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Emerging liver-kidney interactions in nonalcoholic fatty liver disease

Running title: liver-kidney interactions in NAFLD

Giovanni Musso, M.D.[1], Maurizio Cassader, Ph.D.[2], Solomon Cohney MBBS Ph.D[3], Silvia Pinach, M.D.[2] , Francesca Saba M.D.[2] , Roberto Gambino Ph.D.[2]

[1]Gradenigo Hospital, University of Turin, Turin, Italy

[2]Dept. of Medical Sciences, San Giovanni Battista Hospital, University of Turin, Turin, Italy

[3]Department of Nephrology, Royal Melbourne & Western Hospital, Victoria, University of Melbourne, Australia

Corresponding author:

Giovanni Musso

Gradenigo Hospital

C.so Regina Margherita 8

10132 Turin, Italy

E-mail: giovanni_musso@yahoo.it

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Abstract

Mounting evidence connects non-alcoholic fatty liver disease (NAFLD) to chronic kidney disease (CKD). Here we review emerging mechanistic links between NAFLD and CKD, including altered activation of angiotensin converting enzyme(ACE)-2, nutrient/energy sensors Sirtuin-1, and AMP-activated kinase, as well as impaired nuclear erythroid related factor-2-regulated antioxidant defense. Dietary fructose excess may also contribute to NAFLD and CKD. NAFLD affects renal injury through lipoprotein dysmetabolism and altered secretion of hepatokines fibroblast growth factor-21, fetuin-A, insulin-like growth factor-1, and syndecan-1. CKD may mutually aggravate NAFLD and associated metabolic disturbances through altered intestinal barrier function and microbiota composition, accumulation of uremic toxic metabolites, and alterations in pre-receptor glucocorticoid metabolism. We conclude by discussing implications of these findings for the treatment of NAFLD and CKD.

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Evidence connecting nonalcoholic fatty liver (NAFLD) with chronic kidney disease(CKD)

Chronic kidney disease (CKD) afflicts up to 8% of the world's adult population and its prevalence is continuously rising along with the epidemic of its risk factors, including obesity, metabolic syndrome and diabetes[1]. CKD may progress to end-stage renal disease (ESRD) and promote cardiovascular disease (CVD)[1].

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world and an emerging risk factor for liver-related complications (largely limited to its progressive form, i.e. non-alcoholic steatohepatitis, NASH), type 2 diabetes (T2DM) and CVD[2].

Recent experimental and epidemiological data reveal a link between NAFLD and CKD and suggest the presence of NAFLD can accelerate the development and progression of CKD independently of traditional risk factors, while CKD can aggravate cardio-metabolic derangement in obesity-associated disorders and contribute to liver disease progression in NAFLD [3].

We therefore reviewed emerging mechanisms linking NAFLD and CKD and explored novel therapeutic approaches to retard the progression of both disease processes.

The renin-angiotensin system (RAS) in liver and kidney disease

The RAS is believed to play a key role in the pathogenesis of obesity-related disorders, including NAFLD and CKD. Adipocytes express all RAS components including AngII, angiotensin converting enzyme(ACE), renin, and AngII type 1(AT1)- and type 2(AT2)-receptors. In obesity, increased ACE-AngII-AT1 axis activity has been shown to induce organ damage through both autocrine/paracrine and endocrine effects, with adipose tissue contributing up to 30% of systemic circulating AngII (**Figure 1**) [4]. The kidney and liver also express all RAS components, and clinical and experimental studies support a role for both systemic and local (renal and hepatic) paracrine/autocrine ACE-AngII-AT1 activation in the pathogenesis of NAFLD and CKD: in the liver, AngII promotes insulin resistance, *de novo* lipogenesis, mitochondrial dysfunction, reactive oxygen species (ROS) and

proinflammatory cytokine production, and activates hepatic stellate cells (HSCs) to trigger fibrogenesis, thus contributing to the entire spectrum of histological changes of NASH [5].

In the kidney, ACE-AngII-AT1 activation plays a key role in determining renal ectopic lipid deposition, which is a hallmark of obesity-associated CKD and a trigger of oxidative stress, inflammation and fibrogenesis, with both haemodynamic and non-haemodynamic effects, alterations that were all reversed by RAS inhibition (**Figure 1**)[4, 6].

Analysis of limited data from three randomized controlled trials (RCTs) in NAFLD (223 hypertensive patients, 85% nondiabetic) suggests AT_1 receptor blockers(ARBs) ameliorate steatosis, insulin resistance, lipid and inflammatory parameters, independent of blood pressure reduction [7].

Additionally, telmisartan improved also necroinflammation, NAFLD activity score and fibrosis stage in NASH [7] and microalbuminuria in the Fatty Liver Protection Trial by Telmisartan or Losartan Study (FANTASY) [8]. Similar benefits on liver fibrosis have not been observed with losartan and may arise from the distinct peroxisome proliferator-activated receptor(PPAR)-γ-agonist activity of telmisartan, which synergizing with ARB activity may provide stronger HSC inhibition. Concerning the impact of RAS blockade on CKD, the analysis of large, appropriately powered trials showed the benefit on CKD progression are limited to people with advanced stage 3 CKD with proteinuria> 500 mg/day [9].

Collectively, these data suggest alternative modalities of RAS blockade may be needed to more effectively contrast NAFLD and CKD progression.

Beside ACE inhibitors and ARBs, the ACE2-Angiotensin((1-7)-Mas receptor axis is emerging as an important endogenous counter-regulatory mechanism of the ACE-AngII- AT_1 receptor pathway, with potentially relevant therapeutic implications for NAFLD and CKD[10].

ACE2 is a monocarboxypeptidase that degrades AngII to generate Ang(1-7), a peptide with opposing biological activity to AngII (**Figure 1**). Accordingly, it is being increasingly recognized that the RAS activity depends on the balance between the ACE-AngII- AT_1 receptor and the ACE2-Ang((1-7)-Mas receptor axis, whose activation is responsible for part of the benefits of RAS blockers [4].

ACE2-Ang(1-7) axis expression has been found to be down-regulated in obesity [11] and hepatic and experimentally renal ACE2-Ang(1-7) deficiency enhanced high fat diet-induced NASH, adipose tissue inflammation, and CKD [12], whereas Ang(1-7) analogues or ACE2 activators diminazene and xanthenone reversed these changes and ameliorated adipose tissue dysfunction, vascular inflammation, liver and kidney disease [13, 14,15,16,17]. Therefore, approaches increasing ACE2 activation may offer theoretical advantages over ACE/ARBs by enabling both AngII catabolism and production of Ang(1-7) peptide with opposing activity to AngII.

Excessive fructose intake in the pathogenesis of NAFLD and CKD

The intake of sugar-sweetened beverages has dramatically increased worldwide, with consumption approaching 175 kcal/day per head amongst US adults[18]. This corresponds with a 2-fold increase in consumption of fructose, the main constituent of sugar-sweeteners. Notable amongst these is high-fructose corn syrup (HFCS), a synthetic sugar-sweetener containing 55% fructose and 42% glucose, used in “sodas” and pastries [18].

Fructose has the lowest glycaemic index of all natural sugars and its minor impact on blood glucose had previously led to its recommendation as a sugar substitute for patients with diabetes . However, cumulative observational data link increased fructose consumption to the incidence and severity of NAFLD[19] and CKD [20], with potential underlying mechanisms recently described. Fructose reduces resting energy expenditure and fails to induce satiety [21], thereby promoting excessive calorie intake; furthermore, it acts independently of calorie excess through several mechanisms, initiated by fructose phosphorylation to fructose-1-phosphate by fructokinase and ultimately leading to accumulation of uric acid. Uric acid promotes development and progression of NAFLD, CVD, and CKD via several mechanisms involving compromised hepatocyte ATP homeostasis and ATP depletion [22], enhanced hepatic and renal lipogenesis, mitochondrial ROS generation, reduced NO bioavailability and endothelial dysfunction and proinflammatory cytokine secretion [23, 24, 25, 26, 27](**Glossary, online supplementary Table 1**).

Consistent with the role of fructose metabolism in the development of metabolic disturbances, mice unable to metabolize fructose are protected from obesity, metabolic syndrome and NAFLD [28], and a reduction in fructose intake or uric acid production improved experimental NAFLD and CKD [29, 30]. In humans, the novel xanthine oxidase inhibitor febuxostat improved endothelial dysfunction in advanced CKD [31], while the use of allopurinol was associated with a reduction in the progression of CKD [32].

The impact of allopurinol on CKD stage 3-4 progression is currently being evaluated in the CKD-FIX trial (NCT12611000791932).

Role of energy and nutrient sensors 5-AMP activated protein kinase (AMPK) and Sirtuin-1(Sirt-1) in NAFLD and CKD

5-AMP-activated protein kinase (AMPK) is a ubiquitous heterotrimeric serine/threonine kinase, comprising a catalytic α subunit and regulatory β and γ subunits, functioning as a fine cellular energy sensor and a key regulator of cellular metabolism [33]: AMPK is activated under conditions of calorie restriction or high energy demand, that deplete cellular ATP stores and increase the AMP/ATP ratio, while it is inhibited under conditions of calorie excess like obesity [33]. Hence agents mimicking calorie-restriction and/or physical exercise through AMPK activation appeal as treatment options for obesity-associated disorders.

AMPK activators improved insulin resistance by enhancing oxidative glucose disposal and suppressing hepatic gluconeogenesis in preclinical models of NAFLD [33]. They also counteract high-fat diet-induced toxic lipid accumulation in the liver and kidney, a key mediator of obesity-associated injury [34, 35], through down-regulation of key steps in cholesterol and fatty acid synthesis[33, 34] **(Figure 2).** Downregulation of acetyl-CoA carboxylase (ACC) leads to a fall in malonyl-CoA levels, releasing the inhibition of mitochondrial fatty acid β-oxidation and enhancing oxidation of FFA. AMPK activation may also enhance mitochondrial biogenesis and function, an effect demonstrated in hepatocytes but not in the kidney [33, 34]. Beside its metabolic effects, AMPK

activation has also direct anti-inflammatory properties by inducing functional transition of macrophages from a pro-inflammatory M1 to an anti-inflammatory/pro-resolving M2 phenotype [36] **(Glossary),** and antifibrotic effects by inhibiting HSC activation [37].

