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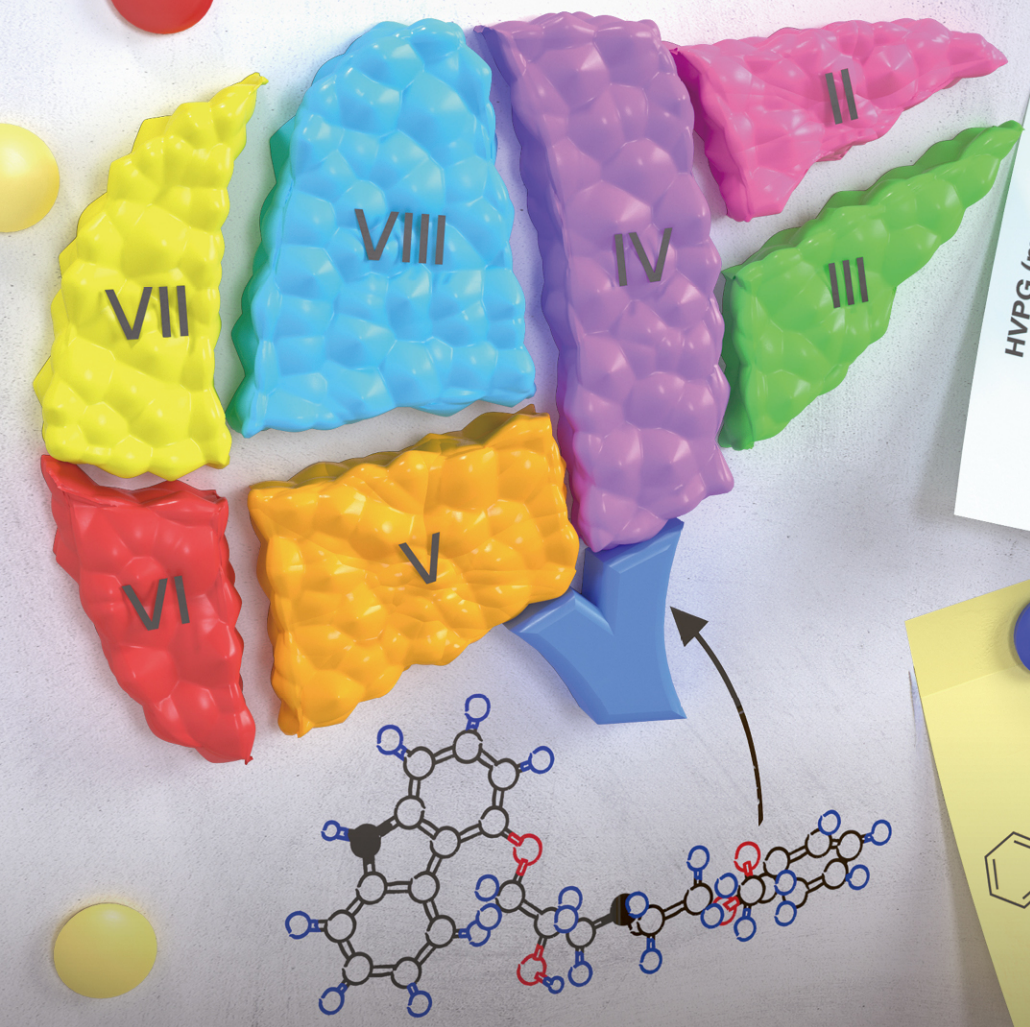

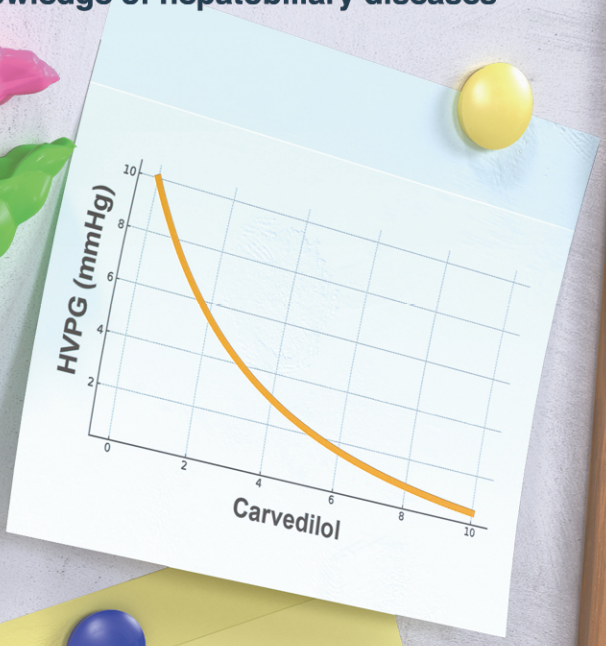

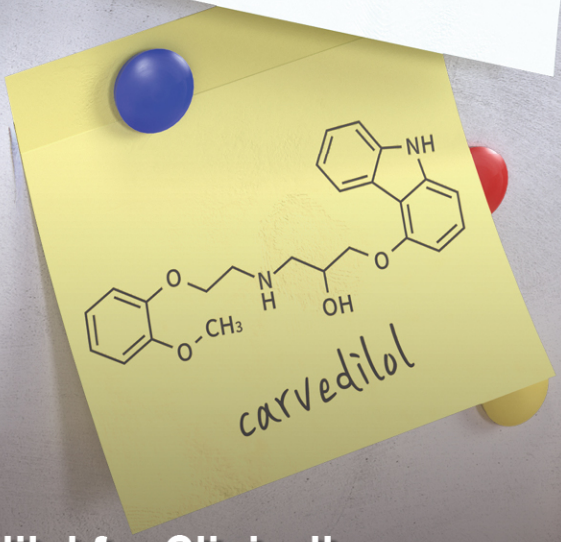

Non-invasive Model guiding Carvedilol for Clinically Significant Portal HTN

Intrapatient variability of tacrolimus on CKD in LT
HCV self-testing and disease burden reduction
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Review

Bioactive metabolites: A clue to the link between MASLD and CKD?

