Fatty Liver and Chronic Kidney Disease: Novel Mechanistic Insights and Therapeutic Opportunities

Chronic kidney disease (CKD) is a risk factor for end-stage renal disease (ESRD) and cardiovascular disease (CVD). ESRD or CVD develop in a substantial proportion of patients with CKD receiving standard-of-care therapy, and mortality in CKD remains unchanged. These data suggest that key pathogenetic mechanisms underlying CKD progression go unaffected by current treatments. Growing evidence suggests that nonalcoholic fatty liver disease (NAFLD) and CKD share common pathogenetic mechanisms and potential therapeutic targets. Common nutritional conditions predisposing to both NAFLD and CKD include excessive fructose intake and vitamin D deficiency. Modulation of nuclear transcription factors regulating key pathways of lipid metabolism, inflammation, and fibrosis, including peroxisome proliferator–activated receptors and farnesoid X receptor, is advancing to stage III clinical development. The relevance of epigenetic regulation in the pathogenesis of NAFLD and CKD is also emerging, and modulation of microRNA21 is a promising therapeutic target. Although single antioxidant supplementation has yielded variable results, modulation of key effectors of redox regulation and molecular sensors of intracellular energy, nutrient, or oxygen status show promising preclinical results. Other emerging therapeutic approaches target key mediators of inflammation, such as chemokines; fibrogenesis, such as galectin-3; or gut dysfunction through gut microbiota manipulation and incretin-based therapies. Furthermore, NAFLD per se affects CKD through lipoprotein metabolism and hepatokine secretion, and conversely, targeting the renal tubule by sodium–glucose cotransporter 2 inhibitors can improve both CKD and NAFLD. Implications for the treatment of NAFLD and CKD are discussed in light of this new therapeutic armamentarium.

Epidemiological Evidence Linking NAFLD and CKD

Chronic kidney disease (CKD) affects up to 8% of the world’s adult population, with its prevalence increasing in an aging population beset by lifestyle-associated diseases such as obesity, the metabolic syndrome, diabetes, hypertension, and smoking (1). CKD may progress to end-stage renal disease (ESRD) and is an important cardiovascular disease (CVD) risk factor. Importantly, most patients with CKD die as a result of CVD before renal replacement therapy is initiated (1).

There is potential for improving recognition and treatment of CKD. In the Third National Health and Nutrition Survey, awareness among patients with stage 3 CKD was <8% (1). Furthermore, ESRD or CVD develop in a substantial proportion of patients with CKD receiving standard-of-care therapy, and all-cause mortality remains unchanged in the CKD population (2). These data suggest that key pathogenetic mechanisms underlying...
renal disease progression are unaffected by current treatment and prompt the search for easily identifiable risk factors and novel pharmacological targets.

The presence and severity of nonalcoholic fatty liver disease (NAFLD) has been related to the incidence and stage of CKD (3) independently of traditional CKD risk factors; conversely, the presence of CKD increases overall mortality in patients with NAFLD compared with the general population (4). Further supporting a pathogenic link between NAFLD and CKD, nonalcoholic steatohepatitis (NASH)–related cirrhosis carries a higher risk of renal failure than other etiologies of cirrhosis, is an increasing indication for liver transplantation, and is an independent risk factor for kidney graft loss and CVD (5,6). Collectively, these data suggest that common pathogenic mechanisms underlie both liver and kidney injury and could be targeted to retard the progression of both NAFLD and CKD.

**POTENTIAL PATHOGENIC MECHANISMS CONTRIBUTING TO NAFLD TO CKD AND THERAPEUTIC IMPLICATIONS**

**Nutritional Factors in NAFLD and CKD: Fructose and Vitamin D Intake**

Dietary intake of fructose, the main constituent of sugar sweeteners, increased twofold over the past decade (7). Fructose may contribute to liver and kidney injury through several mechanisms, including uric acid overproduction, and consistently, uric acid–lowering agents have improved fructose-induced experimental NAFLD and CKD (8,9) (Table 1). On this basis, the impact of xanthine oxidase inhibitors on CKD progression is being evaluated in the trials CKD-FIX (Controlled Trial of Kidney Disease Progression From the Inhibition of Xanthine Oxidase; clinical trial reg. no. ACTRN12611000791932, www.anzctr.org.au) and FEATHER (Febuxostat Versus Placebo Randomized Controlled Trial Regarding Reduced Renal Function in Patients With Hyperuricemia Complicated by Chronic Kidney Disease Stage 3; clinical trial reg. no. UMIN000008343, www.umin.ac.jp/ctr) (Table 2).

Vitamin D attracted considerable interest because of its pleiotropic functions, with roles in regulation of cell proliferation, differentiation, immunity, inflammation, fibrogenesis, and metabolism (Table 1), concurrent with an unsuspected high prevalence of vitamin D deficiency, approaching 25% of the general adult population (37). Vitamin D deficiency has been linked to the pathogenesis and severity of NAFLD and CKD by observational and experimental data (38–40) (Table 1). However, the few trials of vitamin D supplementation yielded mixed results, and the benefit of vitamin D supplementation remains uncertain (41). NAFLD and CKD are characterized by vitamin D resistance, which is partly determined by impaired hepatic 25 hydroxylation and increased renal tubular 25 hydroxyvitamin D loss, and may require higher-dose supplementation of...