AMPK activators ameliorated also high fat-induced CKD through several mechanisms, including inhibition of FFA-induced MCP-1 production, of ROS generation by NADPH oxidase isoform 4(NOX4) and of TGF-β secretion in the kidney(**Figure 2**)[34, 38] .

Several natural AMPK activators, including curcumin, monascin, ankaflavin and berberine yielded promising results in preclinical models of NASH and of CKD [35, 37, 39], and the potent synthetic AMPK-activating dithiolethione oltipraz is being evaluated in non-cirrhotic NAFLD patients in a phase 2 RCT (clinicaltrials.gov ID: NCT01373554).

Sirtuins (SIRTs) are a group of 7 nicotinamide adenine dinucleotide (NAD+)-dependent histone/protein deacetylases (HDACs) belonging to the silent information regulator-2(Sir-2) family. The deacetylation of proteins and histones results in an up- or down-regulation of gene transcription and protein function and plays a crucial regulatory role in numerous cellular functions[40]. Recently, the regulatory function of SIRT1 received much attention due to its calorie restriction-mimicking activity and beneficial effects on obesity-related disorders, including NAFLD and CKD. Upon calorie restriction, increased intracellular NAD+ concentrations activates SIRT1 to promote chromatin silencing and transcriptional repression through deacetylation of histones, eventually resulting in amelioration of glucose and lipid homeostasis in the liver, muscle and adipose tissue; furthermore, SIRT-1 activation also showed anti-oxidant effects, down-regulates proinflammatory genes in the liver and adipose tissue [41], and promoted autophagy, a process which plays a crucial role in various obesity-related disorders, including NAFLD and CKD [42] (**Glossary).**

SIRT-1 activation ameliorated also experimental CKD through indirect effects, mediated by improved glucose and lipid metabolism, and direct, renal-specific effects: SIRT-1 preserves podocyte function and glomerular barrier integrity by down-regulating the tight junction protein Claudin-1[43]; it also down-regulates proinflammatory[44] and pro-fibrogenic pathways[45, 46] and improves

endothelial dysfunction in the kidney, thereby counteracting most pathways at the core of CKD development and progression(**Figure 2**).

Several natural (resveratrol, alpha-lipoic acid) and synthetic (BML-278, which is 1000-fold more potent SIRT-1 activator than resveratrol, and SRT172047) SIRT-1 activators are being evaluated: they improved experimental NAFLD [48, 49] and CKD[50, 51] and ameliorated steatosis and inflammatory markers in NAFLD patients[52]

Impaired antioxidant defense in NAFLD and CKD: role of nuclear erythroid 2-related factor 2 (Nrf2).

Increased oxidative stress is believed to play a key role in the pathogenesis of NAFLD and CKD [33, 53]. Nrf2 is a member of the family of basic region leucine zipper (bZIP) transcription factors, expressed ubiquitously in human tissues, with highest expression in the liver and kidney [54, 55]. Nrf2 up-regulates transcription of numerous antioxidant and detoxification enzymes by binding to their antioxidant response elements (AREs), DNA motifs located in the upstream promoter regions of each target gene. Under basal conditions, Nrf2 is kept transcriptionally inactive through binding to its inhibitor, Kelch-like ECH-associated protein 1 (KEAP1), which targets Nrf2 for proteasomal degradation [54]. KEAP1 is enriched in sulfhydryl groups in its cysteine residues, which act as stress sensors: oxidative or electrophilic cellular stresses, including ROS and reactive nitrogen species (RNS), modify KEAP1 cysteine residues, causing Nrf2 to dissociate from KEAP1, translocate to the nucleus, heterodimerize with small Mafs (sMafs) transcription factors and regulate target gene expression [54]. Furthermore, beyond immediate antioxidant and cytoprotective defense, Nrf2 activation has other anti-inflammatory and pro-autophagic consequences for cellular homeostasis, involving nuclear factor-κB (NF-κB), p53, aryl hydrocarbon receptor, mammalian target of rapamycin (mTOR), heat shock proteins, activator protein 1, Notch homolog 1 (NOTCH1) and Fibroblast growth factor(FGF)-21 [56, 57] (**Figure 3**).

Experimental data support a key protective role for Nrf2 against NAFLD and CKD development: in diet-induced NAFLD, whole-body [58] or myeloid-derived cell [59] Nrf2 deletion promoted

atherosclerosis and steatosis progression to NASH and fibrosis, while Nrf2 activation prevented NASH and fibrosis development [60]. Similarly, Nrf2 activation ameliorated oxidative stress, inflammation, and kidney injury in experimental CKD, while Nrf2 deletion amplified molecular pathways to CKD progression [54].

Numerous natural and synthetic small-molecule Nrf2 activators are being evaluated **(Figure 3):** some are electrophiles that covalently modify cysteine sulfhydryl groups of KEAP1, thereby altering its conformation and preventing KEAP1-Nrf2 protein–protein interaction; however, they non-specifically react with a range of cysteine-rich proteins, lacking selectivity and potentially eliciting off-target toxic effects. One of these electrophile compounds, bardoxolone methyl, generated great enthusiasm for the treatment of diabetic CKD after the phase II BEAM study [61], but its serious molecule-specific side effects led to premature interruption of the subsequent phase III BEACON trial [62].

For this reasons, newer non-electrophile molecules are being developed, that activate Nrf2 through different ways, i.e., by directly interacting with the Nrf2-binding site of KEAP1, thereby preventing its binding to Nrf2; or by inhibiting ubiquitination-proteosomal degradation of Nrf2, thus prolonging its half-life [53]. Whether the enhanced selectivity and potency of these newer Nrf2 activators will translate in different clinical effectiveness and safety remains to be determined.

The liver as a determinant of kidney injury

Growing evidence suggests that the steatotic and inflamed liver may be a more important source of proinflammatory cytokines and antifibrinolytic proteins than adipose tissue. Amongst these proteins are C-reactive protein, plasminogen activator inhibitor (PAI)-1, and TNF-α [63]. Furthermore, an heterogeneous class of liver-secreted molecules, collectively named “hepatokines”, can modulate whole-body metabolism, inflammation and renal injury.

1)Fibroblast growth factor(FGF)21

FGF21 is a 181 amino acid protein belonging to the FGF superfamily, initially named by its ability to stimulate fibroblast proliferation. The FGF gene family can be divided into three subfamilies: the

intracellular FGFs (FGF11/12/13/14), the endocrine FGFs (FGF15/19/ 21/23), and the paracrine FGFs (the rest) [64]. FGFs bind extracellularly to four cell surface tyrosine kinase FGF receptors (FGFRs 1–4).

FGF21 is secreted predominantly by the liver its transcription is stimulated by ER stress [65], sirtuin-1 [66] and by several transcription factors, including PPAR-α, PPAR-γ, retinoid acid receptor(RAR)-β, and NuR77 [64, 67]. FGF21 activity depends on its binding to FGFRs and the transmembrane cofactor β-Klotho, which increases the ability of FGFRs to bind FGF21 and is predominantly expressed in the liver, white adipose tissue, pancreas and kidney [64]. The FGF21–β-Klotho–FGFR complex acts by inducing MAP kinase (MAPK)-1 and MAPK-2 phosphorylation [64].

FGF21 can be considered a metabolic hormone with multiple beneficial effects on energy expenditure and glucose and lipid metabolism: FGF21 administration ameliorated adipose and hepatic insulin sensitivity by stimulating GLUT1 expression and enhancing insulin signaling [68] and suppressing hepatic gluconeogenesis and SREBP-1c mediated lipogenesis [69], it increases energy expenditure FFA oxidation and mitochondrial function via activating the AMPK-SIRT1-PGC-1α pathway and UCP1 [70] and counteracts ER stress [65]. On this basis, experimental FGF21 administration improved obesity, diabetes and NASH [71], and ameliorated diabetic and obesity-related kidney injury in preclinical models of CKD through multiple mechanisms [72, 73] (detailed in **supplementary Table 2).**

Several challenges remain for therapeutic development of FGF21 analogues: in NAFLD and CKD patients, circulating and tissue FGF21 levels are increased rather than reduced, correlate with disease severity [74,75], and are normalized by therapeutic interventions [76]. Furthermore, elevated circulating FGF21 levels precede and predict the incidence of diabetic nephropathy [77], indicating FGF21 resistance is an early and possibly causal factor in the development of obesity-related disorders. Mechanisms underlying FGF21 resistance are under investigation, but may include downregulation of FGFR1 and β-Klotho expression [64]. The administration of pharmacological doses of FGF21 overcomes tissue resistance to endogenous hormone and restores normal metabolic responses. Several pharmacological strategies to achieve and maintain high FGF21 levels are

currently being investigated, including FGF21 conjugation with polyethylene glycol (PEG), recombinant mutant FGF21 analogs and FGF21-mimetic monoclonal antibodies[78;79].

2) Fetuin-A

Fetuin-A is a 64-kDa glycoprotein synthesized and secreted exclusively by hepatocytes in response to ER stress [80] and to high intracellular glucocorticoid levels [81]. Fetuin-A-knockout rodents possess enhanced insulin sensitivity and glucose tolerance as well as resistance to diet-induced obesity and NAFLD, while administration of fetuin-A induces these conditions [82]. Some light has been shed on the mechanisms underlying these effects. Fetuin-A directly induces insulin resistance in myocytes and hepatocytes by inhibiting insulin receptor tyrosine kinase activity and suppresses adiponectin secretion by adipocytes [83]. Furthermore, fetuin-A carries FFA into the circulation and enhances their binding to toll-like receptor (TLR)-4 in adipocytes, triggering proinflammatory adipokine production and insulin resistance [84](**supplementary Table 2)**). Higher serum and hepatic fetuin-A levels have been demonstrated to correlate with the presence and severity of NAFLD [85].