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Metabolites produced as intermediaries or end-products of microbial metabolism provide crucial signals for health and diseases, such as metabolic dysfunction-associated steatotic liver disease (MASLD). These metabolites include products of the bacterial metabolism of dietary substrates, modification of host molecules (such as bile acids [BAs], trimethylamine-N-oxide, and short-chain fatty acids), or products directly derived from bacteria. Recent studies have provided new insights into the association between MASLD and the risk of developing chronic kidney disease (CKD). Furthermore, alterations in microbiota composition and metabolite profiles, notably altered BAs, have been described in studies investigating the association between MASLD and the risk of CKD. This narrative review discusses alterations of specific classes of metabolites, BAs, fructose, vitamin D, and microbiota composition that may be implicated in the link between MASLD and CKD. **(Clin Mol Hepatol 2025;31:56-73)**

Keywords: Metabolic dysfunction-associated steatotic liver disease; Chronic kidney disease; Bioactive metabolites; Bile acids; Gut microbiota

INTRODUCTION

The metabolome is represented by all low-molecular-weight molecules (metabolites) that are present in the cell and modulate other 'omics', such as the genome, epigenome, transcriptome and proteome. Through the inter-

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twined interactions between the metabolome and other 'omics', metabolites directly modulate biological processes and diseases.[1] Several metabolites, including bile acids (BAs), trimethylamine-N-oxide (TMAO), uremic toxins, short-chain fatty acids (SCFA), lipopolysaccharide (LPS), fructose and vitamin D (Vit D), have emerged as important regulators that may interact with the host.[2-4] Abnormalities in the composition and function of metabolites, especially altered BA profiles, might partly contribute to the development of metabolic diseases, such as metabolic dysfunction-associated steatotic liver disease (MASLD),[5,6] also known as metabolic dysfunction-associated fatty liver disease,[7] which may progress to metabolic dysfunction-associated steatohepatitis (MASH), cirrhosis, and hepatocellular carcinoma.[8] Recent studies also reported that individuals with MASLD have significantly lower values of estimated glomerular filtration rate and a greater prevalence of chronic kidney disease (CKD) than those without liver disease, suggesting that MASLD may be associated with an increased risk of developing CKD.[9-12] Our previous study has also indicated that urine protein biomarkers are an accurate tool for the non-invasive diagnosis of liver fibrosis in MASLD.[13] Despite the difficulty in defining a causal relationship between MASLD and CKD (MLKD), increasing evidence suggests that alterations in the BA profile and gut microbiota are involved in the pathogenesis of MLKD.[14,15] Therefore, in this narrative review, we aim to discuss gut microbiota-derived metabolites, with a special focus on the alterations of the BA profile and gut microbiome and the interactions between gut microbiota and the host, via BA-sensing receptors (mainly the Farnesoid X receptor [FXR] and Takeda G protein-coupled receptor 5 [TGR5]) together with other bioactive metabolites, such as fructose, and Vit D that are potentially implicated in the development of MLKD.

BILE ACIDS AND MLKD

Bile acid metabolism

Figure 1 schematically summarizes the metabolism of BAs.[16,17] In humans, the most abundant BAs are the primary bile acids (PBAs), i.e., cholic acid (CA), and chenodeoxycholic acid (CDCA), which are initially produced by the enzymatic activities of cholesterol 7α-hydroxylase and cholesterol 27α-hydroxylase. These enzymatic processes are followed by the conjugation of CA and CDCA to either taurine or glycine by bile acyl-CoA synthetase and bile acid-CoA:amino acid N-acyltransferase to form taurocholic acid (TCA), glycocholic acid (GCA), taurochenodeoxycholic acid (TCDCA) and glycochenodeoxycholic acid (GCDCA).[18] In the intestine, conjugated CA and CDCA are deconjugated and converted by 7-alpha-dehydroxylase to deoxycholic acid (DCA) and lithocholic acid (LCA), i.e., the main secondary BAs (SBAs).[16,18] Subsequently, DCA and LCA can be transformed into iso-DCA and iso-LCA via the so-called iso-BA pathway.[19]

Altered bile acid profiles in MLKD

BAs play a crucial role in maintaining the host's physiological functions and may influence the onset and progression of MLKD. Growing evidence has demonstrated that circulating BA levels are increased in humans or animal models with MASLD.[20-24] A population-based cohort study showed that circulating levels of total BAs, PBAs, and SBAs are significantly higher in patients with MASLD than in healthy controls (HC).[25] Conversely, Caussy et al.[26] elucidated that PBAs are reduced, whereas conjugated PBAs are increased in patients with MASLD. Similarly, increases in individual BA concentrations and alterations of BA com-

Abbreviations:

Apo, apolipoprotein; BAT, brown adipose tissue; CA, cholic acid; CDCA, chenodeoxycholic acid; CKD, chronic kidney disease; DCA, deoxycholic acid; DN, diabetic nephropathy; ER, endoplasmic reticulum; ERRα, estrogen related receptor-α; ESRD, end-stage renal disease; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GCA, glycocholic acid; GCDCA, glycochenodeoxycholic acid; GDCA, glycodeoxycholic acid; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; GUDCA, glycoursodeoxycholic acid; HC; healthy controls; HDCA, hyodeoxycholic acid; HDL-C, high density lipoprotein-cholesterol; HFCS, high-fructose corn syrup; HFD, high fat diet; HSDH, hydroxysteroid dehydrogenase; IS, indoxyl sulfate; LPL, lipoprotein lipase; LPS, lipopolysaccharide; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MCA, muricholic acid; MLKD, MASLD and CKD; NF-κB, nuclear factor-κB; PBA, primary bile acid; PCS, p-cresyl sulfate; PGC-1α, PPARγ coactivator-1α; PPAR, peroxisome proliferator activated receptor; ROS, reactive oxygen species; SBA, secondary bile acid; SCD, stearoyl CoA desaturase; SCFA, short chain fatty acids; SGLT-2, sodium glucose co-transporter 2; SHP, small heterodimer partner; SREBP-1c, sterol regulatory element-binding protein-1c; SSB, sugar-sweetened beverages; TCA, taurocholic acid; TCDCA, taurochenodeoxycholic acid; TDCA, taurodeoxycholic acid; TG, triglyceride; TGF-β, transforming growth factor-β; TGR5, Takeda G protein coupled receptor 5; TLCA, taurolithocholic acid; TMAO, trimethylamine-N-oxide; TUDCA, tauroursodeoxycholic acid; TαMCA, tauro-α-muricholic acid; UDCA, ursodeoxycholic acid; VDD, vitamin D deficiency; Vit D, vitamin D; VLDL, very low density lipoprotein

position have also been reported in patients with MASH. A cross-sectional study showed that increased total PBAs and decreased SBAs are characteristics of MASH; this increase in PBAs might be due to increased PBA synthesis, decreased intestinal SBA conversion, or decreased PBA dehydroxylation and reduced SBA formation.[21] Furthermore, in a study of 102 patients with biopsy-confirmed MASLD, Nimer et al.[27] reported that higher levels of individual BAs (i.e., increased levels of plasma GCDCA, GCA, 7-Keto-DCA, and glycoursodeoxycholic acid [GUDCA]) are associated with higher histological grades of hepatic inflammation and fibrosis. BAs are also important modulators of the intestinal microbiome, but the bidirectional impact between altered BA profile and microbiome composition is not fully understood. Smirnova et al.[22] reported that fecal SBAs are higher in patients with MASLD, whereas 7,12-diketo-LCA, glycodeoxycholic acid (GDCA) and LCA are higher in those with MASH. Furthermore, metabolites of deoxycholate, including 12-dehydrocholate acid (12-DHCA), 7-keto-DCA, DHCA and GDCA, are increased in individu-