---

**Table 1—Nutritional factors involved in liver and renal disease in NAFLD and CKD**

<table>
<thead>
<tr>
<th>Dietary fructose</th>
<th>Biological effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cellular effects</strong></td>
<td>Hypothalamus</td>
</tr>
<tr>
<td></td>
<td>Dopaminergic tone</td>
</tr>
<tr>
<td></td>
<td>FFA oxidation and REE</td>
</tr>
<tr>
<td></td>
<td>Adipocyte</td>
</tr>
<tr>
<td></td>
<td>Adipose tissue dysfunction</td>
</tr>
<tr>
<td></td>
<td>Liver and kidney cells (uric acid mediated)</td>
</tr>
<tr>
<td></td>
<td>NLRP3 inflammasome activation</td>
</tr>
<tr>
<td></td>
<td>AMPK activity</td>
</tr>
<tr>
<td></td>
<td>SREBP-1c activation</td>
</tr>
<tr>
<td></td>
<td>NOX activation</td>
</tr>
<tr>
<td></td>
<td>Pancreatic β-cell</td>
</tr>
<tr>
<td></td>
<td>Postprandial insulin response</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vitamin D deficiency</th>
<th>Biological effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cellular effects</strong></td>
<td>Skeletal myocyte</td>
</tr>
<tr>
<td></td>
<td>IR-1 activity</td>
</tr>
<tr>
<td></td>
<td>Hepatocyte, Kupffer cell</td>
</tr>
<tr>
<td></td>
<td>TLR-2/4/9 expression</td>
</tr>
<tr>
<td></td>
<td>TGF-β secretion and SCD2 activation</td>
</tr>
<tr>
<td></td>
<td>Glomerular podocyte</td>
</tr>
<tr>
<td></td>
<td>p38- and ERK-mediated apoptosis</td>
</tr>
<tr>
<td></td>
<td>RAS activation</td>
</tr>
<tr>
<td></td>
<td>Renal tubule cell and interstitial macrophage</td>
</tr>
<tr>
<td></td>
<td>SREBP-1c/SREBP-2</td>
</tr>
<tr>
<td></td>
<td>FXR/PPAR-α activation</td>
</tr>
<tr>
<td></td>
<td>NF-kB pathway activation</td>
</tr>
</tbody>
</table>

ERK, extracellular signal–regulated kinase; IL, interleukin; IRS-1, insulin receptor substrate 1; NLRP3, NOD-like receptor family, pyrin domain containing 3; NOX, NADPH oxidase; RAS, renin-angiotensin system; REE, resting energy expenditure; TLR, Toll-like receptor; VDR, vitamin D receptor.
<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Molecule</th>
<th>NAFLD</th>
<th>CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xanthine oxidase inhibitors</td>
<td>Allopurinol, febuxostat</td>
<td>Preclinical</td>
<td>Ila</td>
</tr>
<tr>
<td>Vitamin D supplementation</td>
<td>Natural (ergocalciferol, cholecalciferol, calcitriol), Synthetic VDR agonists (doxercalciferol, paricalcitol)</td>
<td>Ila</td>
<td>Clinical trial reg. no. NCT02098317</td>
</tr>
<tr>
<td>PPAR-δ agonists</td>
<td>GW0742, GW81749A</td>
<td>—</td>
<td>Preclinical (50)</td>
</tr>
<tr>
<td>PPAR-α/β agonists</td>
<td>GFT505</td>
<td>Iib GOLDEN-505 (10)</td>
<td>—</td>
</tr>
<tr>
<td>SREBP-2 antagonists</td>
<td>Natural antioxidants (myricetin)</td>
<td>—</td>
<td>Preclinical (13)</td>
</tr>
<tr>
<td>FXR agonists</td>
<td>Obeticholic acid</td>
<td>Ila FLINT (17)</td>
<td>Preclinical (56,57)</td>
</tr>
<tr>
<td>miRNA21 antagonists</td>
<td>Antagomir-21</td>
<td>Preclinical (59)</td>
<td>Preclinical (60)</td>
</tr>
<tr>
<td>AMPK activators</td>
<td>Natural: curcumin berberine, monascin ankaflavin Synthetic: oltipraz</td>
<td>Preclinical (19)</td>
<td>Ila (clinical trial reg. no. NCT01373554)</td>
</tr>
<tr>
<td>HIF-1α inhibitors</td>
<td>YC-1</td>
<td>Preclinical (65)</td>
<td>—</td>
</tr>
<tr>
<td>Dual mTORC1/2 inhibitor</td>
<td>Rapamycin</td>
<td>Preclinical (24)</td>
<td>Preclinical (25)</td>
</tr>
<tr>
<td>NRF2 activators</td>
<td>Oltipraz</td>
<td>Clinical trial reg. no. NCT01373554</td>
<td>Clinical trial reg. no. NCT00316821</td>
</tr>
<tr>
<td>CCR2 receptor antagonist</td>
<td>CCX140-B</td>
<td>—</td>
<td>Ila (82)</td>
</tr>
<tr>
<td>CCR2/5 receptor antagonist</td>
<td>Cenicriviroc, BMS-813160, PF-04634817</td>
<td>Ila: CENTAUR (clinical trial reg. no. NCT02174775)</td>
<td>—</td>
</tr>
<tr>
<td>Galectin-3 inhibitors</td>
<td>GM-CT-01, GR-MD-02, GCS-100</td>
<td>Preclinical (84)</td>
<td>—</td>
</tr>
<tr>
<td>Incretin-based therapies</td>
<td>Incretin mimetics</td>
<td>Ila LEAN (92)</td>
<td>Ila (93,94)</td>
</tr>
<tr>
<td>Gut microbiota manipulation</td>
<td>Prebiotics, probiotics, synbiotics</td>
<td>Ila (106)</td>
<td>Clinical trial reg. no. NCT00183790</td>
</tr>
<tr>
<td>CETP inhibitors</td>
<td>Fc-CETP6</td>
<td>Preclinical (112)</td>
<td>—</td>
</tr>
<tr>
<td>Inhibitors of syndecan-1 shedding</td>
<td>Sphingosine-1-phosphate</td>
<td>—</td>
<td>Preclinical (119)</td>
</tr>
<tr>
<td>FGFR21 analogs</td>
<td>PEG-FGFR21, recombinant FGFR21, anti-FGFR1 mAb</td>
<td>Ila (123)</td>
<td>—</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Remogliflozin etabonate, luseogliflozin, ipragliflozin</td>
<td>Ila (131,132)</td>
<td>—</td>
</tr>
</tbody>
</table>

FGFR, FGFR21 receptor; mAb, monoclonal antibodies; PEG, pegylated; VDR, vitamin D receptor; YC-1, 1-benzyl-3-{(substituted aryl)-5-methylfuro[3,2-c]pyrazole.}
vitamin D, calcitriol, or vitamin D receptor agonists (e.g., paricalcitol) to be overcome (42,43). The effects of vitamin D supplementation in CKD and NASH are being evaluated in several clinical trials (clinical trial reg. nos. NCT00893451, NCT01623024, and NCT02098317, www.clinicaltrials.gov).