Beside its metabolic effects, fetuin-A is also an inhibitor of soft tissue mineralization, and enhances transport and clearing of procalcific cargo from tissues [86]. Fetuin-A complexes with calcium and phosphate to form stable 50-300-nm–sized soluble colloidal mineral-protein spheres, called calciprotein particles (CPPs), which are cleared from circulation by glomerular and hepatic endothelial cells and macrophages. Circulating fetuin-A-containing CPP levels independently correlate with endothelial dysfunction and subclinical atherosclerosis in NAFLD patients [87] and in different stages of CKD [88, 89]. This suggests that when CCP formation is enhanced by the disturbed mineral homeostasis of CKD and/or increased fetuin-A production (NAFLD), circulating CPP levels may accumulate due to insufficient macrophage clearance promoting systemic endothelial inflammation and dysfunction. Metformin, pioglitazone and 11β-hydroxysteroid dehydrogenase type 1(11β-HSD1) inhibitors may reduce fetuin-A levels [81, 85], but the impact of fetuin-A reduction on clinical outcomes in NAFLD and CKD has not been assessed in RCTs.

3)Insulin-like Growth Factor(IGF)-1

Insulin-like growth factor(IGF)-1 and IGF-2 are related structurally to proinsulin and promote cell proliferation, differentiation, and survival, as well as insulin-like metabolic effects, in most cell types and tissues. The effects of IGFs are modulated by their binding to 6 IGF binding proteins(IGFBPs), which provide a reservoir of IGFs and transport IGF to peripheral tissues but may have also IGF-independent actions. IGF-1 derives largely from the liver, and in NAFLD patients IGF-1 levels are reduced, and independently and inversely related to the severity of liver histology [90, 91], suggesting hepatic insulin resistance may inhibit GH-stimulated synthesis of IGF-1 (**supplementary Table 2)**).
In addition, a normal GH/IGF-1/-2 axis is crucial for maintaining physiological glomerular plasma flow and filtration rate in experimental CKD [92] and in obese insulin resistant CKD patients [93] and for podocyte cell survival and function, thereby mantaining glomerular filtration barrier integrity [94]. Pharmacological strategies aiming at restoring normal IGF-1 levels are being intensely investigated

4) Syndecan-1: a mediator of hepatic lipoprotein uptake and beyond

Beside secreting VLDL and LDL, the liver is also a major organ for clearance of triglyceride-rich lipoproteins and their remnants. Recently, the key role for the transmembrane heparan sulfate proteoglycan syndecan-1 in hepatic triglyceride-rich lipoprotein clearance has emerged [95]: syndecan-1 is constitutively bound to hepatocyte membrane, where it binds LPL and apoE through its negatively charged heparan sulfate chains and internalizes apoE-containing lipoproteins [96]. Defective syndecan-1 sulfation by hepatocyte-specific inactivation of sulfotransferases involved in heparan sulfate biosynthesis or accelerated syndecan-1 shedding from hepatocytes by activation of metalloproteinases result in impaired TRLP clearance and dyslipidemia [95,96]. NAFLD patients have an increased shedding of syndecan-1, as a result of increased hepatic metalloproteinase activation, and an inpaired syndechan-1 sulfation as a result of defective hepatic sulfotransferase activity [97, 98], which may alter TRLP clearance and contribte to ahterogenic dyslipidemia. Beside a key role in hepatic TRLP metabolism, syndecan-1 is also a key constituent of glycocalyx layer at the endothelial surface and its shedding has been associatred with loss of endothelial barrier integrity across progressive CKD stages [99].

Inhibitors of syndecan-1 shedding, including sphingosine-1-phosphate[100], for treating dyslipidemia and restoring renal endothelial integrity in CKD gave encouraging results in preclinical models and are currently investigated.

Dysregulated cholesterol metabolism in the pathogenesis of NAFLD and CKD: role of nuclear transcription factors Sterol Regulatory Binding Protein(SREBP)-2 and farnesoid X receptor(FXR).

There is increasing experimental and human evidence that both NASH and CKD are characterized by free cholesterol accumulation in hepatic and renal cells, which triggers oxidative stress inflammation and fibrosis in the liver and kidney [6].

Altered cholesterol metabolism may contribute to liver and kidney injury through multiple mechanisms: liver fat accumulation induces atherogenic dyslipidaemia through oversecretion of large VLDL particles, triggering intravascular lipoprotein remodeling, and the typical atherogenic lipoprotein phenotype of high triglyceride-rich lipoproteins, reduced smaller HDL-C particles and increased circulating levels of small, dense LDL(sLDL) and oxidized LDL particles, which bind to receptors on glomerular endothelial cells, mesangial cells, tubular cells and interstitial macrophages, and trigger glomerular injury, mesangial cell proliferation and foam cell formation [101,102].

Beside altered plasma lipoprotein pattern, a central role for dysregulated intracellular cholesterol metabolism in the pathogenesis of NASH and CKD is increasingly recognized. The master nuclear regulators of cellular cholesterol metabolism in liver and kidney are the nuclear transcription factors Sterol Regulatory Binding Protein(SREBP)-2 and Farnesoid X-receptor (FXR), which are abundantly expressed in all hepatic cell lineages and in glomerular and proximal tubular cells [101, 103].

Evidence from NASH patients and from experimental diet-induced models of NASH and CKD indicate an inappropriate SREBP-2 upregulation, with consequent increase in cholesterol synthesis, influx and retention and intracellular toxic free cholesterol accumulation, impaired bile acid synthesis, and reduced bile acid-stimulated FXR activation: the resulting intracellular cholesterol overload

triggers multiple molecular pathways leading to cell death, inflammation and fibrosis in the liver and kidney [103, 104,105, 106] (**supplementary Table 2**).

While pharmacological antagonism of SREBP-2 has not been evaluated as a therapeutic strategy to date, FXR activation by potent, semisynthetic bile acids like obeticholic acid(OCA) improved NAFLD activity score and fibrosis in the multicenter, double-blind, randomized "FXR Ligand NASH Treatment (FLINT)" in NASH [107] and reversed renal lipid accumulation, oxidative stress, inflammation, fibrosis and proteinuria in diet-induced experimental CKD [103, 103].

The kidney as a contributor to the development of NAFLD and ectopic lipid deposition

While obesity and NAFLD injure the kidney, growing evidence suggests CKD may mutually contribute to NAFLD and insulin resistance**: a**dministration of sera from patients with CKD to rodents or cultured adipocytes or uninephrectomy induce lipodystrophy, ectopic fat redistribution from adipose tissue to liver and muscle, insulin resistance, and glucose intolerance [108, 109]**.**

Molecular mediators of metabolic derangement in CKD are being unraveled: in adipose tissue, the adipokine Zinc α2-glycoprotein (ZAG) is up-regulated while perlipin, lipoprotein lipase (LPL) and VLDL receptor are down-regulated, resulting in enhanced lipolysis and lipid mobilization from adipocytes to liver and muscle and impaired FFA uptake by adipose tissue from chylomicrons and VLDLs [110, 111]. Furthermore, acute kidney injury is followed by an up-regulation of hepatic carbohydrate response element binding protein (ChREBP)-mediated *de novo* lipogenesis and by a down-regulation of PPAR-α-mediated FFA oxidation and diglyceride acyltransferase (DGAT)-mediated FFA incorporation into triglycerides, thereby promoting accumulation of lipotoxic FFA in the liver [112].

The primary dysfunction leading to fat redistribution and metabolic dysregulation following kidney injury is under investigation, and several pathways represent potential therapeutic targets **(Table 1):**

1)CKD modulates gut microbiota composition

CKD may *per se* induce intestinal dysbiosis and systemic inflammation, thereby promoting NAFLD and insulin resistance. Mechanisms whereby CKD modulates intestinal microbiota composition include accumulation of uremic toxic metabolites(URMs) normally eliminated by the kidneys, including urea, indoxyl-sulphate, p-Cresyl sulphate (p-CS) and trimethylamine-N-oxide(TMAO) [113, 114].

The accumulation of urea may lead to influx into the gastrointestinal lumen, where it is hydrolysed to ammonia by microbial urease, then converted to ammonium hydroxide. Ammonia and ammonium hydroxide disrupt intestinal epithelial tight junctions, enhancing passage of LPS and other toxic luminal compounds into the circulation [115], with alteration of intraluminal pH and promotion of the growth of urea-metabolizing microbial strains at the expense of carbohydrate-fermenting strains. Accordingly, CKD patients exhibit significant expansion of bacterial families possessing urease, uricase, and indole and p-cresol forming enzymes, enhancing formation and absorption of uremic toxic metabolites(URMs) ammonia, indoxyl-sulphate, p-CS and TMAO [116].. The relevance of this mechanism to systemic inflammation and dysmeabolism is suggested by two experimental studies: in the first, administration of oral activated charcoal absorbent AST-120 to CKD rats improved intestinal barrier function, and reduced systemic oxidative stress, inflammation and endotoxemia [115]; in the second, treatment with an antioxidant superoxide dismutase (SOD)/catalase mimetic prevented the development of insulin resistance in normal mice after urea infusion, suggesting targeting urea-induced ROS may improve metabolic disturbances associated with CKD [117].

The impact of synbiotics (co-administration of pre- and probiotics) on CKD is being investigated in the SYNbiotics Easing Renal failure by improving Gut microbiologY (SYNERGY) trial [118].

2) Glomerular hyperfiltration and RAS activation.

A potential role of glomerular hyperfiltration and renal hemodynamic alterations as a trigger of renal adipogenesis and ectopic fat deposition is suggested by the increased renal expression of renin, angiotensin and AT2Rs in uninephrectomized rats developing ectopic lipid deposition, NAFLD and associated metabolic disturbances, and by the finding that ACE inhibitors (ACEI) prevented the development of NAFLD and associated metabolic changes following uninephrectomy[119].