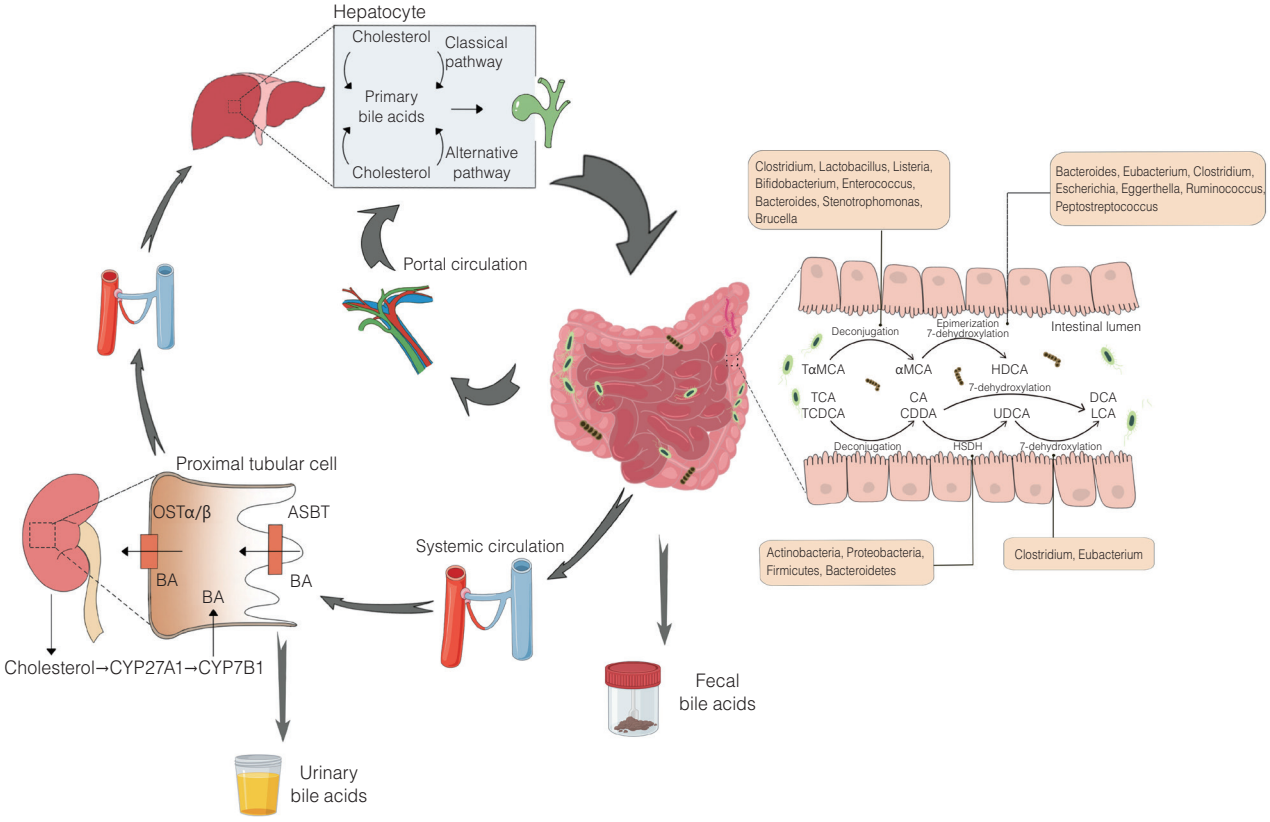

Figure 1. Bile acid biosynthesis, transport pathways, metabolism and excretion. Cholesterol is converted into primary bile acids (PBAs) via classical pathway and alternative pathway and conjugated to glycine or taurine in the hepatocytes, then secreted into bile, which flows through the bile duct to the intestine. At the terminal ileum, most BAs are recycled to the liver via portal circulation. Unabsorbed BAs are passed along from the small to large intestine. In the colon lumen, conjugated PBAs are metabolized into secondary bile acids (SBAs) by microbial enzymes from gut bacteria. Conjugated cholic acid (CA) and chenodeoxycholic acid (CDCA) are deconjugated via bacterium with bile salt hydrolases, including *Clostridium, Lactobacillus, Bifidobacterium, Listeria, Enterococcus, Bacteroides, Stenotrophomonas and Brucella*, and then 7α-dehydroxylated with *Clostridium and Eubacterium* to form deoxycholic acid (DCA) and lithocholic acid (LCA). The majority of CDCA is converted to α-muricholic acid (α-MCA) and β-MCA, which are predominant in mice and scarce in humans. Tauro-α-muricholic acid (Tα-MCA) is deconjugated to form α-MCA. α-MCA is C-6 epimerized with *Bacteroides, Eubacterium, Clostridium, Escherichia, Eggerthella, Peptostreptococcus and Ruminococcus* to form ω-MCA, and then ω-MCA is 7α-dehydroxylated to form hyodeoxycholic acid (HDCA). CDCA is transformed into ursodeoxycholic acid (UDCA) by the hydroxysteroid dehydrogenase (HSDH) with *Actinobacteria, Proteobacteria, Firmicutes, and Bacteroidetes*. BAs that are not absorbed from the small and large intestine excreted in feces. In the kidney, cholesterol is converted into BAs via CYP27A1 and CYP7B1. After the first hepatic pass, BAs that have not been cleared are filtrated by the renal glomerulus and reabsorbed by proximal tubular cell of the kidney, and unabsorbed BAs are excreted into urine.

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als with MASH and liver fibrosis, suggesting a relationship between specific changes in the fecal BA profile and the severity of liver disease activity.[22]

Recent observational studies have demonstrated that MASLD may be an independent risk factor for CKD.[14,28-30] In addition to the alterations of BAs reported in people with MASLD, clinical studies have also reported alterations in serum BA profile and BA homeostasis in people with CKD. For example, Chu et al.[31] reported increased serum BA levels and decreased urinary BA levels in patients with CKD, mainly due to decreased renal filtration of BAs. Increased plasma TCA and decreased CDCA levels were also observed in patients with hypertensive nephropathy compared to those with hypertension alone, possibly due to bile salt metabolism within the gut microbiome influencing renal disease.[32] Moreover, it has been reported that patients with end-stage renal disease (ESRD) have decreased levels of unconjugated BAs and SBAs, such as CA, CDCA, DCA, hyodeoxycholic acid (HDCA), ursodeoxycholic acid (UDCA), α+ω muricholic acid (MCA), γMCA, 7-keto-LCA, 12-keto-LCA and 6,7-diketo-LCA, while conjugated BAs and PBAs, including βMCA, GCA, GCDCA, TCA, TCDCA, taurohyocholic acid, tauro-α-muricholic acid (TαMCA) and tauroursodeoxycholic acid (TUDCA), were all significantly increased.[33] However, the precise roles of distinct BAs in the diagnosis and prognosis of patients with CKD remain unclear, suggesting the need for further studies.