Reversing Ectopic Fat Deposition by Targeting Nuclear Transcription Factors in NAFLD and CKD

NAFLD and CKD are characterized by ectopic toxic lipid accumulation, which is determined by an extensive derangement in hepatic and renal lipid metabolism and triggers lipoperoxidative stress, cell apoptosis, inflammation, and fibrosis (44–46) (Fig. 1). Underlying these abnormalities is an extensive deregulation of nuclear transcription factors that regulate lipid metabolism, inflammation, and fibrogenesis, including peroxisome proliferator–activated receptor (PPAR)-α, PPAR-δ, and PPAR-γ; SREBP-2; and farnesoid X receptor (FXR), which represent an attractive target for the treatment of NAFLD and CKD (47,48) (Fig. 1).

On the basis of the finding that PPAR-α and PPAR-δ are downregulated in NAFLD and CKD (47,49), potent, selective PPAR-α, PPAR-δ, and dual PPAR-α/δ agonists (K-877, GW501516, MBX-8025, and GFT505, respectively) were evaluated in these two conditions, with encouraging results in preclinical models (49–51). Some of these compounds advanced to the clinical stage of development, and GFT505, a dual PPAR-α/δ agonist, improved steatohepatitis, fibrosis, and the glycolipid profile in the recently completed GOLDEN-505 trial (10) (Table 2).

The PPAR-γ agonists thiazolidinediones comprise another pharmacological class that has significantly improved NASH and albuminuria in clinical trials (11,12), but their clinical use was limited by their side effects. These drawbacks prompted the development of new compounds, including dual PPAR-α/γ agonists, which maintained the therapeutic effectiveness of PPAR-γ agonists but were devoid of their unwanted effects (Fig. 1). Saroglitazar, a potent PPAR-α/γ agonist, did not induce weight gain, peripheral edema, or other adverse events after 1 year (52) and improved markers of NASH in patients with diabetes (53), whereas aleglitazar slowed estimated glomerular filtration rate (eGFR) decline in diabetic nephropathy (54) (Table 2). A small, phase IIa trial of patients with biopsy-proven NASH has been completed, but the results are not yet available (clinical trial reg. no. CTRI/2010/091/000108, www.ctri.nic.in). Larger and longer randomized clinical trials (RCTs) are needed to evaluate long-term clinical safety and effectiveness of these compounds in patients with and without diabetes.

Among various lipotoxic species accumulating in NAFLD and CKD, free cholesterol is believed to play a key pathogenic role in liver and renal injury (13,55). Ectopic cholesterol accumulation is driven by an inappropriate upregulation of transcription factor SREBP-2, with consequently increased cholesterol synthesis, influx, and retention and reduced cholesterol excretion by liver and renal cells (13,55) (Fig. 1). Such pervasive deregulation in all steps of cholesterol metabolism may diminish the effectiveness of available cholesterol-lowering drugs that target single steps in cholesterol metabolism (14). Therefore, modulation of SREBP-2 activity represents an attractive therapeutic tool. Although selective SREBP-2 antagonists are under development, several natural antioxidants, such as

Figure 1—The role of nuclear transcription factors in the pathogenesis of NAFLD and CKD. Each nuclear transcription factor is reported in the text box at the center of the scheme and is marked with a superscript number. The various molecular pathways affected by each nuclear transcription factor are shown in the boxes surrounding the central box, with the superscript number referring to the corresponding nuclear transcription factor affecting the pathway. eNOS, endothelial nitric oxide synthase; LPL, lipoprotein lipase; NLRP3, NOD-like receptor family, pyrin domain containing 3; NOS, nitric oxide synthase; NOX, NADPH oxidase; PAI-1, plasminogen activator inhibitor 1.
as myricetin, repress SREBP-2 expression and ameliorate cholesterol-induced inflammation and fibrosis in experimental models (13) (Table 2).

FXR is a nuclear transcription factor with prominent insulin sensitizing, antilipogenic, anti-inflammatory, and antifibrotic properties; furthermore, its activation improves endothelial function (16,56,57) (Fig. 1). FXR expression is downregulated in the liver and kidney of patients with NAFLD and CKD, respectively, and is inversely related to disease severity. On this basis, potent semisynthetic bile acid FXR agonists have been developed (Table 2). Obeticholic acid (or INT-747), a semisynthetic chenodeoxycholic acid derivative, improved liver histology in the phase IIa, multicenter, randomized FXR Ligand NASH Treatment (FLINT) trial and in ameliorated renal histology and proteinuria in nutritional models of CKD (16,57). Several issues remain, however, including the effectiveness of FXR agonists in subjects without diabetes and the impact of HDL cholesterol reduction on long-term CVD risk.

Epigenetic Regulation in NASH and CKD miRNAs (miRNAs) are small (~22 base pairs) endogenous noncoding RNAs that regulate gene expression of at least 60% of protein coding genes. miRNAs recognize mRNA targets through sequence complementarity between the miRNA and binding sites in the 3’ untranslated regions of the target mRNAs or through interaction with RNA-binding proteins.

miRNAs regulate gene expression in one of two ways, depending on the degree of complementarity between the miRNA and its target. miRNAs that bind to mRNA targets with imperfect complementarity block target gene expression through translational silencing while miRNAs binding their mRNA targets with perfect complementarity enhance target gene expression (15,58). To date, >2,500 miRNAs have been identified in the human genome, and each can regulate several hundred target genes involved in diverse developmental and cellular processes, including cellular metabolism proliferation, differentiation, and apoptosis. Several miRNAs have been found to be dysregulated in NAFLD and CKD (15,58). On this basis, approaches inhibiting overexpressed miRNAs by antisense oligonucleotides or restoring the expression of downregulated miRNAs by synthetic miRNA mimics have been attempted. miRNA21 in particular is an attractive target because it regulates key metabolic, proinflammatory, and profibrogenic pathways and its hepatic and renal overexpression in NASH and CKD leads to PPAR-α downregulation, SREBP-2 upregulation, mitochondrial dysfunction, and profibrogenic hepatic stellate cell activation and proximal tubular cell epithelial-to-mesenchymal transition (EMT) (59,60). Consistently, in experimental models of NASH and CKD, anti-miRNA21 antisense oligonucleotides induced weight loss, normalized metabolic dysregulation, and improved hepatic and renal inflammation and fibrosis, effects at least partly mediated by PPAR-α upregulation (59,60). Despite these premises, several issues remain, including the stability and selective delivery of the pharmacological modulators to the target organs and long-term safety of this approach because miRNAs also regulate cell proliferation and cell cycle progression in diverse tissues and long-term consequences of their modulation on tumor onset and progression are unclear (15,59).