3)Asymmetric dimethylarginine(ADMA)

Asymmetric dimethylarginine (ADMA) is formed through methylation of arginine residues by the enzyme protein methyltransferase (PRMT) and is metabolized by dimethylarginine dimethylaminohydrolase (DDAH), an enzyme that exists in 2 isoforms with different activity and tissue distribution: DDAH-1 is mainly expressed in the liver and the kidney, the major sites of ADMA metabolism, while DDAH-2 is highly expressed in the vascular endothelium, heart, placenta and the kidney [120].

ADMA is and endogenous inhibitor of NO synthase and can induce endothelial dysfunction, insulin resistance, ER stress and TGF-β production in hepatocytes and glomerulo-tubular endothelial cells, promoting hepatic and kidney injury and fibrosis [121,122]. Accordingly, plasma ADMA levels are increased in patients with NAFLD and/or with CKD, correlate with renal dysfunction and predict CKD progression, early atherosclerosis and CVD events in these patient populations [123, 124]. Molecular mechanisms underlying ADMA elevation in CKD include both and increased ADMA production by PRMT and an impaired ADMA catabolism by hepatic and renal DDAH, the latter being the predominant factor and a strong predictor of CKD [125]. Several pharmacological agents evaluated in preclinical/phase 2b studies hold promise to neutralize the deleterious effects of ADMA in NAFLD and CKD, including pentoxifylline [126], quercetin [127] and the FXR agonist obeticholic acid [128], but their impact on clinical endpoints has to be assessed.

4)altered prereceptor glucocorticoid metabolism: role of 11β-hydroxysteroid dehydrogenase type 1(11β-HSD1).

11β-Hydroxysteroid dehydrogenase (11βHSD) enzymes regulate intracellular glucocorticoid levels independently of circulating hormone concentrations: 11βHSD type 1 (11βHSD1) catalyzes the conversion of inactive cortisone to active cortisol (11-dehydrocorticosterone to corticosterone in rats), thus amplifying local glucocorticoid levels, whereas 11βHSD2 catalyzes the opposite reaction. While 11βHSD1 is expressed at high levels in the liver, adipose tissue, renal proximal tubules and interstitium, 11βHSD2 is largely confined to the distal nephron [129]. In NAFLD patients, hepatic

and adipose tissue 11βHSD1 is upregulated and parallels the severity of hepatic inflammation[130, 131] .Selective hepatic or adipose tissue 11βHSD1 overexpression promotes NAFLD and induces gluconeogenesis, lipogenesis, and insulin resistance, while 11βHSD1 functional deletion has opposite effects [129, 132, 133]. In renal medulla, 11βHSD1 activation induced salt-sensitive hypertension, which was reversed by 11βHSD1 inhibition [134]. Recent experimental data demonstrate that in CKD hepatic and adipose tissue 11βHSD1 is upregulated, as a result of increased oxidative stress and proinflammatory cytokines Il-1, TNF-α and IL-6, and promotes NAFLD, insulin resistance, hypertension, hyperglycemia and dyslipidaemia, all reversed by the 11βHSD1 inhibitor carbenoxolone[135]. These data make 11βHSD1 inhibition an appealing strategy for managing CKD-associated metabolic disorders: accordingly, in a recent phase 1b RCT, the 11βHSD1 inhibitor RO5093151 significantly improved radiological steatosis in NAFLD [136].

Concluding remarks and future perspectives

Accumulated evidence demonstrates a link between NAFLD and CKD, prompting investigation of factors promoting both liver and kidney disease to more effectively tackle progression of both disease conditions. Reviewed data suggests a complex picture, where NAFLD and CKD share common pathogenic factors but can also mutually interact, influencing each other(**Figure 4**). The disclosure of these relationship offers novel therapeutic strategies with incremental effectiveness on both liver and kidney disease in experimental models. The translational potential of these approaches will have to the evaluated in large, appropriately powered RCTs with clinical end-points. As an example, FXR agonists improved liver disease in randomized clinical trials, but their long-term safety and their impact on hepatic and renal clinical outcomes remain unclear [137], and resveratrol showed great promise in preclinical studies, but pharmacokinetic issues need to be overcome to bring this drug into clinical use[137]. Furthermore, the theoretical benefits of correcting altered hepatokine secretion on the incidence and progression of CKD remain to be demonstrated (**BOX 1**). Given the increasing prevalence of CKD and NAFLD, their direct effects and their acceleration of CVD, strategies to

reduce the incidence, progression and complications of these twin plagues are an important priority in healthcare.

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Author Contributions.

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Giovanni Musso, as the corresponding author, had full access to all the data and takes final responsibility for the decision to submit for publication.

Maurizio Cassader: undertook literature search and acquired data, critically analyzed the results, contributed to draft of the article, gave final approval

Solomon Cohney: undertook literature search and acquired data, critically analyzed the results, contributed to draft of the article, gave final approval

Silvia Pinach: undertook literature search and acquired data, critically analyzed the results, contributed to draft of the article, gave final approval

Francesca Saba: undertook literature search and acquired data, critically analyzed the results, contributed to draft of the article, gave final approval

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FIGURE LEGENDS

Figure 1: mechanisms connecting renin-angiotensin system (RAS) to liver and renal disease in NAFLD and CKD.

Panel A: impact of RAS-AT1 receptor activation on liver and kidney injury. In the liver, AT1 receptor activation promotes steatosis through stimulation of SREBP-1c-mediated de novo lipogenesis and inhibition of mitochondrial FFA oxidation. AT1 receptor activation also promotes hepatic insulin resistance, mitochondrial and NOX-mediated ROS production and synthesis of pro-inflammatory and profibrogenic cytokines IL-6, MCP-1, PAI-1 and TGF-β, thereby contributing to the whole spectrum of liver injury in NASH.

In the kidney, AT1 receptor activation promotes glumerular efferent arteriole vasoconstriction, glomerulosclerosis amd glomerular injury through ROS and TGF-β production. In the proximal tubule, AT1 recdeptor activation promotes Na resorption and tubulointerstitial inflammation and fibrosis by enhancing secretion of proinflammatory and profibrogenic cytokines MCP-1 and TGF-β,

respectively. TGF-β is a key pro-fibrogenic cytokine and promotes epithelial-to-mesenchimal transition (EMT) of tubule cell, thus triggering interstitial fibrosis.

Panel B: impact of ACE2-Angiotensin(1-7)-Mas receptor activation on liver and kidney disease.

ACE2-Angiotensin(1-7)-Mas axis counteracts most of the deleterious effects of RAS-AT1 receptor activation: it enhances insulin sensitivity in hepatocytes and adipocytes, it inhibits ROS production and down-regulates proinflammatory and profibrogenic pathways in the liver, adipose tissue and kidney

Abbreviations: ACO-1: acyl-CoA oxidase-1; CCL5: Chemokine (C-C motif) ligand 5; CPT-1: carnitine palmitoyltransferase-I**;** EMT: epithelial-to-mesenchymal transition; ERK: extracellular signal-regulated kinase; FFA: free fatty acids; IL-6: interleukin-6; IRS-1: insulin receptor substrate-1; JAK: Janus kinase; LPL: lipoprotein lipase; LPS: lipopolysaccharide; MCP-1: monocyte chemotactic protein-1; NO: nitric oxide; NOX: NADPH oxidase; PAI-1: plasminogen activator inhibitor-1; PI3-K: phosphoinositide 3-kinase; PKC: protein kinase C; TGF-β: transforming growth factor- β.

Figure 2: AMP-activated Kinase (AMPK) and sirtuin-1(Sirt-1) in the pathogenesis of NAFLD and CKD.

Panel A: mechanisms whereby AMPK activation protects against NAFLD and CKD. In the liver and in he skeletal muscle, AMPK activation ehannces insulin sensitivity and mitochondrial FFA oxidation and inhibits hepatic *de novo* lipogenesis and gluconeogenesis. AMPK activation has also anti-inflammatory and anti-fibrotic effects by shifting macrophage phenotype towards an anti-inflammatory, M2 phentype and by inhibiting hepatic stellate cell activation by ROS and by TGF-β. In the kidney, AMPK activation inhibits toxic FFA and cholesterol accumulation by modulating the same metabolic pathways as those regulated in the liver; additionally, AMPK blunts ROS production and pro-inflammatory and pro-fibrotic cytokine secretion by mesangial and tubular cells.

The Figure reports also several AMPK activators that are currently evaluated in preclinical and clinical studies

Panel B: mechanisms whereby Sirt-1 activation protects against NAFLD and CKD.

In the liver , Sirt-1 activation inhibits de novo lipogenesis and enhances insulin action and oxidative FFA and glucose metabolism. Additionally, Sirt-1 activation counteracts several important pro-inflammatory and pro-fibrogenic pathways in the liver and in the kidney, including the NF-κB pathway and the Smad7/TGF-β pathway. In renal glomeruli, Sirt-1 enhances endothelial NO production and podocyte function, thereby preserving glomerular barrier integrity. A peculiar effect of Sirt-1 activation is the enhancement of autophagy in hepatocytes and renal podocytes: defective autophagy is being increasingly recognized to play a key pathogenic role in NAFLD and CKD.