In addition to the altered BA profiles observed in individuals with MASLD or CKD, similar studies evaluating BA profile have also been conducted in rodent models.[34,35] For example, MASLD mice fed with a high-fat diet (HFD) had significantly higher levels of taurodeoxycholic acid (TDCA), DCA, TCA, CA, and lower levels of MCA and TUDCA than control mice.[36] Similarly, MASH mice fed a methionine- and choline-deficient diet exhibited significantly higher serum levels of TDCA, CDCA, LCA, and taurolithocholic acid (TLCA) than control mice.[35] On the other hand, in diabetic nephropathy (DN) mice, Wei et al.[37] found that serum levels of total BAs, TCA, and Tβ-MCA were increased. Furthermore, in the feces of DN rats, there were increased total BAs, CA, DCA, and a decreased DCA-to-CA ratio, which might partly contribute to the progression of renal impairment by increasing mucosal permeability and gut inflammation.[38]

Due to discrepancies in the published literature, we have focused on concordant results where the circulating levels of BA metabolites are described in patients with MASLD or CKD alone and in those with combined MLKD (Supplementary Table 1).[33,39] When comparing MLKD patients to healthy individuals, a consistently altered BA signature was observed in the circulating levels of PBAs (principally increased plasma TCA,[27,32,39-41] GCA,[21,27,33] TUDCA[33,41] and GCDCA[21,27,39,41]). Similarly, in our unpublished study, we found an increase in plasma TCDCA and GCDCA levels in patients with MLKD, which is consistent with previously published literature.[21,27] Furthermore, some plasma BAs show an opposite trend in patients with MASLD (increased levels of CA,[5] CDCA,[5] HDCA,[27] UDCA[5]) compared to those with CKD (decreased levels of CA,[15] CDCA,[32] HDCA,[33] UDCA[33]). Previous studies also reached contradictory conclusions regarding the BA profile in MASLD or CKD. For example, increases in TCDCA and DCA are reported in MASLD or CKD patients,[15,27] whereas Tan et al. have shown that TCDCA is decreased in MASLD and Li et al. found that DCA is reduced in ESRD patients.[33,40] Furthermore, HDCA is a metabolite of βMCA, generated by bacterial 6β-epimerization and additional 7β-dehydroxylation in the small intestine.[42] A recent study has indicated that MASLD was specifically characterized by decreased plasma levels of HDCA.[43] This study showed an improvement in hepatic steatosis via activation of the BA alternative synthetic pathway by inhibiting intestinal FXR signaling. Additionally, HDCA significantly increased the abundance of probiotic species by peroxisome proliferator-activated receptor (PPAR)-α signaling (further validated in mouse models) to upregulate hepatic FXR.[43] However, the underlying mechanisms linking HDCA and CKD are poorly understood. UDCA is a hydrophilic BA synthesized in the colon by bacterial 7β epimerization of CDCA and is considered the first-line treatment for primary biliary cholangitis.[44,45] It has been reported that UDCA strongly affects cholesterol and BA synthesis and induces neutral lipid accumulation in the liver by exerting FXR-antagonistic effects in patients with MASLD.[46] UDCA also affects the kidney by preventing over-expression of sodium-glucose cotransporter and oxidative stress, as shown in diabetic rats.[47] However, the precise mechanisms by which BAs may affect kidney disease in MLKD are not fully understood, and further research is needed.

BA-related gut microbiome changes and MLKD

Enteric dysbiosis increases gut permeability to produce active metabolites, such as TMAO, SCFA, and SBAs, and these are implicated in several conditions linked to MASLD.[48-50] Microbial enzymes from gut bacteria indirectly metabolize BAs via SCFA and TMAO, as described in detail in the following section.

The microbial genera involved in BA metabolism are Clostridium, Lactobacillus, Bifidobacterium, Listeria, Enterococcus, Bacteroides, Stenotrophomonas and Brucella for BA deconjugation; Clostridium and Eubacterium for 7-dehydroxylation; and Bacteroides, Eubacterium, Clostridium, Escherichia, Eggerthella, Peptostreptococcus, and Ruminococcus for epimerization and oxidation of hydroxyl groups at ring positions 3, 7, or 12. Actinobacteria, Proteobacteria, Firmicutes, and Bacteroidetes with hydroxysteroid dehydrogenases (HSDH) attributed to the oxidation of hydroxyl, as well.[16,42] Enteric metabolites, such as SCFA and TMAO, play crucial roles in BA metabolism in patients with MLKD. SCFA (including acetate, sodium butyrate and propionate) originate from dietary fiber and escape fermentation until their passing into the colon and cecum, where they are metabolized by microbes. A study from China reported that circulating SCFA levels (mainly butyrate) were lower in patients with CKD than control subjects, thus increasing the synthesis of uremic toxins, such as tryptophan metabolites and TMAO, and inducing kidney dysfunction.[51] TMAO is mainly produced from the microbial processing of dietary components, such as choline and carnitine.[52] Emerging evidence suggests that plasma TMAO levels are increased in patients with MLKD.[53,54] Recent data have also shown disturbances in TMAO-mediated crosstalk with gut microbiota may disrupt the sinusoidal vasculature to promote liver fibrosis in MASH.[55] TMAO may also aggravate the progression of kidney dysfunction by promoting tubular-interstitial fibrosis and collagen deposition.[56] A previous animal study in apolipoprotein (Apo) $E^{-/-}$ mice reported that increased TMAO levels may alter cholesterol transport and decrease the total BA pool size.[57] However, Tan et al. reported that in a murine model, TMAO administration increased hepatic steatosis, increased BA synthesis and shifted hepatic BA composition towards FXR-antagonistic activity.[40]

Using results from the bacterial contribution to metabolite production, we have focused on the bacterial effects on BA synthesis metabolism, summarizing results according to the taxonomic level (bacterial phylum, class, family and genus) associated with the presence and severity of MLKD. Compared to healthy controls, there are significant increases in the phylum *Bacteroidetes* and decreases in the phylum *Firmicutes* in the feces of MASLD patients, accounting for more than 90% of the total gut microbiota in humans.[49,58-64] In contrast, the phylum *Proteobacteria* was consistently increased, leading to increased levels of microbial gut toxins in MASLD patients.[60,61,65] Two predominant members of the Firmicutes family, i.e., *Lachnospiraceae* and *Ruminococcaceae* were markedly decreased in MASLD patients, which can affect the SCFA synthesis and potentially impact intestinal integrity and permeability in the pathogenesis of MASLD.[58,66,67] Furthermore, the genus *Escherichia_Shigella* is an ethanol-producing bacterium that affects fatty acid metabolism and exacerbates gut leakiness, and this organism was found to be markedly increased in patients with MASLD.[68-72] Additionally, the genus *Lactobacillus* was increased across the whole spectrum of MASLD (MASL, MASH, advanced fibrosis, and cirrhosis).[60,61,73]

That said, several findings disagree with previous results in the study of the gut microbiota in MASLD. For example, it has been reported that patients with MASLD have reduced abundance of the phylum *Bacteroidetes*,[73,74] but increased phylum *Firmicutes*,[65,74] family *Lactobacillaceae* and *Ruminococcaceae*.[49,61] Moreover, some studies have concentrated on microbiome signatures in MASLD severity. Schwimmer et al.[60] found that the phyla *Bacteroidetes* and *Proteobacteria* and genus *Lactobacillus* were more abundant in MASLD patients with moderate-to-severe liver fibrosis ($F \geq 2$), whereas *Firmicutes* were more abundant in those with absent or mild fibrosis ($F \leq 1$).