ROLE OF CELLULAR ENERGY, OXYGEN, AND NUTRIENT SENSORS In mammals, cellular metabolism is finely orchestrated by molecular sensors of energy, nutrient, and oxygen status to adapt to changing substrate availability. The dysregulation of some of these sensors, including AMPK, hypoxia-inducible factor (HIF)-1α, and mammalian target of rapamycin (mTOR), has been implicated in the pathogenesis of NASH and CKD and could be targeted for the treatment of NAFLD and CKD. AMPK is a ubiquitous kinase that preserves cell survival under calorie restriction or high energy demand (18). In response to cellular ATP depletion or an increase in AMP/ATP...
HIF-1α overexpression 
- Inappropriate HIF-1α 
- Oxidative stress 
- Nonhypoxic stimuli like cholesterol 
  survival in response to cellular hypoxia and 
  nutrient levels, growth factors like insulin 
  and IGF, and other stressors associated with 
  companion proteins to form two distinct 
  signaling molecular complexes, 
  mTOR complex 1 (mTORC1) and mTORC2 
  (23). mTORC1 has been more extensively 
  studied and found to promote cellular 
  autophagy and maintain cellular 
  viability. 
  The impact of mTORC1 inhibition in 
  NASH and CKD progression, single antioxidant 
  supplementation strategies have yielded 
  variable results (11), and other 
  approaches targeting common effectors 
  of redox regulation, like apoptosis signal-
  regulating kinase 1 (ASK1) and nuclear 
  erythroid 2-related factor 2 (Nrf2), are 
  being investigated. ASK1 is a serine/threonine 
  kinase belonging to the mitogen-activated protein 
  kinase (MAPK) kinase family, which is 
  activated in response to stresses like reactive 
  oxygen species (ROS), tumor necrosis factor-
  α (TNF-α), lipopolysaccharide (LPS), and 
  endoplasmic reticulum (ER) stress (71). 
  ASK1 activates downstream terminal 
  MAPK kinases p38 and c-Jun N-terminal 
  kinase (JNK), which promote insulin 
  resistance, cell death, proinflammatory 
  cytokine/chemokine production, and fibro-
  genesis (71) (Fig. 3).

Data have implicated ASK1 activation in 
oxidative stress–induced inflammation 
and fibrogenesis in NASH and CKD, 
and pharmacological ASK1 inhibition 
prevented diet-induced NASH and 
halted progression of diabetic and non-
diabetic experimental CKD (72,73). 
On this basis, the highly selective oral 
ASK1 inhibitor GS-4997 is being evalu-
ated in patients with NASH with moder-
ate advanced fibrosis (clinical trial reg. no. 
NCTR02466516, www.clinicaltrials.gov) 
and in patients with diabetes with stage 
3/4 nephropathy (clinical trial reg. no. 
NCTR02177786, www.clinicaltrials.gov) 
(Table 2). Several issues need to be clari-
fied, however. ASK1 inhibition did not im-
prove podocyte loss and albuminuria in 
experimental diabetic CKD, suggesting 
that this kinase is not central for glomer-
ular injury (73). Furthermore, the impact 
of ASK1 inhibitors in nondiabetic CKD is 
unknown.

Nrf2 is a transcription factor expressed 
ubiquitously in human tissues and most 
abundantly in the liver (74), where it 
regulates the expression of several anti-
oxidant and detoxifying enzymes and has 
direct metabolic, anti-inflammatory, and 
proautophagic actions (74) (Fig. 3).
Under basal conditions, Nrf2 is kept transcriptionally inactive through binding to its inhibitor, Kelch-like ECH-associated protein 1 (KEAP1) (74). ROS and reactive nitrogen species interact with KEAP1 and cause the loosening of Nrf-2, which translocates to the nucleus and modulates transcription of its target genes (75, 76). On this basis, several natural and synthetic small-molecule Nrf2 activators are currently being evaluated in patients with NASH and CKD (Table 2). Following early encouraging data, clinical development of bardoxolone methyl, a synthetic Nrf2 activator, was interrupted for safety concerns related to heart failure (77). A reanalysis of the potential risk/benefit ratio of the drug for a Japanese population and the observation that most of the severe adverse effects occurred in the first month of therapy prompted initiation of a dose-escalating RCT in Japan (clinical trial reg. no. NCT01373554, www.clinicaltrials.gov). Another potent synthetic Nrf2 activator, oltipraz, is being evaluated in patients with NAFLD (clinical trial reg. no. NCT01752985, www.clinicaltrials.gov).

Figure 3—Role of effectors of redox regulation ASK1 and Nrf2 and role of galectin-3 in the pathogenesis of NAFLD and CKD. ASK1, Nrf2, and galectin-3 are reported in the text box at the center of the scheme and are marked with a superscript number. The various molecular pathways affected by these three molecules are shown in the boxes surrounding the central box, with the superscript number referring to the corresponding factor affecting the pathway. COX, cyclooxygenase; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal–related kinase; G6PD, glucose-6-phosphate dehydrogenase; Glt-Px, glutathione peroxidase; Glt-R, glutathione reductase; GST, glutathione S-transferase; HPC, hepatic progenitor cells; iNOS, inducible nitric oxide synthase; IRS, insulin receptor substrate; NKT, natural killer T; NOS, nitric oxide synthase; PAI-1, plasminogen activator inhibitor 1; TXN-R, thioredoxin reductase.