The Figure reports also several Sirt-1 activators that are currently evaluated in preclinical and clinical studies

Abbreviations: ABCA1: **A**TP-binding cassette transporters A1; ACC: acetyl-CoA carboxylase; *ALDH3A1* Aldehyde dehydrogenase 3A1; ATGL: adipose triglyceride lipase; *Cat:* Catalase; CDDO: 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oicacid; DMF: dimethylfumarate,Glt-Px: Glutathione peroxidase; Glt-R: Glutathione reductase ; *G6PD:* Glucose-6-phosphate 1-dehydrogenase; HO-1: Heme oxygenase-1; *TXN-R: GST:* Glutathione *S*-transferase, Thioredoxin reductase; *SOD* Superoxide dismutase; *EPHX1* Microsomal epoxide hydrolase 1 *MGST:* Microsomal glutathione *S*-transferase, NK-252: (1-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)-3-(pyridin-2-ylmethyl)urea).*NQO1* NAD(P)H:quinone oxidoreductase; *PSMB5:* Proteasome 26S PSMB5 subunit; tBHQ: tert-Butylhydroquinone; *UbC* Ubiquitin C; : *UGT:* UDP glucuronosyltransferase; AICAR: 5-Aminoimidazole-4-carboxamide-1-β-D- ribonucleoside; CA: cholic acid; CDCA. chenodeoxycholic acid; CD36: cluster of differentiation-36; CHOP: C/EBP homologous protein; CPP: calciprotein particles; CPT-1: carnitine palmitoyltransferase-**I;** ; EMT : epithelial-to-mesechymal transition ; ER: endoplasmic reticulum; FAS: fatty acid synthase; FFA: free fatty acids; GLUT: glucose transporter; HMGB1 : High-mobility group box 1 ; HMG-CoAR: 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IL: interleukin; IRS-1: insulin receptor substrate-1; KLF: Kruppel-like factor; LDL: low-density lipoprotein; LDL-R: low-density lipoprotein receptor; MCP-1: monocyte chemotactic protein-1; NO: nitric oxide; NOX: NADPH oxidase; OCA: obeticholic acid; PGC-1α: peroxisome

proliferator-activated receptor-γ coactivator-1 α; RAGE: Receptor for Advanced Glycation End-products SCD-1: stearoyl-CoA desaturase-1; SR-A1: scavenger receptor-A1; SR-B1: scavenger receptor-B1; SREBP: sterol-responsive element binding protein; TGF-β: transforming growth factor-β; TLR: toll-like receptor; TNF: tumor necrosis factor; TZD: thiazolidinediones; VLDL: very low density lipoprotein; VSCMs: vascular smooth muscle cells;

Figure 3: nuclear erythroid 2-related factor 2 (Nrf2) in the pathogenesis of NAFLD and CKD.

Nrf2 activation enhances transcription of main antioxidant and detoxifying Phanse I and phase II enzyme systems in the liver, macrophages, glomerular and tubular cells. Additionally, Nrf2 activation has also direct anti-inflammatory and anti-fibrotic effects by down-regulating NF-κB, PAI-1 and TGF-ß pathways in the liver and kidney. The Figure reports also the main natural and synthetic Nrf2 activators currently evaluated in preclinical and clinical studies.

Abbreviations: *ALDH3A1* Aldehyde dehydrogenase 3A1; ATGL: adipose triglyceride lipase; *Cat:* Catalase; CDDO: 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oicacid; DMF: dimethylfumarate,Glt-Px: Glutathione peroxidase; Glt-R: Glutathione reductase ; *G6PD:* Glucose-6-phosphate 1-dehydrogenase; HO-1: Heme oxygenase-1; *TXN-R: GST:* Glutathione *S*-transferase, Thioredoxin reductase; *SOD* Superoxide dismutase; *EPHX1* Microsomal epoxide hydrolase 1 *MGST:* Microsomal glutathione *S*-transferase, NK-252: (1-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)-3-(pyridin-2-ylmethyl)urea).*NQO1* NAD(P)H:quinone oxidoreductase; *PSMB5:* Proteasome 26S PSMB5 subunit; tBHQ: tert-Butylhydroquinone; *UbC* Ubiquitin C; : *UGT:* UDP glucuronosyltransferase; AICAR: 5-Aminoimidazole-4-carboxamide-1-β-D- ribonucleoside; CA: cholic acid; CDCA. chenodeoxycholic acid; CD36: cluster of differentiation-36; CHOP: C/EBP homologous protein; CPP: calciprotein particles; CPT-1: carnitine palmitoyltransferase-I**;** ; EMT : epithelial-to-mesechymal transition ; ER: endoplasmic reticulum; FAS: fatty acid synthase; FFA: free fatty acids; GLUT: glucose transporter; HMGB1 : High-mobility group box 1 ; HMG-CoAR: 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IL: interleukin; 11β-HSD1: 11β-hydroxysteroid dehydrogenase type 1; IRS-1: insulin receptor substrate-1; KLF: Kruppel-like factor; LDL: low-density lipoprotein; LDL-R: low-density

lipoprotein receptor; MCP-1: monocyte chemotactic protein-1; NO: nitric oxide; NOX: NADPH oxidase; OCA: obeticholic acid; PGC-1α: peroxisome proliferator-activated receptor-γ coactivator-1 α; RAGE: Receptor for Advanced Glycation End-products SCD-1: stearoyl-CoA desaturase-1; SR-A1: scavenger receptor-A1; SR-B1: scavenger receptor-B1; SREBP: sterol-responsive element binding protein; TGF-β: transforming growth factor- β; TLR: toll-like receptor; TNF: tumor necrosis factor; TZD: thiazolidinediones; VLDL: very low density lipoprotein; VSCMs: vascular smooth muscle cells;

Figure 4: interactions between liver, kidney, gut and adipose tissue in promoting NAFLD and CKD.

Gut microbial dysbiosis increases production of uremic toxins (URMs) ammonia, p-Cresyl sulphate, indoxylsulphate, trimethylamine (TMA) and of lipopolysaccharide (LPS) and reduced synthesis of short chain fatty acids (SCFA) by microflora. URMs and LPS diffuse into the circulation through an increased intestinal permeability and reach the liver, the kidney and adipose tissue, where they promote inflammation, insulin resistance and fibrosis thereby leading to NAFLD and CKD. In CKD, renal excretion of URMs is impaired and these molecules further diffuse into interstitial fluids and intestine, thus aggravating intestinal dysbiosis and barrier disruption

In NAFLD, the steatotic and inflamed liver overproduces proinflammatory cytokines (including IL-6, and TNF-α), the inhibitor of fibrinolysis plasminogen activator inhibitor (PAI)-1, and the hepatokine fetuin-A, which inhibits adiponectin secretion, induces insulin resistance and complexes with calcium and phosphate to form soluble colloidal mineral-protein spheres, called calciprotein particles (CPPs), which are cleared from circulation by glomerular and hepatic endothelial cells and macrophages and promote endothelial dysfunction and vascular wall inflammation. The steatotic liver determines also a highly pro-atherogenic lipoprotein pattern by oversecreting large VLDL particles, which exchange their triglycerides with cholesteryl esters of HDL and LDL particles and give rise to oxidized LDLs and reduced HDL-C (atherogenic dyslipidaemia). Furthermore, in NAFLD the liver, kidney and adipose tissue are resistant to endogenous FGF-21. Finally, upon excessive fructose intake the liver

synthesizes uric acid, which is now recognized to induce insulin resistance, inflammation and oxidative stress in many tissus.

CKD contributes to NAFLD and associated systemic inflammation and insulin resistance through reduced excretion of uric acid and URMs. In NAFLD and CKD adipose tissue is inflamed and displays the features of adipose tissue dysfunction, i.e. resistance to the suppressive activity of insulin on lipolysis, and abnormal pattern of adipokine secretion: overall, these phenomena result in an increased flow of toxic free fatty acids(FFAs) to the liver and kidney, a reduced secretion of the key anti-inflammatory, insulin-sensitizing, antifibrotic and antioxidative adopokine adiponectin, and an increased secretion of proinflammationy profibrotic adipokines, including the renin-angiotensin-aldosterone system, IL-6, TNF-α. In CKD, renal excretion of URMs is reduced and these toxins induce insulin resistance and inflammation in adipose tissue in a negative feed-forward loop: this has been recently demonstrated with p-Cresyl sulphate . The reader can refer to Figures and Table 1 for a detailed description of molecular mechanisms underlying gut-liver-kidney-adipose tissue connection,

GLOSSARY

ATP depletion and fructose metabolism[22]: the first step in fructose metabolism, i.e. phosphorylation to fructose-1-phosphate by fructokinase in the liver, is a rapid, substrate-dependent reaction that results in a fall in intracellular phosphate and ATP levels: in humans, the ingestion of relatively low doses of fructose (60 g fructose alone or 39 g fructose with 39 g glucose, i.e., the amounts contained in a popular soft beverage drinks serving size, acutely induces a substantial hepatic ATP depletion. The decrease in intracellular phosphate stimulates AMP Deaminase-2 (AMPD-2), which catalyzes the degradation of AMP to inosine monophosphate and eventually uric acid.

Autophagy[42]: a lysosomal degradation process that removes protein aggregates and damaged or excess organelles under various stress conditions and recycles them into new building blocks and energy for cellular renovation and homeostasis. In nutrient excess conditions, autophagy is reduced, but once nutrients are depleted, autophagy is activated to provide energy resources for cells. Defective autophagy under nutrient excess conditions have been recently involved in the pathogenesis of aging-related or metabolic diseases.

CKD[1]: chronic kidney disease, defined by the National Kidney Foundation as a persistent(>3 months) GFR of less than 60 ml per minute per 1.73 m2 of body surface area or the presence of kidney damage, regardless of the cause, and kidney function

HDAC: histone deacetylase[40]. Histone acetylation mediated by histone acetyltransferases promotes an open chromatin formation, which provides binding sites for basal transcription factors and RNA polymerase II to facilitate gene transcription. In contrast, histone deacetylases (HDACs) remove acetyl group from lysine residues of histone, resulting in chromatin compaction and transcription repression . Furthermore, histone acetylation and methylation are often coordinately regulated. Histone deacetylation by SIRT1 may also enhance histone methylation, which activates or represses gene expression, depending on the methylation sites.

