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Review Article

Reasons for using carnitine in managing dioxins-induced metabolic dysfunction-associated steatotic liver disease: A scoping review

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Abstract

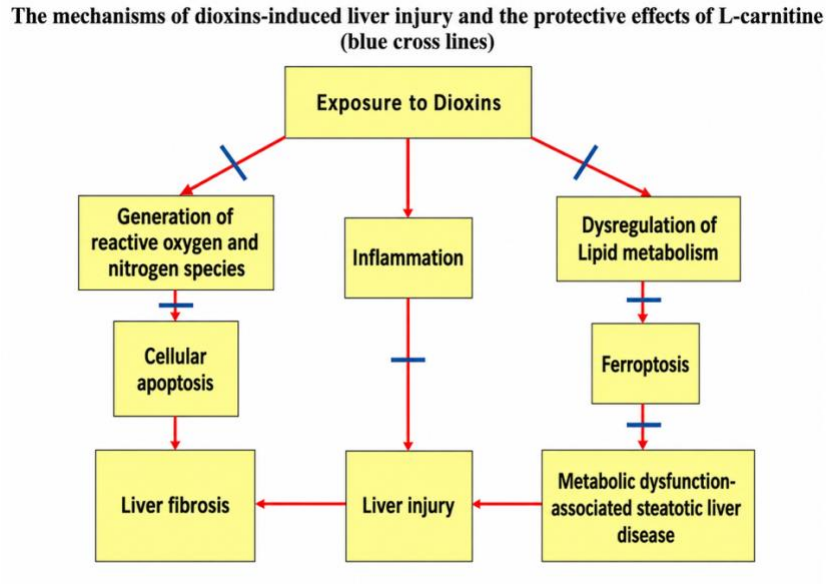
Introduction: Preclinical studies and epidemiological observational surveys showed that dioxin is a toxic substance that causes hepatic steatosis, metabolic dysregulation, insulin resistance, and type 2 diabetes mellitus. Workers in industries who live near the contaminated areas or consume contaminated food are at risk of metabolic dysfunction-associated steatotic liver disease (MASLD).

Materials and Methods: This scoping review was conducted according to the Joanna Briggs Institute (JBI) methodology and summarised the published literature on the mechanisms of action of carnitine (s) that counteract the mechanisms of dioxin(s)-inducing MASLD/MDAFLD/NAFLD/NASH/ in the preclinical studies. We addressed this exploratory review as a broad question and did not intend to conduct a systematic review; for that reason, we did not follow PRISMA guidelines.

Results and Discussion: The mechanisms by which dioxin-induced MASLAD can be counteracted by L-carnitine or acetyl-L-carnitine at the same site of dioxin effects are discussed in this scoping review. Carnitine acts as a metabolic antagonist against dioxin, according to the findings of preclinical, clinical observational, controlled clinical trials, and meta-analysis studies. Therefore, using competitive or non-competitive aryl receptor-blocking drugs to stop dioxin's harmful effects is not necessary.

Conclusion: L-carnitine or acetyl-L-carnitine as a supplementary nutrient could prevent or improve the clinical picture of MASLD in people at risk of dioxin toxicity.

Graphical Abstract



Keywords

acetyl-L-carnitine; aryl hydrocarbon receptors; carnitine; dioxin; metabolic dysfunction associated steatotic liver disease; reactive oxygen species