TARGETING MOLECULAR EFFECTORS OF INFLAMMATION AND FIBROSIS

Chemokines are small proteins that regulate leukocyte migration into tissues and consequent inflammation, tissue remodeling, and fibrosis (78). Among the >40 chemokine ligands and 20 chemokine receptors currently identified, chemokine (C-C motif) ligand 2 (CCL2 or MCP-1) and its receptor CCR2 have been implicated in the pathogenesis of NASH and CKD. In NAFLD, hepatic cells and adipocytes secrete CCL2, which attracts proinflammatory cells to the liver to promote NASH development (79, 80), whereas genetic or pharmacological inhibition of the CCL2/CCR2 axis reverses steatohepatitis and advanced hepatic fibrosis (80). In the kidney, tubule cells and podocytes secrete chemokines CCL2 and CCL5 in response to diverse proinflammatory stimuli to promote tubulointerstitial inflammation and fibrosis, which are reversed by chemokine antagonists (81). On this basis, chemokine antagonists are advancing to the clinical stage of development: The small-molecule CCR2 antagonist CCX140-B has reduced albuminuria and slowed eGFR decline in diabetic nephropathy (82), whereas the dual chemokine receptor CCR2/CCR5 antagonists BMS-813160, PF-04634817, and cenicriviroc are being evaluated in diabetic nephropathy (clinical trial reg. nos. NCT01752985 and NCT01712061, www.clinicaltrials.gov) and in NASH (clinical trial reg. no. NCT02217475, www.clinicaltrials.gov) (Table 2). Galectin-3 is a lectin broadly expressed by immune and epithelial cells where it localizes mainly in the cytoplasm as well as in the nucleus, cell surface, and extracellular space (83). Galectin-3 regulates cell proliferation, apoptosis, cell adhesion, and affinity for advanced glycation end products (AGEs), exerting multiple and sometimes contrasting effects, depending on its cellular location, cell type, and mechanisms of injury (83) (Fig. 3). Galectin-3 is upregulated in the liver and kidney of patients with NASH and CKD and correlates with the severity of liver
and renal disease (26,84). Furthermore, circulating galectin-3 levels predict renal function decline and cardiovascular and all-cause mortality in patients with CKD (85). Consistent with epidemiological data, functional galectin-3 manipulation has shown important proinflammatory and profibrotic effects of this lectin (26,83,84). On this basis, pharmacological galectin-3 inhibition with small-molecule competitive inhibitors, including GR-MD-02 (galactoarabinino-rhamnogalaturonan), GM-CT-01 (galactomannan), and N-acetyllactosamine, prevents hypertensive nephropathy (86) and reverses diet-induced NASH and cirrhosis (87). GR-MD-02 was well tolerated and improved markers of hepatic fibrosis in a phase I RCT enrolling patients with NASH and advanced fibrosis (clinical trial reg. no. NCT01899859, www.clinicaltrials.gov), whereas a phase IIa RCT is exploring the effect of the galectin-3 antagonist GCS-100 on eGFR in CKD (clinical trial reg. no. NCT01843790, www.clinicaltrials.gov) (Table 2).

Data on galectin-3 inhibition are not univocal, however, and galectin-3 deletion exacerbates systemic inflammation, hyperglycemia, and liver and kidney injury in diet-induced obese rodents (88). It has been suggested that inhibition of AGE uptake by the liver, which clears >90% of these end products from the circulation, promotes the systemic accumulation of AGEs and receptor for AGE (RAGE)–mediated uptake by other tissues, thereby aggravating extrahepatic toxicity of these molecules. Because both NASH and CKD are characterized by AGE accumulation, a better understanding of the impact of galectin-3 inhibitors on AGE-mediated tissue injury in vivo is warranted.

THE GUT CONNECTION: TARGETING INCRETINS AND GUT MICROBIOTA FOR THE TREATMENT OF NAFLD AND CKD

Incretin-based therapies, including GLP-1 mimetics and dipeptidyl peptidase 4 (DPP-4) inhibitors, increase insulin release from the pancreas, reduce gluca
gon production, and possess numerous extrapancreatic metabolic benefits, which prompted the evaluation for the treatment of NAFLD and CKD (89,90) (Table 3). Preliminary human data suggested that incretin mimetics improve NAFLD. A meta-analysis of six RCTs from the Liraglutide Effect and Action in Diabetes (LEAD) program found a significant improvement in biochemical and radiological features of steatosis (91). Furthermore, in the Liraglutide Efficacy and Action in NASH (LEAN) trial, liraglutide 1.8 mg/day for 48 weeks induced NASH resolution and improved markers of lipotoxicity, inflammation, and metabolic dysfunction compared with placebo (92) (Table 2).

Incretin-based therapies also have the potential for nephroprotection independent of improved glycemic control through several mechanisms (Table 3). GLP-1 administration induced natriuresis through inhibition of proximal tubular Na-H exchanger 3 (NHE3) and reduced activation of the angiotensin II (AngII) axis (93). These actions counteract the increase in proximal tubular sodium reabsorption, which has been hypothesized to trigger glomerular hyperfiltration, the functional defect believed to be central to obesity-associated and diabetic CKD (93). Furthermore, GLP-1 mimetics have demonstrated direct renal anti-inflammatory, antibi
otic, and antiproteinuric actions (27,94). Collectively, these properties may explain the attenuated progression of overt diabetic nephropathy in two small preliminary RCTs of treatment with liraglutide (27,94). In addition to inactivating GLP-1, DPP-4 cleaves multiple other peptides, including brain-derived natriuretic peptide, neuropeptide Y, peptide YY, and stomal-derived factor 1α (Table 3). Thus, the effect of DPP-4 inhibition depends on the actions of the various substrates inactivated in each tissue and organ. This may theoretically explain the slightly lower antihyper
tensive effect observed with DPP-4 inhibitors compared with GLP-1 mimetics (28). Although the impact of DPP-4 inhibitors on NAFLD must be assessed, results from the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR-TIMI) 53 trial (29) and from four other RCTs (95) have suggested that saxagliptin and linagliptin reduce the development and progression of albuminuria. Renal effects of linagliptin are currently being investigated in the MARLINA-T2D (Efficacy, Safety, & Modification of Albuminuria in Type 2 Diabetes Subjects With Renal Disease With Linagliptin; clinical trial reg. no. NCT01792518, www.clinicaltrials.gov) and CARMEMLNA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus; clinical trial reg. no. NCT01897532, www.clinicaltrials.gov) trials. In conclusion, incretin-based therapies address several pathophysiological mechanisms common to experimental NAFLD and CKD, but their impact on renal disease in nondiabetic CKD is unknown. Furthermore, incretin-based therapies did not affect the risk of CVD, a major cause of death in NAFLD and CKD (96).

The capacity for gut microbiota to interact with host metabolic and immune responses and to contribute to the development of obesity-associated disorders has been increasingly recognized (97). Patients with NAFLD and CKD exhibit an altered gut microbiota composition, with a relative decrease in healthy Bacte
roïdites, Lactobacillaceae, and Prevotellaceae families and disruption of the normal gastrointestinal barrier (98,99). The resulting accumulation of gut-derived toxins induces inflammation (100), insulin resistance, and ectopic fat deposition in liver and muscle through several mechanisms (Table 3). Some of these molecules, including endotoxin, indoxylsulfate, p-cresyl sulfate, and trimethylamine-N-oxide (TMAO), have documented clinical relevance for the development and progression of CKD (101–104).