HSC: hepatic stellate cells

Macrophage M1-M2 phenotype[36]: two distinct functional states of polarized activation for macrophages have been defined: the classically activated (M1) macrophage phenotype and the alternatively activated (M2) macrophage phenotype **T**he M1 macrophage subtype shows a "pro-inflammatory" cytokine (e.g. TNF, il-12, IL-23) and chemokine (CXCL9 and CXCL10) profile, while M2 macrophage has an "anti-inflammatory" cytokine (e.g. Il-10, IL-1RA) and chemokine(CCL17, CCL22 and CCL24) profile and is involved in immunosuppression and tissue repair. Importantly, macrophages *in vitro* are capable of complete repolarization from M2 to M1, and change again in response to fluctuations in the cytokine environment. The change in polarization is rapid and occurs at the level of gene expression, protein, metabolite, and microbicidal activity.

Microalbuminuria[1]:: defined by a urinary albumin-creatinine ratio of 30-300 mg/o or by an albumin excretion rate of 30-300 mg/day

NAFLD: nonalcoholic fatty liver disease

NASH: nonalcoholic steatohepatitis

SOD[117]: superoxide dismutase

SYNERGY[118]: SYNbiotics Easing Renal failure by improving Gut microbiologY

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Table 1: Mechanisms promoting NAFLD and ectopic fat deposition following kidney injury.

Urea		
Cellular mechanism	**Biological effect**	**Therapeutic implications**
Hepatocyte, skeletal miocyte, adipocyte[115]: ↑mitochondrial ROS production Modification of insulin signalling molecules by O-GlcNAc molecules→↓ insulin-stimulated IRS tyrosine phosphorylation, Akt phosphorylation and glucose transport ↑ adipokine retinol binding protein 4 (RBP4) and resistin expression	oxidative stress insulin resistance adipose tissue dysfunction systemic inflammation	antioxidant SOD/catalase mimetic[117]
URMs (Ammonia, indoxyl-sulphate, p-Cresyl sulphate and TMAO)		
Cellular mechanism[114-116]	**Biological effect**	**Therapeutic implications**
Skeletal miocyte: ↑ ERK-1/2 phosphorylation of IRS-1→↓ IRS-1 signalling **Hepatocyte:** ↑ *de novo* lipogenesis and ↓ VLDL secretion **Adipocyte:** ↑ leptin secretion and ↓ *de novo* lipogenesis ↑ ZAG and ↓ perlipin →↑ lipolysis **Macrophage:** ↑ LPS-induced NF-kB nuclear translocation→NF-kB activation	Insulin resistance Lipid redistribution from adipose tissue to liver and muscle Systemic inflammation	Uremic toxins absorption by AST-120 [115]
Asymmetric dimethylarginine(ADMA)		
Cellular mechanism [121, 122]	**Biological effect**	**Therapeutic implications**
Hepatocytes, renal glomerular endothelial and proximal tubule cells: ↓ eNO synthase →↓ NO production→ ↑ endothelial dysfunction→ microvascular ischemia ↑ PERK and IRE1-α phosphorylation→ER stress→↑ cellular apoptosis, TGF-β production→↑ hepatic and renal necrosis and fibrogenesis	Hepatic steatosis and necroinflammation Insulin resistance Glomerular/tubule-interstitial ischemia and sclerosis	Quercetin, pentoxifylline, FXR agonist obeticholic acid [126-128]
11β-hydroxysteroid dehydrogenase type 1(11β-HSD1)		

Cellular mechanism	Biological effect	Therapeutic implications
Liver, adipose tissue[129, 132, 133]: ↑ intracelllar cortisol-->↑ gluconeogenesis and lipogenesis, ↓ PKB/Akt phosphorylation→↓ insulin signaling **Renal proximal tubule, macula densa, interstitium:** ↑ tubular canne NKCC2 activity→↑ Na reabsorption[134]	Insulin resistance Hepatic steatosis Glucose intolerance Dyslipidemia Salt-sensitive hypertension	**11β-HSD1 inhibitors**: carbenoxolone, UE2316, RO5093151 [134-136]

Abbreviations: AMPD: AMP deaminase; FAS: fatty acid synthase; ACC: acyl-CoA carboxylase; DAG: diglyceride; DGAT: diglyceride acyltransferase; L-FABP**:** liver-fatty acid binding protein**;** CPT1A: carnitine palmitoyltransferase-1A; ATP: adenosine triphosphate; HMGCR: HMG-CoA reductase; LPL: lipoptorein lipase; O-GlcNAc: *O*-linked ®-*N*-acetylglucosamine; AICAR: 5-amino-imidazole-4-carboxamide ribonucleoside; FAS: fatty acid synthase; ACO-1: acyl-CoA oxidase-1; ACC: acyl-CoA carboxylase; EMT: epithelial-mesenchymal transition; ATP: adenosine triphosphate; HMGCR: HMG-CoA reductase; PPAR: peroxisome proliferators-activated; LPL: lipoptorein lipase; VLDL: very low density lipoprotein;; 11β-HSD1: 11β-hydroxysteroid dehydrogenase type 1; NLRP3: NOD-like receptor superfamily, pyrin domain containing 3; O-GlcNAc: *O*-linked □-*N*-acetylglucosamine; PGC-1α: peroxisome-proliferator-receptor (PPAR)-γ coactivator-1α; REE: resting energy expenditure; SOPCS-3: suppressor of cytokine signaling 3; SRA-1: scavenger receptors A1; SRB-1: scavenger receptor B1; EGFR: epithelial growth factor receptor;

PERK: protein kinase RNA-activated-like ER kinase; IRE1α: inositol requiring-1α

ERK1/2: extracellular signal-regulated kinases 1-2; IRS-1: insulin receptor substrate-1;

NHE3:N a+-H+ exchanger 3; TMAO: trimethylamine-N-oxide;

PAI-1: plasminogen activator inhibitor-1

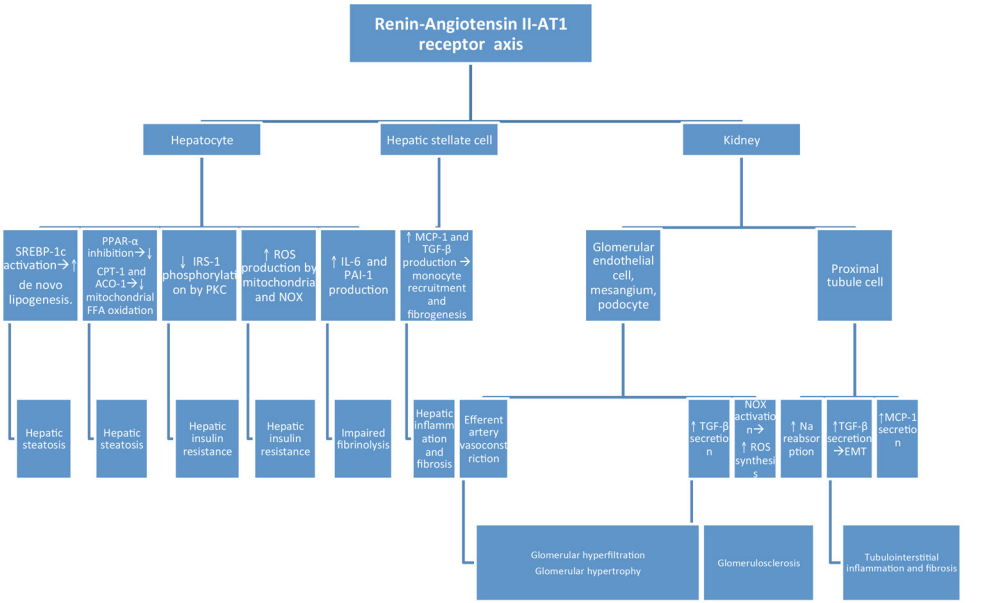
PKA: protein kinase A; PKB: protein kinase B; MCP:

FAS: fatty acid synthase; ACC: acetyl-CoA carboxylase; SCD-1: stearoyl-CoA desaturase-1;