Introduction

Recently, in June 2023, during the European Association for the Study of the Liver Congress in Vienna, a transformative revolution happened in hepatology generally and in fatty liver terminology specifically. Instead of the old term of non-alcoholic fatty liver disease (NAFLD), a more reasonable broader substitute, metabolic dysfunction-associated steatotic liver disease (MASLD), became the spotlight because it can cover huge and diverse causes of steatosis under its umbrella (Rinella et al. 2023). Among the five common and well-known cardiometabolic risk factors, at least one is certainly included in these updated definitions, while individuals without a known cause for steatosis or metabolic risk factors are categorized as cryptogenic steatotic liver disease (Rinella et al. 2023). Nowadays, the most common cause of systemic complications and cirrhosis of the liver is known to be induced by MASLD, which usually starts with lipid droplet accumulation within hepatocytes, causing lipotoxicity and inflammation, magnified according to the genetic susceptibility of affected individuals. Then, activation of various inflammatory cells such as macrophages and hepatic stellate cells augments the synthesis of intracellular matrix and subsequent hepatic fibrosis known as metabolic associated steatotic hepatitis (MASH) (Grgurevic et al. 2020). Advanced fibrosis may easily shift to an irreversible advanced stage of hepatic cirrhosis and related complications such as hepatocellular carcinoma (Grgurevic et al. 2020). The 10th revision of the International Classification of Disease (ICD-10) created by WHO in 1983, is one of the widely used codes for diagnosis of disease or clinical presentations/complaints for many illnesses, including Non-Alcoholic Fatty Liver Disease (NAFLD). As a result of new terminologies and updated nomenclatures, many studies were carried out to assess the appropriateness of using the existing ICD NAFLD and NASH codes to code MASLD and MASH, respectively (Song et al. 2024). A study performed by Hagström et al. (2024) concluded that the ICD code for previous nomenclature could be updated based on the new terminologies and definitions and be used effectively without the efforts to make new codes for MASLD and MASH. The clinical course and features of MASLD are highly variable among different individuals and cannot be easily predicted. Most affected individuals remain asymptomatic until progression to cirrhosis is ensured. Others may complain of right upper quadrant pain, reduced health-related quality of life, psychological symptoms and fatigue related to sarcopenia which are nonspecific to liver disease at early stages of fat disposition in the hepatocytes (Spengler and Loomba 2015). Elevations in the levels of serum alanine

aminotransferase (ALT) and aspartate aminotransferase (AST) may also occur as a result of hepatocellular injury, and sometimes the level fluctuates over time especially at early stages of the disease (Torres et al. 2012). These symptoms are not easily recognized by patients and physicians as characteristic of MASLD, especially in patients with comorbidities (Younoss et al. 2020). Thus, the variable nature of the disease presentation, especially in those with generally good health conditions, may make it difficult for most patients to accept the fact of being diagnosed with MASLD even if they are at risk of early development of complications (Eskridge et al. 2021). With progression to more advanced stages, the patients may present with itching, ascites, hepatic encephalopathy, variceal bleeding and even thrombocytopenia (Eskridge et al. 2023).

The change in NAFLD terminology to MASLD was deemed necessary to include the coexistence of hepatic steatosis broadly and at least one of the following risk factors for cardiometabolic diseases such as obesity evidenced by high body weight or large waist circumference, impaired glucose metabolism, elevated blood pressure, high level of triglyceride (TG), and low level of high-density cholesterol (HDL-C) (Chalasani et al. 2018) (Fig. 1).

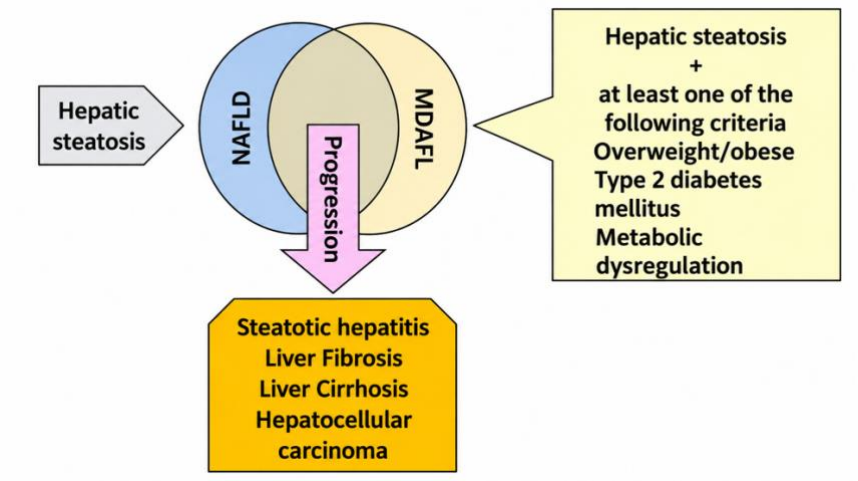


Figure 1. Overlapping features between hepatic steatosis and metabolic dysfunction associated steatosis liver disease with their progression.

