kidney in Cardioprotection

The crosstalk between remote ischaemic preconditioning (RIPC) and warm liver ischaemia has been earlier suggested by non-conditioned animals after 4 days of reperfusion. These animals appeared unable to protect the liver both through RIPC and warm ischaemia. Latency effect of the liver preconditioning was invoked by the time taken to induce the anti-apoptotic heat shock protein 70 (HSP70) and tumour necrosis factor alpha (TNF-α) [46-47]. Therefore, it is well within reach that the bidirectional interaction between remote conditioning techniques can deeply influence the health state of organs found remote in the body. Importantly, these interactions are independent of the neuroendocrine system and intrinsic elements of the organ such as stellate cells or bile ductular epithelia. Apart from the well-known coupling between kidney and heart, marked by the concept of cardiorenal syndrome, the dialogue between liver and kidney was found in complex phenomena of remote tacrolimus preconditioning [48-49]. Tacrolimus administration leads to significant liver injury, which is not prominent in renal tissue. Nevertheless, tacrolimus-treated animals, which underwent liver surgery, improved kidney function to a similar extent as animals that underwent remote kidney surgery. The beneficial effects of remote tacrolimus preconditioning on liver and kidney function have been effectively impaired through the blockage of liver adrenergic receptors [11-13].

Impact of Liver and Kidney Dysfunction on Cardioprotective Properties

Ezetimibe simulator coronary atherosclerosis is the role of redox balance and liver and kidney function. The main findings of our study on these master findings include the following findings from this analytical study. An ideographic relationship was noted for the accumulation of advanced carbohydrate end products, an important mediator of complications, would be best in patients, recounting patients with chronic kidney disease who also had liver dysfunction [8-9]. Then the triglyceride accumulation would be amplified in those with hepatic dysfunction, as would the levels of human enhanced C3 and scores of the glomerular filtration rate. 433 Inflammation and hypertriglyceridemia had previously been recognized as complicating comorbidities in patients who had liver and kidney function at baseline [10-13]. Together with the adverse cardiac events, are they part of a principled and rhythm where they amplify the severity of CKD? The role of single and combined liver and kidney dysfunction on cardioprotective abilities is less examined. In a study consisting of 1770 stable CAD patients enrolled in the multicenter REMEDY registry, those individuals having CAD, chronic kidney disease (CKD; serum creatinine 2 mg/dL), and liver dysfunction were at the highest risk for adverse events and thereby may be ideal candidates for strategies to limit such adverse events [12-17]. Renal dysfunction poses an important cardiovascular risk that is increased by non-integrative thoracic disease; the risk is further multiplied when combined with liver diseases, which together largely affect the clinical outcomes. The risk for adverse cardiac events is significantly higher in CAD patients having CKD [12-16]. Patients with CKD

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and liver dysfunction are at an even greater risk for adverse events, underscoring that the coexistent liver impairment accentuates risk and results of such comorbidity are largely unknown, and assessment may not be completed fully. Individuals with potential comorbidities have potentially greater adverse cardiovascular outcomes that likely leverage lowering the threshold for policies for prevention and treatment. Where no such measurement is being considered, an optimal treatment for proper recovery of function also remains unknown.

CONCLUSION

The interplay between the liver, kidney, and heart represents a complex network of regulatory mechanisms that influence metabolic homeostasis and cardiovascular health. Understanding the molecular pathways and physiological interactions among these organs is crucial for identifying novel therapeutic targets and strategies for managing cardiometabolic disorders. Future research should focus on elucidating the specific mechanisms underlying liver-kidney-heart cross-talk and translating these findings into clinical interventions to improve patient outcomes in cardiovascular disease.

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