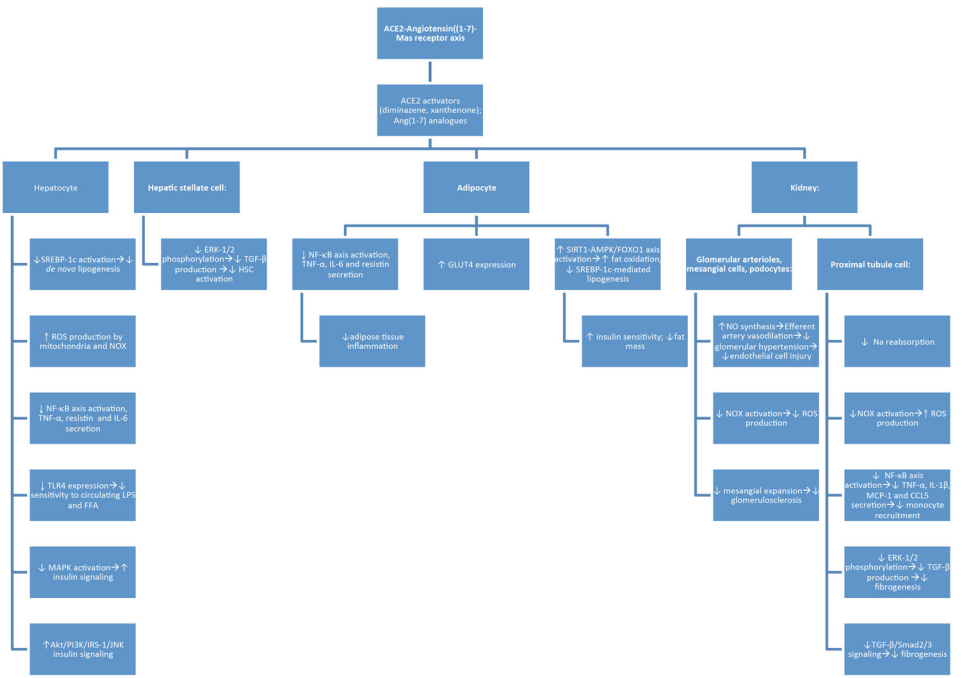
ZAG: Zinc-α2-glycoprotein

Figure

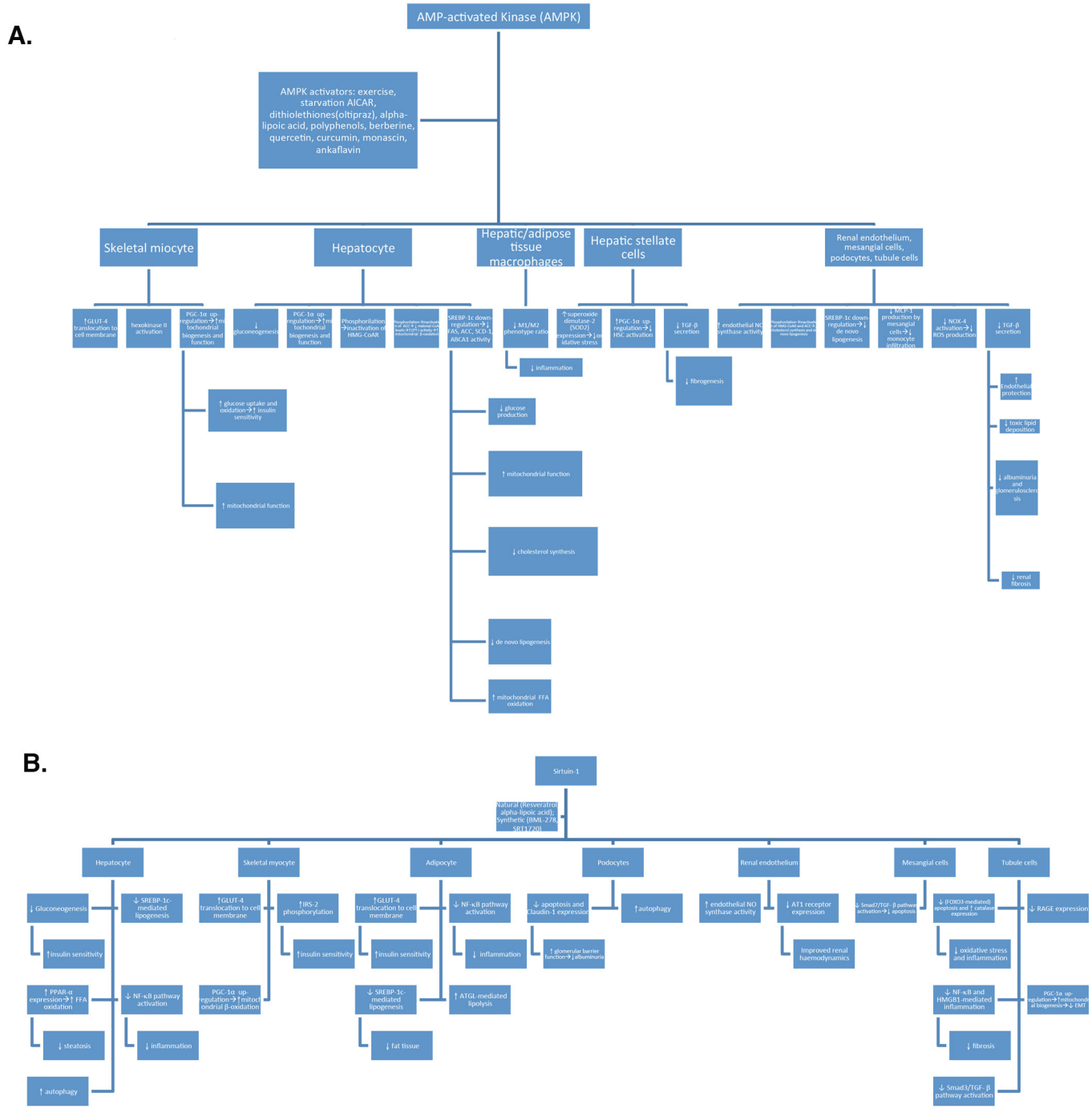
A.


Renin-Angiotensin II-AT1 receptor axis
Hepatocyte
Hepatic stellate cell
Kidney
SREBP-1c activation→↑ de novo lipogenesis.
PPAR-α inhibition→↓ CPT-1 and ACO-1→↓ mitochondrial FFA oxidation
↓ IRS-1 phosphorylation by PKC
↑ ROS production by mitochondria and NOX
↑ IL-6 and PAI-1 production
↑ MCP-1 and TGF-β production → monocyte recruitment and fibrogenesis
Glomerular endothelial cell, mesangium, podocyte
Proximal tubule cell
Hepatic steatosis
Hepatic steatosis
Hepatic insulin resistance
Hepatic insulin resistance
Impaired fibrinolysis
Hepatic inflammation and fibrosis
Efferent artery vasoconstriction
↑ TGF-β secretion
NOX activation→ ↑ ROS synthesis
↑ Na reabsorption
↑TGF-β secretion →EMT
↑MCP-1 secretion
Glomerular hyperfiltration
Glomerular hypertrophy
Glomerulosclerosis
Tubulointerstitial inflammation and fibrosis

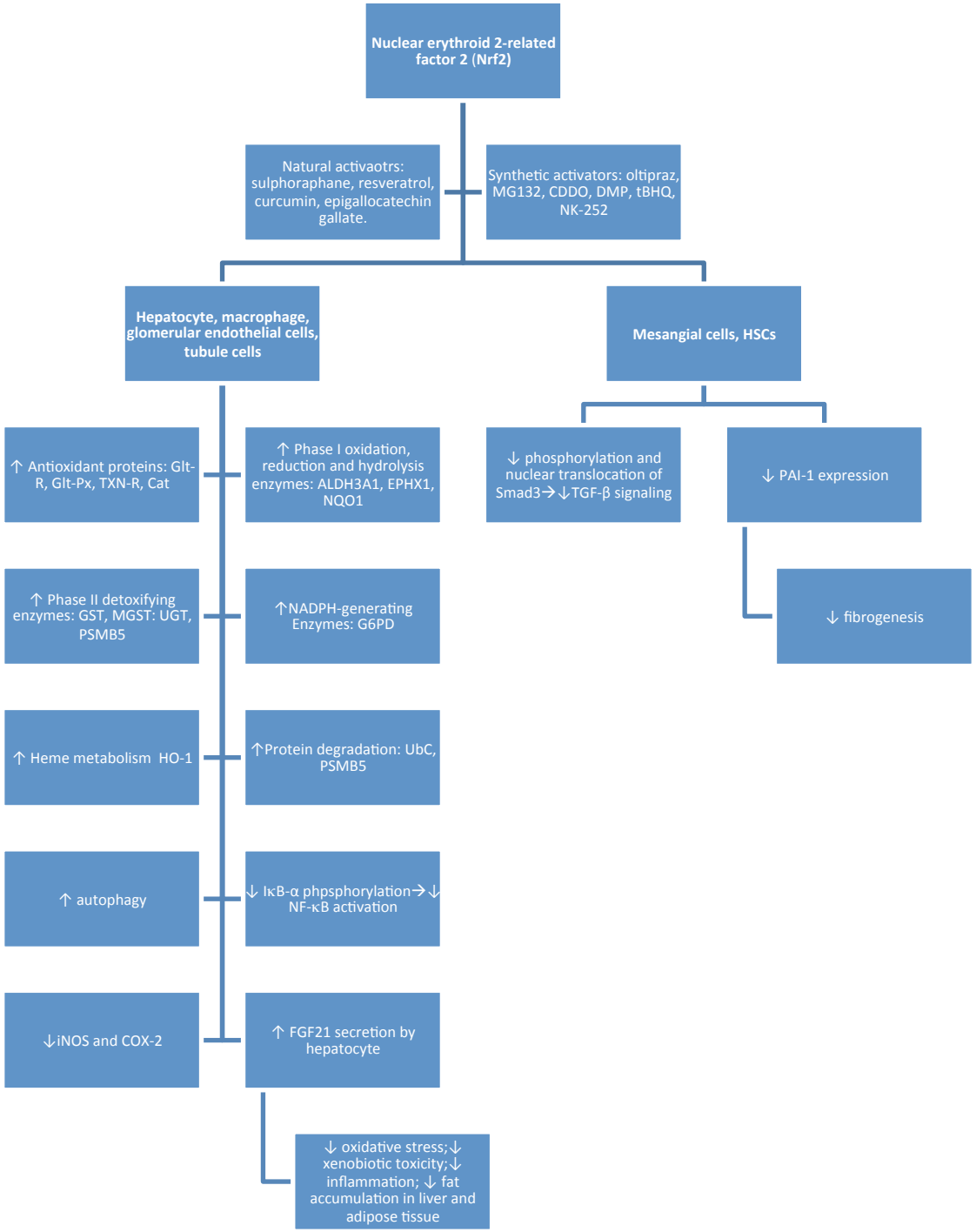
B.