Exceptions are underweight patients with MASLD (Younossi et al. 2018). A retrospective study by Yoneda et al. (2021) analyzed 2,452,949 MASLD patients' registered data to examine cardiovascular disease (CVD) as an associated risk factor. The result showed that the incidence rates of CVD were 1.01 (95% CI, 0.98 to 1.03) and 2.69 (95%CI, 2.55 to 2.83) per 1000 person-years in the non-MASLD and MASLD groups, respectively. Furthermore, the overall prevalence of hypertriglyceridemia and diabetes was 13.6 and 4.3%, respectively, in the non-MASLD group versus 64.1 and 20.6% in the MASLD group, which concluded that the risk for CVD is increased with elevated triglyceride and blood glucose level. A meta-analysis of 20 studies investigated the association of central obesity with the development of MASLD after adjusting for general obesity and found that the pooled odds ratio in waist circumference and body mass index was of 2.34 (95%CI, 1.83 to 3.00) and 2.85 (95%CI, 1.60 to 5.08), respectively (Pang et al. 2015). On the other hand, other studies linked MASLD to hypertension, and a meta-analysis of 11 studies tried to discover the nature and strength of this association (Li et al. 2022). Eventually, it concluded that the presence of elevated blood pressure was significantly associated with an increased risk of incident MASLD (hazard ratio 1.63; 95%CI, 1.41 to 1.88) and a bidirectional association between the two conditions exists independently of cardiometabolic risk factors. Metabolic dysfunction-associated steatotic liver disease (MASLD) is a risk factor for liver cirrhosis, hepatocellular carcinoma, and systemic complications such as cardiovascular diseases, type 2 diabetes mellitus (T2DM), chronic kidney disease or systemic inflammation, etc. (Angulo et al. 2015; Adams et al. 2020; Targher et al. 2024; Thomas et al. 2024).

Dioxins are a group of compounds chemically related to polyhalogenated organic compounds, including polychlorinated dibenzo-p-dioxins (PCDDs) such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), polychlorinated biphenyl, polychlorinated dibenzofurans, and polybrominated analogues, which are considered persistent environmental pollutants (Tuomisto 2019). These compounds are eliminated slowly from animals, humans, and the environment, making them persistent organic chemicals. The mechanism of toxicity occurs through the binding of dioxins to the aryl hydrocarbon receptor (AhR). Dioxins are principally

produced as unintentional byproducts of various industrial processes, particularly those involving combustion, or it may occur from natural sources, e.g., food contamination (red meat, fish and dairy products); combustion processes (waste incineration and burning of fuels); and chemical manufacturing (chlorine, halogenated organic chemicals, and papers). Also, forest fires and volcanic eruptions can contribute to producing dioxins (Kulkarni et al. 2008). Therefore, it is expected to get dioxin toxicity in the population when the following factors are provided: contaminated food; workers in industries (e.g., paper or herbicides and pesticides industries), people who live near the industries, and certain people are more vulnerable to dioxin toxicity like children, pregnant women, breastfed infants, and those with a lower socioeconomic status because they lived in poor or highly industrialized contaminated areas (Weir 2005; Schecter et al. 2006; EFSA Panel on Contaminants in the Food Chain et al. 2018). Acute, subacute and chronic toxicities affect many organs and systems in the body (Fig. 2). The chronic toxicity of dioxins is associated with: cancer (soft-tissue sarcoma, non-Hodgkin lymphoma, and lung cancer); disrupts hormonal (thyroid, estrogen and progesterone) signaling pathways causing many reproductive and metabolic diseases; developmental impairment (intrauterine growth retardation, cognitive impairments, and developmental delays in children); cardiovascular events; and hepatic toxicity (NAFLD and cirrhosis) (Chen et al. 2010; Całkosiński et al. 2014; Hattori et al. 2014; Petriello et al. 2018; Vuong 2022). In addition to the determination of circulating levels of dioxins which are expressed per gram lipids, there are certain specific and non-specific biomarkers indicating exposure to the dioxins. These biomarkers are hepatocellular enzymes, inflammatory markers, hepatic accumulation of lipids, hormonal assay, oxidative stress markers (e.g. superoxide dismutase), lipid peroxidation marker (e.g. malondialdehyde (MDA), which is also used for assessment of ferroptosis), and DNA methylation markers (Yoshida and Ogawa 2000; Das et al. 2017; Wang et al. 2024).