Some evidence has also related CKD to the microbial metabolites and composition of the intestine.[75-77] A study of 50 patients with CKD and 22 healthy control subjects has shown that patients with CKD had reduced abundance of the phylum *Actinobacteria* and increased genera *Lactobacillus* in their fecal samples.[78] Studies involving different animal models of CKD have also reported the presence of intestinal dysbiosis. Hu et al.[79] found that in the high salt-induced CKD mouse, there were decreased levels of *Firmicutes* and increased levels of *Bacteroidetes*. However,

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DN mice exhibited increased levels of the phylum *Firmicutes* but decreased *Bacteroidetes* compared to nondiabetic control mice. Simultaneously, *Bacteroides* and *Ruminococcus* were reduced at the genus level.[80] An experimental study of an adenine-induced CKD mouse model showed that the genus *Lactobacillus* was increased[81] and an unclassified Lactobacillaceae family and Clostridia class were decreased, whereas genus *Bifidobacterium* and *Clostridium* were increased in this adenine-induced CKD mouse model.[82] Similarly, gut microbiota and its metabolites, indoxyl sulfate (IS), p-cresyl sulfate (PCS) and TMAO, are also known as uremic toxins, and may also contribute to the progression of CKD.[83] As a potent uremic toxin, IS is generated by intestinal bacteria such as *Lactobacilli,* exerting its adverse effects on the kidney and vascular system.[84,85] IS may also promote vascular inflammation in CKD.[86] PCS is another uremic toxin specifically produced by microbiome like *Bacteroides fragilis* that may promote renal fibrosis by increasing reactive oxygen species (ROS), transforming growth factor-β (TGF-β) and stimulating the renal-angiotensin-aldosterone system, thus inducing renal tubular damage.[87,88]

Studying the alterations of the gut microbiome in MLKD, we noted that there are four bacteria, phylum *Firmicutes* and *Proteobacteria,* and genus *Lactobacillus, Escherichia_Shigella* that are changed in patients with MLKD (Supplementary Table 2). In particular, *Proteobacteria* and *Lactobacillus* were increased in patients with MLKD. *Escherichia_Shigella* was increased in patients with MASLD but decreased in those with CKD. In contrast, *Firmicutes* was reduced in patients with MASLD but increased in those with CKD.

It is well known that a HFD may alter the gut microbiome composition.[74,89] Exposure to oral antibiotics in HFD-fed mice induced lower levels of the genera *Lactobacillus* and decreased bile salt hydrolase activity, which led to in-

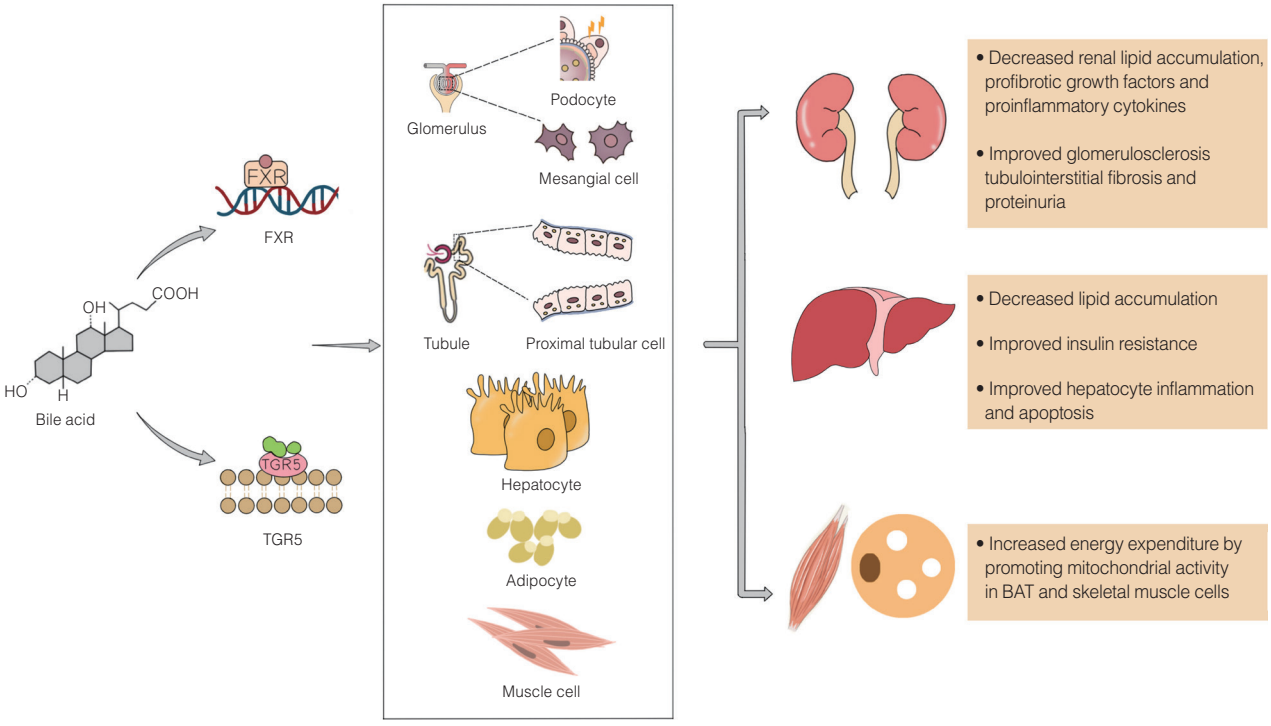

Figure 2. Differential expression of FXR and TGR5 receptors and putative pathogenic mechanisms in MASLD and CKD. FXR and TGR5 are expressed in the liver (mainly in hepatocytes), kidney (mainly in the glomerulus and tubular cells, especially the proximal tubular cells), and other tissues, such as skeletal muscle and adipose tissue (BAT, brown adipose tissue). Activation of both FXR and TGR5 facilitates a decrease in lipid accumulation in the liver and kidneys, whilst improving insulin sensitivity and hepatocyte inflammation and apoptosis by inhibiting endoplasmic reticulum stress and oxidative stress in MASLD. Activation of both FXR and TGR5 represses the expression of multiple profibrotic growth factors and proinflammatory cytokines to improve glomerulosclerosis, tubulointerstitial fibrosis and proteinuria in CKD. Activation of both FXR and TGR5 promotes mitochondrial activity in BAT and skeletal muscle cells and increases energy expenditure.