ACE2-Angiotensin(1-7)-Mas receptor axis
ACE2 activators (diminazene, xanthenone); Ang(1-7) analogues
Hepatocyte
Hepatic stellate cell:
Adipocyte
Kidney:
↓SREBP-1c activation→↓ de novo lipogenesis
↑ ROS production by mitochondria and NOX
↓ NF-κB axis activation, TNF-α, resistin and IL-6 secretion
↓ TLR4 expression→↓ sensitivity to circulating LPS and FFA
↓ MAPK activation→↑ insulin signaling
↑Akt/PI3K/IRS-1/INK insulin signaling
↓ ERK-1/2 phosphorylation→↓ TGF-β production →↓ HSC activation
↓ NF-κB axis activation, TNF-α, IL-6 and resistin secretion
↓adipose tissue inflammation
↑ GLUT4 expression
↑ SIRT1-AMPK/FOXO1 axis activation→↑ fat oxidation, ↓ SREBP-1c-mediated lipogenesis
↑ insulin sensitivity; ↓fat mass
Glomerular arterioles, mesangial cells, podocytes:
Proximal tubule cell:
↑NO synthesis→Efferent artery vasodilation→↓ glomerular hypertension→ ↓endothelial cell injury
↓ NOX activation→↓ ROS production
↓ mesangial expansion→↓ glomerulosclerosis
↓ Na reabsorption
↓NOX activation→↑ ROS production
↓ NF-κB axis activation→↓ TNF-α, IL-1β, MCP-1 and CCL5 secretion→↓ monocyte recruitment
↓ ERK-1/2 phosphorylation→↓ TGF-β production →↓ fibrogenesis
↓TGF-β/Smad2/3 signaling→↓ fibrogenesis

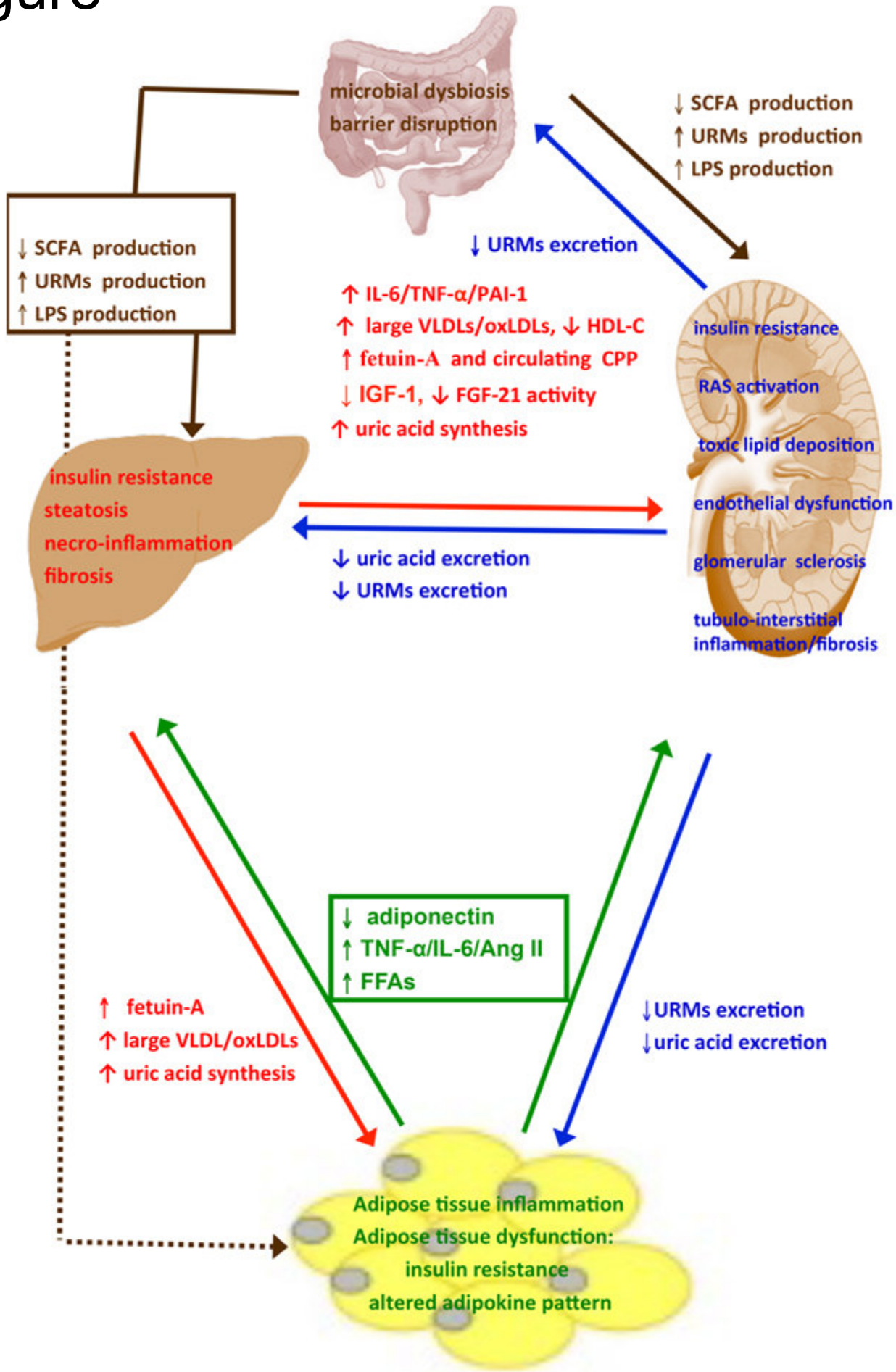
Figure


A.
AMP-activated Kinase (AMPK)
AMPK activators: exercise, starvation AICAR, dithiolethiones(oltipraz), alpha-lipoic acid, polyphenols, berberine, quercetin, curcumin, monascin, ankaflavin
Skeletal miocyte
Hepatocyte
Hepatic/adipose tissue macrophages
Hepatic stellate cells
Renal endothelium, mesangial cells, podocytes, tubule cells
↑GLUT-4 translocation to cell membrane
hexokinase II activation
PGC-1α up-regulation→↑mitochondrial biogenesis and function
↑ glucose uptake and oxidation→↑ insulin sensitivity
↑ mitochondrial function
↓ gluconeogenesis
PGC-1α up-regulation→↑mitochondrial biogenesis and function
Phosphorilation →inactivation of HMG-CoAR
SREBP-1c down regulation→↓ FAS, ACC, SCD & ABCA1 activity
↓ de novo lipogenesis
↑ mitochondrial FFA oxidation
↓ M1/M2 phenotype ratio
↓ inflammation
↓ glucose production
↑ mitochondrial function
↓ cholesterol synthesis
↑superoxide dimutase-2 (SOD2) expression→↓oxidative stress
↑PGC-1α up-regulation→↓ HSC activation
↓ TGF-β secretion
↓ fibrogenesis
↑ endothelial NO synthase activity
SREBP-1c down regulation→↓ de novo lipogenesis
↓ MCP-1 production by mesangial cells→↓ monocyte infiltration
↓ NOX-4 activation→↓ ROS production
↓ TGF-β secretion
↑ Endothelial protection
↓ toxic lipid deposition
↓ albuminuria and glomerulosclerosis
↓ renal fibrosis
B.
Sirtuin-1
Natural (Resveratrol, alpha-lipoic acid); Synthetic (BML-278, SRT1720)
Hepatocyte
Skeletal myocyte
Adipocyte
Podocytes
Renal endothelium
Mesangial cells
Tubule cells
↓ Gluconeogenesis
↓ SREBP-1c-mediated lipogenesis
↑insulin sensitivity
↑ PPAR-α expression→↑ FFA oxidation
↓ NF-κB pathway activation
↓ steatosis
↓ inflammation
↑ autophagy
↑GLUT-4 translocation to cell membrane
↑IRS-2 phosphorylation
↑insulin sensitivity
PGC-1α up-regulation→↑mitochondrial β-oxidation
↑GLUT-4 translocation to cell membrane
↑insulin sensitivity
↓ SREBP-1c-mediated lipogenesis
↓ fat tissue
↓ NF-κB pathway activation
↓ inflammation
↑ ATGL-mediated lipolysis
↓ apoptosis and ↑claudin-1 expression
↑ glomerular barrier function→↓albuminuria
↑autophagy
↑ endothelial NO synthase activity
↓ AT1 receptor expression
Improved renal haemodynamics
↓Smad7/TGF-β pathway activation→↓ apoptosis
↓ (FOXO3-mediated) apoptosis and ↑ catalase expression
↓ oxidative stress and inflammation
↓ NF-κB and HMGB1-mediated inflammation
↓ fibrosis
↓ Smad3/TGF-β pathway activation
↓ RAGE expression
PGC-1α up-regulation→↑mitochondrial biogenesis→↓ EMT

Figure


Nuclear erythroid 2-related factor 2 (Nrf2)
Natural activaotrs: sulphoraphane, resveratrol, curcumin, epigallocatechin gallate.
Synthetic activators: oltipraz, MG132, CDDO, DMP, tBHQ, NK-252
Hepatocyte, macrophage, glomerular endothelial cells, tubule cells
Mesangial cells, HSCs
↑ Antioxidant proteins: Glt-R, Glt-Px, TXN-R, Cat
↑ Phase I oxidation, reduction and hydrolysis enzymes: ALDH3A1, EPHX1, NQO1
↓ phosphorylation and nuclear translocation of Smad3→↓TGF-β signaling
↓ PAI-1 expression
↑ Phase II detoxifying enzymes: GST, MGST: UGT, PSMB5
↑NADPH-generating Enzymes: G6PD
↓ fibrogenesis
↑ Heme metabolism HO-1
↑Protein degradation: UbC, PSMB5
↑ autophagy
↓ IκB-α phpsphorylation→↓ NF-κB activation
↓iNOS and COX-2
↑ FGF21 secretion by hepatocyte
↓ oxidative stress;↓ xenobiotic toxicity;↓ inflammation; ↓ fat accumulation in liver and adipose tissue

Figure


microbial dysbiosis
barrier disruption
↓ SCFA production
↑ URMs production
↑ LPS production
↓ SCFA production
↑ URMs production
↑ LPS production
↓ URMs excretion
↑ IL-6/TNF-α/PAI-1
↑ large VLDLs/oxLDLs, ↓ HDL-C
↑ fetuin-A and circulating CPP
↓ IGF-1, ↓ FGF-21 activity
↑ uric acid synthesis
insulin resistance
RAS activation
toxic lipid deposition
endothelial dysfunction
glomerular sclerosis
tubulo-interstitial
inflammation/fibrosis
insulin resistance
steatosis
necro-inflammation
fibrosis
↓ uric acid excretion
↓ URMs excretion
↓ adiponectin
↑ TNF-α/IL-6/Ang II
↑ FFAs
↑ fetuin-A
↑ large VLDL/oxLDLs
↑ uric acid synthesis
↓URMs excretion
↓uric acid excretion
Adipose tissue inflammation
Adipose tissue dysfunction:
insulin resistance
altered adipokine pattern