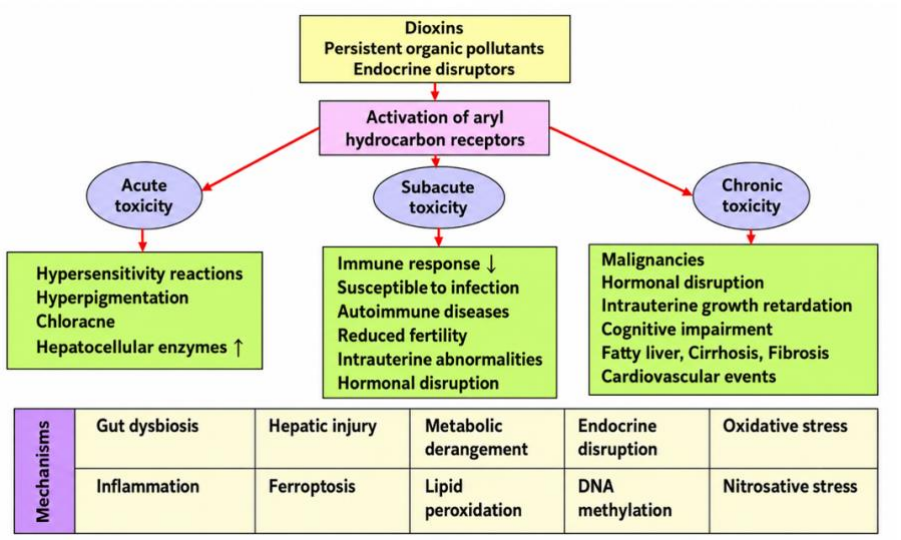


Figure 2. Dioxins-induced toxicities and the proposed mechanisms of toxicities.

Carnitine is a natural nutrient substance formed inside the body (endogenous), and it can be obtained from exogenous sources in the diet. It transports the long-chain free fatty acids into mitochondria for β-oxidation. In humans, it is available as free carnitine or acetylated derivatives. Methionine, lysine, niacin, pyridoxine, ascorbic acid, and iron are the precursor sources of endogenous L-carnitine, which makes up 25% of total body levels. In contrast, exogenous L-carnitine, which makes up 75% of total body levels, is found in dairy products, fish, and red meat; and as pharmaceutical supplements for individuals with nutritional deficiencies (Rebouche 1992). The circulating L-carnitine levels are significantly lower in women than men, and a plasma level of less than 20μmol/L indicates L-carnitine deficiency in all age groups (Valkner and Bieber 1982). Since acetyl-L-carnitine is easily absorbed from the gut, it has a higher bioavailability than L-carnitine.

Acetyl-L-carnitine has potential therapeutic uses in neurodegenerative conditions, e.g., Alzheimer's dementia because it crosses the blood-brain barrier. Despite carnitines having numerous pharmacological properties that mitigate the detrimental consequences of NAFLD, their use as therapeutic medicines has not been fully explored. Clinical studies showed that many

medicines are useful in the management of NAFLD, and they are acting in different directions against the risk-associated factors, some of them improve the full picture of NAFLD, while others improve some clinical findings of NAFLD. Table 1 summarizes the pharmacological intervention reported in the clinical studies for treating fatty liver disease (Rong et al. 2023). We hypothesized that carnitine or its derivatives could prevent the mechanisms of action of dioxin-induced NAFLD because they both have a similar set of effects. This scoping review's goal is to provide an answer to the question, "Do carnitines have a clinical application in the management of NAFLD?" Taking into account that dioxins are ecologically harmful chemicals that cause NAFLD with various effects.