CKD may also aggravate gut dysbiosis and systemic inflammation through accumulation of uremic toxic metabolites (URMs) normally eliminated by the kidneys, including urea and p-cresyl sulfate. The accumulation of urea may lead to influx into the gastrointestinal lumen where it is hydrolyzed to ammonia by microbial urease and then converted to ammonium hydroxide. Ammonia and ammonium hydroxide promote the growth of urea-metabolizing bacteria at the expense of carbohydrate-fermenting strains and disrupt intestinal epithelial tight junctions, enhancing passage of LPS and other toxic luminal compounds into the circulation (105). Further highlighting the relevance of this mechanism to systemic inflammation, administration of oral activated charcoal absorbent AST-120 improves intestinal barrier function and reduces systemic oxidative stress, inflammation, and endotoxemia in rodent models of CKD (105). Gut
<table>
<thead>
<tr>
<th>Biological effect</th>
<th>Role of incretin-based therapies and gut microbiota in the pathogenesis of NAFLD and CKD</th>
<th>Table 3 Role of incretin-based therapies and gut microbiota in the pathogenesis of NAFLD and CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celluar mechanism</td>
<td></td>
<td>Biological effect</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>↓ Calorie intake</td>
<td></td>
</tr>
<tr>
<td>↓ Appetite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skeletal myocyte</td>
<td>↑ Insulin sensitivity</td>
<td></td>
</tr>
<tr>
<td>↑ Glucose uptake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ Glycogen synthesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocyte</td>
<td>↑ Insulin sensitivity</td>
<td></td>
</tr>
<tr>
<td>↑ Glycogen synthesis and ↓ gluconeogenesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ Autophagy</td>
<td>↓ Hepatic steatosis</td>
<td></td>
</tr>
<tr>
<td>↑ cAMP→AMPK and SIRT-1 activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ FGF21 secretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adipocyte</td>
<td>↑ Insulin sensitivity</td>
<td></td>
</tr>
<tr>
<td>↑ Lipolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ Glucose uptake</td>
<td>↓ Adipose tissue</td>
<td></td>
</tr>
<tr>
<td>↑ Lipogenesis (↑ FFA synthesis, uptake, and reesterification)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ LPL activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ Adiponectin secretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal tubule cell</td>
<td>† Na delivery to distal tubule→</td>
<td></td>
</tr>
<tr>
<td>↓ NHE3 activity→↑ Na urea→↓ Na hyperreabsorption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ PPAR-α→↑ FFA oxidation</td>
<td>† Tubuloglomerular feedback→</td>
<td></td>
</tr>
<tr>
<td>Glomerular endothelial cell, mesangial cell, tubule cell</td>
<td>↓ Glomerular hyperfiltration</td>
<td></td>
</tr>
<tr>
<td>↓ Apoptosis</td>
<td>↓ Inflammation and fibrosis</td>
<td></td>
</tr>
<tr>
<td>↓ AGE/RAGE axis activation</td>
<td>↓ Endothelial dysfunction</td>
<td></td>
</tr>
<tr>
<td>↓ IL-1/MCP-1/TGF-β secretion→↓ monocyte recruitment and fibrogenesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ NOS activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ cAMP→NOX downregulation→↓ ROS generation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ AngII activity→↓ IRS-1 phosphorylation→↑ IRS-1 signaling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incretin analogs: DPP-4 inhibitors</td>
<td>Liver, kidney</td>
<td>Same effects of GLP-1R agonists</td>
</tr>
<tr>
<td>Liver, kidney</td>
<td>↑ GLP-1 activity</td>
<td>Ultimate effect depends on local tissue activity of various substrates inactivated by DPP-4</td>
</tr>
<tr>
<td>Kidney</td>
<td>↑ BNP→↑ natriuresis and vasodilation, ↓ RAAS and sympathetic activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ NPY and PYY→↑ AngII-mediated vasoconstriction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ SDF-1α→↑ mesenchymal stem cells recruitment</td>
<td></td>
</tr>
<tr>
<td>Altered gut microbiota composition and intestinal barrier disruption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocyte, macrophage, HSC, renal vascular endothelial cell, podocytes</td>
<td>Hepatic and renal inflammation, hepatic and renal fibrogenesis</td>
<td></td>
</tr>
<tr>
<td>↑ LPS-TLR-4 axis activation→↑ proinflammatory cytokines/TGF-β</td>
<td>Endothelial dysfunction</td>
<td></td>
</tr>
<tr>
<td>↑ LPS-TLR-4 axis activation→↑ NOX type II activity→ROS production</td>
<td>Gut barrier disruption</td>
<td></td>
</tr>
<tr>
<td>Enterocyte</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ SCFA production→↑ epithelial injury and ↓ GLP-1 secretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocyte</td>
<td>Hepatic steatosis</td>
<td></td>
</tr>
<tr>
<td>↑ Conversion of intestinal TMA to TMAO by flavin-containing monoxygenases</td>
<td>Hepatic necroinflammation</td>
<td></td>
</tr>
<tr>
<td>Tubule cells</td>
<td>Atherosclerosis</td>
<td></td>
</tr>
<tr>
<td>↑ TMAO-induced TGF-β/SMAD3 axis activation</td>
<td>Tubule-Interstitial fibrosis</td>
<td></td>
</tr>
<tr>
<td>Skeletal myocyte</td>
<td>Insulin resistance</td>
<td></td>
</tr>
<tr>
<td>↑ URM-induced phosphorylation of IRS-1→↑ IRS-1 signaling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocyte</td>
<td>Insulin resistance</td>
<td></td>
</tr>
<tr>
<td>↑ URM-induced de novo lipogenesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ URM-induced VLDL secretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adipocyte</td>
<td>Insulin resistance</td>
<td></td>
</tr>
<tr>
<td>↑ URM-induced leptin secretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ URM-induced de novo lipogenesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ URM-induced zinc-α2-glycoprotein and ↓ perilipin expression→↑ lipolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrophage</td>
<td>Adipose tissue dysfunction</td>
<td></td>
</tr>
<tr>
<td>↑ LPS-induced NF-κB activation</td>
<td>Adipose tissue and systemic inflammation</td>
<td></td>
</tr>
</tbody>
</table>