Table 1. FXR and TGR5 expression levels in patients with MASLD or CKD and preclinical models of MASLD or CKD

Author	Groups	Subject	Model	Level of receptors	Findings
Jiao et al.[5] (2018)	MASH (n=16) vs. HC (n=11)	Human	MASLD	Hepatic FXR expression↑	Patients with MASH have increased production of DCA, which may suppress FXR signaling in the liver and gut
Tang et al.[24] (2019)	MASLD (n=5) vs. HC (n=5)	Rats	MASLD	Hepatic FXR mRNA↑	THDCA ameliorates hepatic steatosis by activating FXR in vitro
Li et al.[34] (2021)	MASH (n=8) vs. HC (n=8)	Mice	MASLD	Hepatic, Intestinal and Colonic FXR protein↓ Intestinal and Colonic TGR5 protein remain unchanged	SNN increases colonic FXR expression and suppresses liver metabolic inflammation by reducing macrophage accumulation and hepatic IL-1β expression
He et al.[36] (2021)	MASLD (n=6) vs. HC (n=6)	Mice	MASLD	Hepatic FXR and TGR5 mRNA↓	PTFC increases the FXR and TGR5 protein level and mRNA expression, attenuating HFD-induced MASH symptoms
Li et al.[35] (2020)	MASH (n=12) vs. HC (n=12)	Human	MASLD	Hepatic TGR5 and FXR mRNA↓ Hepatic TGR5 and FXR protein↓	QGE treatment prevents MASH by regulation of gut microbiota-mediated LCA production, promotion of TGR5 expression and suppression of NF-κB activation
Tan et al.[40] (2019)	MASLD (n=34) vs. HC (n=14)	Human	MASLD	Hepatic FXR mRNA↓	TMAO aggravates hepatic steatosis by suppressing BA-mediated hepatic FXR signaling
Li et al.[89] (2020)	MASLD (n=8) vs. HC (n=8)	Mice	MASLD	Hepatic FXR mRNA↓ Intestinal FXR and FGF15 protein↓	Salidroside improves inflammation and lipid metabolism disorders by increasing FXR expression and modulating bile acid metabolism
Nobili et al.[92] (2018)	MASH (n=19) vs. MAFL (n=14) vs. HC (n=5)	Human	MASLD	Hepatic FXR protein ↓	Levels of FXR protein progressively decrease from subjects with normal liver to MAFL and MASH
Liu et al.[98] (2020)	HFD (n=12) vs. HC (n=12)	Mice	MASLD	Hepatic FXR mRNA and protein ↓	Schaftoside alleviates HFD-induced hepatic lipid accumulation via upregulating FXR
Xiong et al.[99] (2014)	MASLD (n=6) vs. HC (n=6)	Mice	MASLD	Hepatic FXR mRNA and protein ↓ LXR and LRH-1 mRNA unchanged	FXR downregulation plays a role in dysregulated hepatic lipid metabolism and activation of ER stress
Shen et al.[101] (2021)	MASLD (n=50) vs. HC (n=12)	Mice	MASLD	Hepatic FXR mRNA and protein ↓	EMO improves HFD-induced lipid accumulation, insulin resistance, inflammation, and oxidative stress by up-regulating FXR expression
Wang et al.[107] (2018)	DM (n=6) vs. HC (n=6)	Mice	CKD	Renal TGR5 and FXR mRNA↓ Renal TGR5 and FXR protein↓	INT-767 stimulates FXR and TGR5 mRNA and protein expression, by decreasing albuminuria, mesangial matrix expansion, podocyte loss, renal fibrosis, extracellular matrix protein fibronectin, oxidative stress, and inflammation
Zhao et al.[108] (2016)	Fibrotic kidney (n=15) vs. HC (n=15)	Human	CKD	Hepatic FXR mRNA↓	Activation of FXR suppresses kidney fibrosis and downregulates Smad3 expression

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Table 1. Continued

Author	Groups	Subject	Model	Level of receptors	Findings
Yang et al.[116] (2016)	DM (n=6) vs. HC (n=6)	Rats	CKD	Renal TGR5 protein↓	TGR5 activation decreases expression of ICAM-1, TGF-β1 and FN induced by high glucose in GMCs
Gay et al.[133] (2022)	MASH (n=10) vs. HC (n=10)	Mice	MASLD	Hepatic FXR mRNA and protein↓ Hepatic FGFR4 protein↓	FXR expression is decreased in the livers of CDE-fed mice compared to control livers, and proglumide restores FXR expression to normal levels
Luo et al.[134] (2021)	MASLD (n=6) vs. HC (n=6)	Mice	MASLD	Hepatic FXR and FGF15 mRNA↑ Hepatic FXR protein and FGF15 protein↓	Probiotics increase expression of FXR, FGF15 mRNA and protein levels in the liver to improve plasma lipids and liver pathology
Deng et al.[138] (2013)	MASLD (n=8) vs. HC (n=8)	Mice	MASLD	Hepatic FXR mRNA↓	Chemerin, a novel target gene of FXR, is associated with MASH

MASLD, metabolic dysfunction-associated steatotic fatty liver disease; MASH, metabolic dysfunction-associated steatohepatitis; MAFL, metabolic dysfunction-associated fatty liver; HC, healthy control; DM, diabetes mellitus; BA, bile acid; HFD, high-fat diet; DCA, deoxycholic acid; THDCA, taurohyodeoxycholic acid; FGFR, fibroblast growth factor receptor; TMAO, trimethylamine-N-oxide; SNN, Salvia-Nelumbinis naturalis; QGE, Qiang-Gan formula extract; NF-κB: nuclear factor-κB; EMO, emodin; ICAM-1, intercellular adhesion molecule-1; TGF-β1, transforming growth factor β-1; FN, fibronectin; GMCs, glomerular mesangial cells; CDE, choline deficient ethionine; AA, acanthoic acid; PTFC, pure total flavonoids from citrus.

creased levels of Tβ-MCA, by inhibiting activation of intestinal FXR and resisting HFD-induced MASLD, thus suggesting that there is an endogenous pathway controlling metabolic fitness that involves BAs, gut bacteria and FXR receptors.[90] Treatment with Lactobacillus in CKD rats ameliorated the increased urinary protein excretion and inflammation associated with renal failure, suggesting that Lactobacillus may be protective against CKD progression.[91] However, the precise role of gut microbiota in the progression of MLKD is not fully understood and requires further extensive research.