Table 1. Pharmacotherapy for non-alcoholic fatty liver disease

Groups	Drug(s)	Mechanism of action	Net results
Thyroid hormone receptor-β agonists	Resmetirom	Pleiotropic	Reduces intra-hepatic lipid accumulation Improves mitochondrial function of hepatocyte
Anti-diabetes type 2	Liraglutide Semaglutide Dulaglutide	Glucagon-like peptide-1 receptor agonist	Improves insulin resistant Improves liver fatty content; improves liver enzymes Reduces body weight Do not affect liver fibrosis
	Empagliflozin Ipragliflozin Dapagliflozin Canagliflozin	Sodium-glucose co-transporter inhibitors	Improves liver fatty content; improves liver enzymes Reduces body weight Reduces hepatocellular inflammation Improves hepatic steatosis and fibrosis
	Metformin	Reduces endogenous glucose production Activates AMPK Inhibits mitochondrial glycerophosphate dehydrogenase	Reduces body weight Improves liver fatty content; improves liver enzymes Reduces hepatic steatosis
	Pioglitazone	Peroxisome proliferator-activating receptor PPAR-γ agonists	Improves insulin resistant Improves steatosis Improves inflammation Improves liver injury Improves liver fibrosis
Lipid-lowering agents	Simvastatin Atrovastatin Rosovastatin	Blocks 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase	Reduces the development of steatosis Reduces liver fibrosis Reduces the systemic complications of fatty liver
	Ezetimibe	Inhibits intestinal absorption of cholesterol	Improves liver fibrosis Do not affect hepatic steatosis
Endogenous synthetic bile acid	Ursodeoxycholic acid	Antioxidant Anti-inflammatory Protects mitochondria	Inhibits inflammation Improves insulin resistance
Farnesol X receptor agonist	Obeticholic acid	Enhances insulin sensitivity Inhibits the synthesis of bile acid Promotes mitochondrial oxidation of fatty acids	Reduces hepatocellular inflammation Reduces liver fibrosis
Probiotics, prebiotics, and synbiotics	Fructo-oligosaccharides Lactobacillus bulgaricus and Streptococcus thermophilus Bifidobacterium preparations and Lactobacillus acidophilus Saccharomyces boulardii	Counteracts gut dysbiosis	Improves insulin resistant Reduces fatty liver content Improves hepatocellular enzymes Inhibits inflammation Reduces hepatic steatosis
Peroxisome proliferation-activated receptor agonist	Saroglitazar	A dual PPRA-α/γ agonist	Improves insulin resistant Reduces fatty liver content Reduces liver fibrosis
	Lanifibranor	Pan PPRA agonist	Inhibits liver fibrosis

Materials and Methods

This scoping review was conducted according to the Joanna Briggs Institute (JBI) methodology for scoping (https://synthesismanual.jbi.global, https://doi.org/10.46658/JBIMES-24-09). This scoping review summarised the published literature on the mechanisms of action of carnitine (s) that counteract the mechanisms of dioxin(s)-inducing MASLD/MDAFLD/NAFLD/NASH/ in the preclinical studies. We addressed this exploratory review as a broad question and did not intend to conduct a systematic review; for that reason, we did not follow PRISMA guidelines.

Research question and search strategy

The research question was "What are the mechanisms of action of carnitine (s) that attenuated or counteracted the dioxin(s)-inducing fatty liver, to be a reason for using it in the management of MASLD/MDAFLD/NAFLD/NASH?". The relevant information on the mechanisms of action of dioxin (or its derivatives) in inducing MASLD/MAFLD/NAFLD/NASH as well as the mechanism of action of carnitine (or its derivatives) that is helpful in the management of these pathological conditions was obtained from a literature search conducted through MEDLINE (via PubMed), European PMC, Semantic Scholar, Dimensions, Scopus and Web of Science. Medical subheadings (MeSH) terms used for the search were "metabolic dysfunction associated steatotic liver disease", "non-alcoholic fatty liver disease", "non-alcoholic steatotic hepatitis", "dioxin (s)" and "carnitine (s)". The quality of studies using the JBI SUMARI Critical Appraisal Checklist was followed, and any disagreement was resolved by declining the study. Only full manuscripts written in English were considered.

Results and Discussion

According to the mechanisms of the dioxin-inducing fatty liver and the actions of carnitine at these mechanisms, the following sections summarized the results that explained why carnitine could be a promising agent against dioxin toxicity.