BNP, brain-derived natriuretic peptide; HSC, hepatic stellate cell; IL, interleukin; IRS-1, insulin receptor substrate 1; LPL, lipoprotein lipase; NOS, nitric oxide synthase; NOX, NADPH oxidase; NPY, neuropeptide Y; PYY, peptide YY; SCFA, short-chain fatty acid; SDF-1α, stromal-derived factor 1α; SIRT, sirtuin; TLR, Toll-like receptor; TMA, trimethylamine.
microbiota manipulation with probiotics or prebiotics improved surrogate markers of NAFLD in small RCTs of short duration (106) and reduced URM levels in patients with CKD (107). The impact of symbiotic administration on renal function in CKD is being investigated in the Symbiotics Easing Renal Failure by Improving Gut Microbiology (SYNERGY) trial (clinical trial reg. no. ACTRN12613000493741, www.anzctr.org.au).

**NAFLD AS A DETERMINANT OF CKD: TARGETING THE LIVER TO IMPROVE CKD**

In NAFLD, liver disease per se contributes to kidney injury through several mechanisms. The liver contains up to 80% of all macrophages of the body, and the steatotic liver may represent a more relevant source of proinflammatory cytokines than adipose tissue (30). Furthermore, the liver is a central regulator of lipoprotein metabolism and secretes hepatokines like fibroblast growth factor 21 (FGF21), which can modulate whole-body metabolism and inflammation.

**Hepatic Secretion of VLDL, Cholesteryl Ester Transfer Protein, and Syndecan-1 in the Pathogenesis of Atherogenic Dyslipidemia and Kidney Injury**

Atherogenic dyslipidemia is the most common lipid abnormality in CKD and an independent predictor of the incidence and progression of CKD and of CVD in patients with CKD (108,109). Atherogenic dyslipidemia promotes CKD through receptor-mediated uptake of qualitatively abnormal lipoproteins by glomerular and tubulointerstitial cells (110). NAFLD may promote atherogenic dyslipidemia through several mechanisms, which represent potential therapeutic targets. Liver fat accumulation per se proportionally increases the hepatic secretion rate of large VLDL1, which exchanges triglycerides with cholesterol contained in circulating LDL and HDL particles, resulting in small LDL and HDL3 formation (55). Furthermore, recent studies demonstrated that circulating cholesteryl ester transfer protein (CETP) derives largely from hepatic Kupffer cells, and its levels parallel the severity of histological necroinflammations in NASH (111). Of note, CETP inhibitors alleviate high-fat diet–induced steatohepatitis and fibrosis, possibly by reducing oxidized LDL uptake by hepatic Kupffer and stellate cells (112), and represent a potential therapeutic target for the treatment of both NAFLD and CKD (Table 2).

**Syndecan-1** is another key mediator of hepatic clearance of triglyceride-rich lipoproteins (TRLPs) (113). It is a transmembrane heparan sulfate proteoglycan constitutively bound to hepatocyte membrane, where it binds lipoprotein lipase and apolipoprotein (apo) E through its heparan sulfate chains and internalizes apoE-containing lipoproteins (31). Sulfation by hepatic sulfotransferases and binding to hepatocyte membrane are required for syndecan-1 biological activity.

NAFLD is characterized by an increased shedding of syndecan-1 (114), as a result of increased hepatic metalloproteinase activity, and by a defective syndecan-1 sulfation, as a result of defective hepatic sulfotransferase activity (115,116). These changes in hepatic syndecan-1 metabolism impair TRLP clearance and, accordingly, predicted atherogenic dyslipidemia in CKD (117). Beside mediating hepatic TRLP clearance, syndecan-1 is a key constituent of the endothelial glycocalyx layer, and its shedding has been associated with loss of endothelial barrier integrity and endothelial dysfunction across progressive CKD stages (118). Inhibitors of syndecan-1 shedding, including the phospholipid sphingosine-1-phosphate, restored endothelial integrity experimentally (119) and may represent a potential therapeutic tool for the treatment of CKD.

**FGF21**

FGFs are signaling proteins that regulate embryonic development, tissue regeneration, and diverse metabolic functions by binding extracellularly to four cell surface tyrosine kinase FGF receptors (FGFRs 1–4) (120). FGF21 is mainly secreted by the liver and exerts its multiple beneficial metabolic effects by binding to FGFRs in the presence of coreceptor β-Klotho (120). FGF21 administration ameliorates adipose and hepatic insulin sensitivity, suppresses hepatic glucoseogenesis and lipogenesis, and enhances free fatty acid (FFA) oxidation and mitochondrial function, at least in part by activating the AMPK-SIRT1-PGC-1α pathway (32,120). Furthermore, FGF21 has recently been demonstrated to direct anti-inflammatory and anti-brown adipogenesis by inhibiting the key nuclear factor κB (NF-κB) and transforming growth factor-β (TGF-β) mothers against decapentaplegic homolog (SMAD) 2/3 signaling pathways (121). By virtue of these properties, FGF21 administration has improved experimental NASH and CKD (32,120,121). The clinical development of FGF21, however, is hampered by its short half-life (0.5–5 h) and by tissue FGF21 resistance, which is subtended by FGF1 and β-Klotho downregulation (122) and is overcome by pharmacological doses of FGF21. To this aim, engineering of the native molecule yielded FGF21 analogs with improved biophysical properties, and one of these FGF21 analogs, LY2405319, ameliorated atherogenic dyslipidemia, insulin resistance, and adiponectin in obese patients with diabetes (123).