Bile acid signaling pathways

Pathogenic mechanisms of FXR

The human BA composition is influenced by microbial transformations and gut metabolites, affecting the activity of BA-associated receptors, such as FXR and TGR5. In Figure 2, we illustrate the possible molecular mechanisms relating to BA metabolism that underlie the development of liver and kidney damage in the process of MLKD. It is reported that levels of FXR and TGR5 are associated with the presence of MASLD;[92] several studies have also demonstrated that hepatic and renal expression of FXR and TGR5 are mainly downregulated in the presence of MLKD (Table 1). FXR is a ligand-activated transcription factor highly expressed in the liver, intestine and kidneys that controls all aspects of metabolism, including BA homeostasis and glucose-lipid metabolism. The FXR agonist activity ranking for BAs is CDCA, DCA, CA, and LCA in sequence, whereas TαMCA, Tβ-MCA, TUDCA and GUDCA serve as inhibitors of FXR.[93] FXR can modulate BA homeostasis via three main pathways: the small heterodimer partner (SHP) pathway, the mouse fibroblast growth factor-15 (FGF-15) or fibroblast growth factor-19 (FGF-19) pathway, and the c-Jun N-terminal kinase (JNK) pathway. SHP, as a downstream target of FXR, inhibits the expression of CYP7A1, which is a rate-limiting enzyme responsible for the hydroxylation of the cholesterol ring structure at carbon atom position 7 in BA biosynthesis.[94,95] Additionally, when FXR is activated, FGF-15/19 are upregulated in the intestine, thus entering the liver through the enterohepatic circulation. FGF-15/19 may act on the fibroblast growth factor receptor-4 and SHP in the liver mainly via the JNK-depend pathway to inhibit the CYP7A1 expression, thus reducing the BA pool.[96] With

regards to FXR involvement in lipid metabolism, FXR suppresses the upregulation of sterol regulatory element-binding protein-1c (SREBP-1c), which is essential in the fatty acid biosynthesis, thus resulting in the repression of lipogenic genes, such as fatty acid synthase, acetyl CoA carboxylase and stearoyl CoA desaturase (SCD).[97-99] This FXR-induced effect may reduce the production of triglyceride (TG) and very low-density lipoprotein (VLDL) particles. Moreover, FXR may induce the expression of the VLDL receptor and the microsomal TG transfer protein to suppress VLDL formation. Additionally, FXR activation increases the expression of the lipoprotein lipase (LPL) activator, apolipoprotein (Apo) CII, and inhibits the expression of the LPL inhibitor, Apo CIII, thereby increasing LPL activity that promotes the clearance of TG-rich lipoproteins by stimulating TG hydrolysis in VLDL.[17] Not only is VLDL clearance affected, but high-density lipoprotein (HDL) metabolism is also subject to modulation by FXR agonists. Administration of an FXR ligand increases the expression of scavenger receptor B1, a molecule in charge of hepatic HDL uptake that increases HDL clearance and consequently lowers plasma HDL-cholesterol levels.

In addition, FXR activation may exert a significant effect on glucose metabolism. It has been reported that impaired insulin sensitivity and elevated blood glucose levels are found in FXR-deficient mice in random-fed and fasting states. Activation of the hepatic FXR nuclear receptor induces the expression of phosphoenolpyruvate carboxykinase and glucose 6-phosphatase, decreasing hepatic glucose production and lowering plasma glucose levels in both wild-type and diabetic mice, thus improving glucose tolerance and insulin sensitivity.[100,101] However, in a mouse model of gestational diabetes mellitus, McIlvride et al.[102] reported that FXR activation by obeticholic acid reduced the impact of pregnancy on insulin resistance but did not change glucose tolerance. Thus, the overall effects of FXR agonism on glucose levels need to be elucidated. Additionally, activation of gut-restricted FXR may induce STC-1 in enteroendocrine cells to stimulate glucagon-like peptide-1 (GLP-1) secretion to improve glucose tolerance and hepatic insulin sensitivity.[103] In addition to its impact on physiological metabolism, FXR also suppresses low-grade inflammation, endoplasmic reticulum (ER) stress, oxidative stress, and hepatocyte death in patients with MASLD. Yan et al.[104] have studied the mechanism(s) of the hepatoprotective effects of FXR agonists in MASLD progression by hepatocytes or other tissue/cell-specific FXR-null mice. Hepatic FXR activation enables the antagonization of nuclear factor kappa B (NF-κB) activation to reduce hepatic inflammation. FXR activation also represses ER stress by downregulating protein kinase-like ER kinase (p-PERK)/CCAAT-enhancer-binding protein homologous protein pathway Metallothionein 1, which is an antioxidant protein primarily induced by FXR to suppress ROS. Meanwhile, in rodent models of MASH, activation of FXR via obeticholic acid enables the inhibition of p53 activation, protecting hepatocytes from cell death and reducing hepatic fibrogenesis in MASH.[104]

FXR is also localized in renal glomeruli and proximal tubules, but its expression in proximal tubules is higher than in glomeruli.[105] Studies indicate a crucial role for FXR in regulating lipid metabolism, fibrogenesis, and inflammation in the kidney. Virchow et al.[106] first reported that the progression of CKD was associated with abnormal lipid metabolism. SREBP-1, SCD-1 and SCD-2, which are genes regulating lipogenesis pathways, were all increased in HFD-fed mice. In contrast, this effect was reversed by FXR activation, which was also observed in DN mice models.[105,107] Additionally, in DN mice models, FXR activation ameliorates glomerulosclerosis, tubulointerstitial fibrosis, and proteinuria by reducing renal gene expression, such as mesangial matrix proteins fibronectin, fibrosis markers fibroblast-specific protein-1 and α-smooth muscle actin, as well as the profibrotic growth factors TGF-β, the proinflammatory cytokines tumor necrosis factor-β; these experimental data collectively support a renal-protective role for FXR.[105] Further, it is reported that activation of FXR may suppress kidney fibrosis and downregulate Smad3 expression, which has a central role in renal fibrogenesis.[108] Marquardt et al.[109] also found that the TUDCA-induced FXR-dependent genes suppressor of cytokine signaling and dimethylarginine dimethylaminohydrolase-1 expression in tubular cells ameliorates maladaptive ER stress signaling and protects the tubular compartment via FXR agonism in DN mice, thereby suggesting another potentially protective mechanism linking FXR agonism to protection from renal disease.

Pathogenic mechanisms of TGR5

TGR5 is activated by natural or synthetic ligands and it is

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widely expressed in adipocytes, myocytes, Kupffer cells, enteroendocrine cells and renal cells.[110] TGR5 is, therefore, relevant for regulating energy expenditure, glucose metabolism and immunity in MASLD/MASH.[110] In the intestine, activation of TGR5 induces the release of GLP-1 from enteroendocrine L-cells and acts on pancreatic β cells to potentiate insulin secretion in response to glucose.[111] The activation of TGR5 increases thermogenesis in the brown adipose tissue (BAT) and skeletal muscle by upregulating the gene encoding type 2 iodothyronine-deiodinase; this enzyme converts inactive thyroxine to active 3,5,3´-tri-iodothyronine, thus increasing oxygen consumption and energy expenditure.[110, 112] In Kupffer cells, the activation of TGR5 is implicated in the inflammatory response, inducing an anti-inflammatory effect mainly through inhibition of nuclear NF-κB translocation and suppression of cytokine production.[113,114]

Wang et al.[115] have studied CKD mice models and human renal cells, establishing a role for TGR5 in CKD. TGR5 is expressed in the highest levels in the renal tubules. In DN mice, a selective TGR5 synthetic agonist INT-777 induced renal mitochondrial biogenesis, reduced oxidative stress, and induced fatty acid β-oxidation.[115] Meanwhile, TGR5 activation reduced TGF-β1 and fibronectin expressions by suppressing sphingosine 1-phosphate/sphingosine 1-phosphate receptor signaling to ameliorate DN.[116] This was thought to prevent DN development by decreasing urinary albumin excretion, glomerular mesangial expansion, accumulation of extracellular matrix proteins, macrophage accumulation, and podocyte injury in the kidneys. Similar to DN mice models, there is a higher abundance of p-AMPK, PGC-1α, and SIRT3 in obesity-associated nephropathy mice treated with the TGR5 synthetic agonist INT-777. TGR5 activation in these obesity-associated nephropathy mice also attenuated proteinuria, podocyte injury, mesangial expansion, and renal fibrosis by reducing the accumulation of extracellular matrix proteins fibronectin and type IV collagen, profibrotic growth factors TGF-β, CD68 macrophages, and proinflammatory cytokine monocyte chemoattractant protein (MCP)-1.[115] Additionally, in human podocytes exposed to high glucose, TGR5 activation-induced mitochondrial biogenesis, decreased oxidative stress and increased fatty acid β-oxidation,[115] thus further suggesting a favorable effect of TGR5 activation in the kidney to protect against renal disease.