Metabolic antagonism of carnitine against dioxin-induced fatty liver

Oxidative stress syndrome: the antioxidant properties of carnitine

The role of reactive oxygen species (ROS) in the development of MASLD is related to the upregulation of the lipid peroxidation process (García-Monzón et al. 2000; Sanyal et al. 2001; Videla et al. 2004), hepatic iron overload, and hyperinsulinemia (Muriel 2009). The sources of oxidative stress in this pathological condition are the oxidation of free fatty acids, forming hydrogen peroxides, superoxide anions, and lipid peroxides (Nehra et al. 2001). The metal iron is a direct pro-oxidant metal, and it is involved in the enzymatic catalytic process in the production of ROS. There is evidence that insulin under the state of hyperinsulinemia in MASLD can produce ROS (Goldstein et al. 2005) and stimulate certain growth factors, which are responsible for inducing the profibrogenic process in the liver (Wanless et al. 1989). One mechanism of dioxin-induced liver toxicity is the activation of the AhR in the hepatocytes, which results in a continuous production of higher levels of ROS and a significant increase in lipid droplets in the liver, producing a similar change observed in NAFLD (Furue et al. 2021; Ohashi et al. 2018). So, it is reasonable to suggest that L-carnitine could have promising beneficial effects on MASLD by inhibiting the generation of ROS and counteracting the accumulation of hepatic lipids and hypertriglyceridemia induced by dioxins (Choi et al. 2020). Synthesized carnitine in the liver showed hepatoprotection against toxins, including ammonia and inflammatory mediators in hepatic encephalopathy (Martí-Carvajal et al. 2019). This hepatoprotective effect is not related to the antioxidant property, but to its metabolic effect by reducing the ammonia output urea cycle. In addition, patients with chronic liver diseases are more likely to have low plasma levels of carnitine (Hanai et al. 2020). Moreover, the creatinine fractions detected by tandem mass spectrometry are significantly associated with stages of liver cirrhosis assessed by the Child-Pugh score (Miyaaki et al. 2020). The mechanism of L-carnitine action in the NAFLD is still unclear. The isomer D-carnitine lacks biological activity, but it inhibits the carnitine acetyltransferase and ultimately reduces the formation of acetyl-L-carnitine (Vashistha and Bhushan 2015). In contrast to L-carnitine, it has been found experimentally that D-carnitine supplementation induces hepatic inflammatory changes, production of ROS, and cellular apoptosis (Li et al. 2019). The antioxidant property of L-carnitine is achieved via the following mechanisms:

i. Scavenging superoxide anion, hydrogen peroxide, and 2,2-diphenyl-1-picrylhydrazyl;
ii. Inhibiting the free radical formation by chelating the metals (e.g., iron); inhibiting the enzymes that played a role in the production of ROS (e.g., xanthine oxidase);

iii. Upregulatimg the antioxidant activity of catalase, glutathione peroxidase, glutathione reductase, and nitric oxide synthetase (endothelial) (Modanloo and Shokrzadeh 2019).

Metabolic derangements, including hepatic lipids and the development of Type 2 diabetes mellitus

An accumulation of fat at least ≥ 5% of the liver weight is considered the onset of MDAFL, and the grade of MASLD is grouped according to the accumulated percentages of fat (Chalasani et al. 2018). Hepatic lipids are regulated by four factors (Badmus et al. 2022):

i. Lipids uptake. It is regulated by fatty acid binding-proteins (FABPs). FABP-1 plays an important role in this process, and significantly higher levels of FABP-1 are significantly correlated with hepatic steatosis in MASLD (Lu et al. 2023). A significant expression of the cluster of differentiation 36 (CD36) is associated with a significantly high hepatic fat content (Miquilena-Colina et al. 2011).

ii. *De novo* lipogenesis: Dysregulation in the acetyl-CoA carboxylase, fatty acid synthase, and stearoyl-CoA desaturase-1 resulted in hepatic steatosis and hypertriglyceridemia (Hong et al. 2020). Increased activity of *de novo* lipogenesis led to the production of toxic lipid species that cause non-alcoholic steatotic hepatitis (Badmuset al. 2022).