**TARGETING THE RENAL TUBULE TO IMPROVE CKD AND NAFLD**

Sodium-glucose cotransporter-2 (SGLT2) inhibitors block the activity of the SGLT2 protein, which is expressed in the S1 segment of the renal proximal tubule, leading to substantial glucosuria and a reduction in plasma glucose levels. Experimental evidence has demonstrated that SGLT2 inhibitors confer nephroprotection independently of their glucose-lowering or blood pressure–lowering properties. SGLT2 inhibitors attenuate glomerular hyperfiltration, which is believed to be the initial pathogenic alteration in diabetic and obesity-related CKD. In diabetes, hyperglycemia induces an increase in SGLT2-mediated proximal tubule NaCl reabsorption. The consequent reduction in NaCl distal delivery to the macula densa decreases tubuloglomerular feedback–mediated afferent arteriolar vasoconstriction, thereby increasing glomerular afferent-to-effluent arteriolar tone, intraglomerular ultrafiltration pressure, and glomerular filtration rate (124). Proximal tubule SGLT2 upregulation and increased NaCl reabsorption also have been documented in obesity-related CKD as a result of enhanced sympathetic activity (33,125) and TGF-β1/SMAD3 axis activation (126). By virtue of these actions, SGLT2 inhibitors synergize with renin-angiotensin-aldosterone system (RAAS) inhibitors, and their combination may confer incremental renal benefits.
Simultaneous SGLT2-RAAS blockade induces afferent arteriole constriction (SGLT2 inhibition) and efferent arteriole vasodilatation (RAAS blockade), thereby more thoroughly counteracting early intrarenal hemodynamic abnormalities underlying glomerular hyperfiltration in CKD. Additionally, SGLT2 inhibitors have decreased inflammatory and fibrogenic responses, oxidative stress, and cell apoptosis in diverse experimental models of CKD (128).

Available data on the impact of SGLT2 inhibitors on CKD have derived from an analysis of RCTs conducted with efficacy and safety end points in a diabetic population where SGLT2 inhibitors slowed renal function decline and reduced albuminuria independently of glycemic control (129), and dedicated nephroprotection trials are under way (Evaluation of the Effects of Canagliflozin Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy [CREDENCE]; clinical trial reg. no. NCT02065791, www.clinicaltrials.gov). Besides directly antagonizing the action of noxious factors described in A, NAFLD and CKD can be ameliorated at intestinal levels by incretin mimetics and modulation of gut microbiota composition with prebiotics, probiotics, or synbiotics and at systemic levels by activating cellular energy sensor AMPK and several nuclear transcription factors, including PPAR-a, PPAR-d, PPAR-g, FXR, and Nrf2. Tables 1–3 and the text provide a detailed description of molecular mechanisms underlying the gut-liver-kidney connection. Chol, cholesterol; IR, insulin resistance.
of antihyperglycemic action (34,35). Potential mechanisms underlying liver-related benefits of these drugs include insulin sensitizing (131) and body fat loss–inducing properties mediated by enhanced lipolysis and fatty acid oxidation (34,35), attenuation of adipose tissue dysfunction and inflammation (133), increased ACE2 activation (134), and intrinsic drug-specific antioxidant and anti-RAGE axis activation properties (36). Furthermore, SGLT2 mRNA expression has been documented in the liver, where its biological and clinical significance remain unknown (135).

Several issues with SGLT2 inhibitors warrant assessment, including the renoprotective effects in patients with CKD but without diabetes, the impact on liver histology, long-term safety in patients with various degrees of renal and hepatic impairment, and risk of ketoacidosis, which led the U.S. Food and Drug Administration to issue a safety warning in 2015 (136).

**CONCLUSIONS AND FUTURE PERSPECTIVES**

Despite progress made in the past decade, CKD still remains a major health problem for two reasons. CKD often goes unrecognized, and the current therapeutic armamentarium has limited effectiveness in retarding disease progression. NAFLD is the most common chronic liver disease and, given the lack of an effective treatment, is becoming the leading indication for liver transplantation in the Western world (5). The shared unmet needs of NAFLD and CKD, therefore, are boosting research on novel therapeutic targets in these two conditions.

Epidemiological data suggest a tight relationship between the presence and severity of NAFLD and the presence and stage of CKD and place NAFLD as an important contributor to the development and progression of CKD independently of traditional risk factors. When analyzing the pathophysiological basis for this association, striking analogies can be found between fatty liver and CKD. Like NAFLD, CKD is characterized by a deranged cellular substrate metabolism; ectopic fat deposition, which triggers oxidative stress; and inflammatory and profibrotic responses to drive the progression of both disease processes. This review shows a wealth of cellular pathways and mechanisms that represent key contributors to liver and kidney injury and potential therapeutic targets (Fig. 4). Most of these targets currently are being evaluated in phase II RCTs, and some of them, such as PPAR-α/δ agonists, FXR agonists, and incretin analogs, have promising results (137), although few of them have advanced to the same developmental stage in both NAFLD and CKD, reflecting a continued low awareness of the similarities in the pathogenic mechanisms underlying these two conditions. Besides shared pathogenic mechanisms that promote both liver and kidney injury, the fatty liver per se may promote...
kidney injury and vice versa, with potentially relevant therapeutic implications. For example, SGLT2 inhibitors target the renal tubule but may improve both CKD and NAFLD. Whether the relative merits of the various therapeutic approaches will translate into a clinical benefit needs assessment in adequately powered, larger RCTs of longer duration with clinical end points. A key challenge to therapeutic success of these various approaches will be the selection of the optimal therapeutic strategy for each patient. NAFLD and CKD progression is likely a multifactorial process, involving varied molecular pathways that may operate in different patient subsets and at different stages of disease. Within this context, recent developments in metabolic phenotyping with metabolomics and systems biology technologies will hopefully enable individualized treatment tailored to individual profiles. Given the increasing prevalence of CKD and NAFLD and their direct effects on acceleration of CVD, strategies to reduce the incidence, progression, and complications of these twin conditions are an important priority in health care.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. G.M. contributed to the study conception and design, literature search, data acquisition, critical analysis of the results, and drafting and final approval of the manuscript. M.C., S.C., F.D.M., S.P., F.S., and R.G. contributed to the literature search, data acquisition, critical analysis of the results, and drafting and final approval of the manuscript. G.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References
4. Stepanova M, de Avila L, Birendic A, et al. In female patients with non-alcoholic fatty liver disease (NAFLD) presence, of type 2 diabetes (DM) and chronic kidney disease (CKD) are independently associated with the risk of mortality. Hepatology 2015;62(Suppl.):2205
24. Sapp V, Gaffney L, EauClaire SF, Matthews RP. Fructose leads to hepatic steatosis in zebrafish that is reversed by mechanism-specific rapamycin (mTOR) inhibition. Hepatology 2014;60:1581–1592


49. Dattaroy D, Pourhoseini S, Das S, et al. Micro-RNA 21 inhibition of SMAD7 enhances fibrogenesis via leptin-mediated NADPH oxi-