FRUCTOSE AND MLKD

Fructose metabolism and pathology in MLKD

Fructose that is mainly metabolized by the liver in humans is commonly found in high-fructose corn syrup (HFCS) and sugar-sweetened beverages (SSB).[117] Due to its lipogenic potential, an increased fructose intake may also promote the development of MASLD.[118] Fructose intake is nearly 2-3 fold higher in patients with MASLD than in healthy controls.[119] Additionally, serum uric acid concentrations are increased in individuals who consume HFCS-sweetened beverages compared with those consuming SSB.[118] Increased fructose intake might also contribute, directly or indirectly, to the development of MLKD possibly through a fructose-induced increase in uric acid concentration and/or a fructose-induced stimulation of hepatic lipogenesis.

Fructose-induced gut microbiome changes and MLKD

Various human gut microbiota species encode fructose uptake and metabolizing genes, thus fructose may contribute to the development of MASLD through effects on the gut.[120] Increased fructose consumption may contribute to intestinal dysbiosis as observed in recent studies. Experimentally, it has been reported that the composition of the phyla *Bacteroidetes* or *Proteobacteria,* which are the major phyla constituting the Gram-negative bacteria, was substantially increased in mice fed with high fructose intake.[121] Alteration of the Gram-negative bacteria, featured by bacterial endotoxin or LPS, was a significant factor for increasing gut permeability and inducing low-grade inflammation.[122] On the other hand, dietary fructose intake increases the abundance of *Escherichia*, which is required for the generation of trimethylamine that is metabolized into TMAO, a risk factor for CKD.[117] It is believed that bacteria are coupled with the host pathologies of MLKD in the presence of high fructose intake.[123]

VIT D AND MLKD

Vit D metabolism and pathologies in MLKD

Vit D is an essential steroid hormone, which is synthesized initially in the skin, predominantly in the liver to produce 25-hydroxyvitamin D, and dominantly occurs in the proximal tubule of the kidney to generate 1α,25-dihydroxyvitamin D.[124] Vit D deficiency (VDD) is frequently present in MLKD, with an estimation of over 1 billion people worldwide suffering a Vit D deficiency (<15 ng/mL) or Vit D insufficiency (<30 ng/mL).[4] Nelson et al.[125] found that VDD is associated with increased histologic severity of hepatic steatosis, ballooning, lobular inflammation grade and fibrosis in people with MASLD, possibly through upregulating liver tissue expression of multiple genes involved in hepatic inflammation and oxidative stress. On the other hand, VDD is a risk factor for all-cause mortality in patients with advanced CKD due to disturbance of calcium and phosphorus homeostasis, dysregulation of the innate and adaptive immune system, and low-grade chronic inflammation.[126] Conversely, patients with CKD are also susceptible to developing VDD, which may further exacerbate the progression of CKD.[126]

Vit D-induced gut microbiome changes in MLKD

Recent studies have revealed the functions of Vit D, particularly its role in regulating the immune system, one of which is mediated by a Vit D-induced modulation of gut microbiota.[127] Bacterial-produced LPS is involved in developing low-grade inflammation and activating the immune system in MASLD. Besides, gut microbiota can interact with the progression of MASLD, possibly through toll-like receptors (TLR), expressed on the gut epithelium, to mediate immune functions and stimulate inflammation.[128] Meanwhile, the immune system is also affected in patients with CKD, particularly TLRs, which play an essential role in synthesizing multiple proinflammatory cytokines in response to a bacterial challenge.[129] VDD causing intestinal dysbiosis, such as an increase in *Bacteriodetes* and *Proteobacteria* phyla, may contribute to the dysregulation of the immune system of host pathologies in MLKD.[130]

POTENTIAL TREATMENTS FOR MLKD BY ALTERATION OF GUT MICROBIOTA

Despite there being no single definitive treatment available for MLKD, drugs like vitamin E, statins, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter 2 (SGLT2) inhibitors were extensively reviewed.[14] In particular, GLP-1RAs and SGLT2 inhibitors, which are drugs approved for the treatment of type 2 diabetes, have the potential to benefit MLKD due to their abilities to reduce obesity and improve MASLD and CKD at least partly via regulating gut microbiota.[123] Experimentally, the GLP-1RA liraglutide can modify the gut microbiota structure by increasing *Lactobacillus reuteri* species, which enhance the weight-loss and fat-browning effects of GLP-1RAs.[131] Conversely, SGLT2 inhibitors can reduce metabolites from uremic toxins to improve CKD by increasing *Akkermansia* and *Lachnoclostridium* species.[132]

CONCLUSION

A growing body of experimental and clinical evidence indicates that alteration of metabolites from the intestine and BA metabolism can influence the physiopathology of MLKD.[21,31] BAs and microbiota signatures could serve as non-invasive diagnostic biomarkers[27,68,78] and potential therapeutic targets for MLKD,[133,134] but further research is needed. The presence of MASLD and advanced liver fibrosis is associated with a higher prevalence and incidence of CKD,[28,135] and certain circulating BAs, increased fructose intake, VDD and altered gut microbiota may influence the development and progression of CKD via various mechanisms. GLP-1RAs and SGLT-2 inhibitors are attractive and promising treatments for MLKD, partly exerting their beneficial effects through drug-induced changes in the gut microbiota composition.[136,137] Three individual BAs are significantly higher in MASLD patients with coexisting CKD, and FXR and TGR5, as two BA-associated receptors, are potentially involved in the development and progression of MLKD.[115,138] Reliable biomarkers of BAs and their signaling pathways and microbiota signature are now needed to test therapeutic responses in MLKD.

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Authors' contributions

Dan-Qin Sun, Ming-Hua Zheng and Wen-Ying Chen drafted the manuscript and prepared the figures. Jia-Hui Zhang and Liang Luo collected the paper. Li-Li Chen drew the figures. Christopher D. Byrne, Giovanni Targher, and Yan Ni contributed to writing and proofreading the manuscript.

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Conflicts of Interest

The authors declare no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary material is available at Clinical and Molecular Hepatology website (http://www.e-cmh.org).

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