iii. Lipid β-oxidation: As a result of lipid accumulation, ω-oxidation of fatty acids by cytochrome P450 enzymes has occurred and generated ROS. Normally, the beta-oxidation of fatty acid occurs in mitochondria, and peroxisome proliferator-activated receptor-α (PPARα) plays a role in this process. It has been found that a decline in the expression of PPARα is associated with advanced MASLD and liver fibrosis (Francque et al. 2015).

iv. Exportation of fatty acids: This process is achieved by apolipoprotein B100 and microsomal triglyceride transfer protein. A close relationship between a defect or down-regulation of microsomal triglyceride transfer protein is associated with the development of MASLD (Peng et al. 2014).

Dioxin-like polychlorinated biphenyls cause liver steatosis by inducing alteration in the gut microbiome, leading to a disruption in the lipid metabolism. At the same time, the non-dioxin derivatives act through different mechanisms by promoting diet-induced NAFLD (Wahlang et al. 2019). Livers of mice exposed to TCDD for 28 days showed a significant increase in free fatty acid, triglycerides, cholesterol esters, ceramides, and inhibiting secretion of very low-density lipoprotein, which is similar to that picture of hepatic steatosis (Nault et al. 2017). TCDD induced hepatic inflammation by accelerating arachidonic acid's metabolism to up-regulate cyclooxygenase and lipoxygenase's activity to produce leukotrienes, leading to steatohepatitis (Doskey et al. 2020). Some authors explained the progression of steatosis to steatohepatitis and fibrosis to the one-carbon metabolism induced by persistent AhR activation (Fling et al. 2020); others believed that incomplete β-oxidation of fatty acid is the reason for the progression (Cholico et al. 2021). TCDD targeted the aryl hydrocarbon receptor in the intermembrane space of organelles in mitochondria (miAhR), leading to degradation of miAhR and dysfunction of mitochondria, which clinically manifested as metabolic dysfunction, e.g. hepatic steatosis (Hwang et al. 2016). T2D is a contributing factor, and one of the diagnostic criteria of MASLD is also reported as a result of dioxin toxicity (Gang et al. 2022; Lee et al. 2022).

Dioxin is one of the six persistent organic pollutants that contribute to altering the metabolic and oxidative stress pathways, impairing glucose homeostasis and β-cell dysfunction (Hoyeck et al. 2022). There is much evidence that reports an association between dioxin exposure and the development of diabetes, as dioxin is considered an endocrine disruption pollutant. In one study carried out on 2898 participants who lived in an area with factory-released dioxin, 425 diabetes (14.7%) subjects were identified, and a higher serum dioxin level is a risk factor for developing diabetes mellitus (Huang et al. 2015). A systematic review and meta-analysis included 10 epidemiological studies that showed an inconsistency in the association between dioxin exposure and diabetes mellitus (Goodman and Narayan 2015). A recent preclinical study showed that the signalling of AhR in the beta-cell of the pancreas is a regulatory key for beta-cell function and glucose homeostasis (Hoyeck et al. 2024). Dioxin, like any endocrine-disrupting chemical, can induce insulin resistance by its direct effect on the β-cell of the pancreas, in addition to its indirect effect by inducing adipogenesis, stimulating lipid storage, and altering the production of adipocytokines via activation of peroxisome proliferator-activated receptor-alpha (PPARα) (Street et al. 2018; Papalou and Kandaraki 2019; Rotondo and Chiarelli 2020).

L-carnitine specifically antagonized the effect of dioxin on the lipid metabolism as it stimulates the lipolysis and inhibits the lipogenesis in the adipocyte, i.e. a metabolic antagonism at the molecular cell level (Lee et al. 2006). Carnitine derivatives can ameliorate steatosis by facilitating the β-oxidation of fatty acids and improving the metabolic dysfunction associated with a fatty liver, e.g. reducing the circulating glucose, enhancing insulin sensitivity, preserving the function of mitochondria, and restoring the oxidative phosphorylation activity (Hong and

Lee 2021). Others suggested that L-carnitine reduces the hepatic lipids by reducing the production of ROS and increasing the activity of proteins that regulate the antioxidant properties, e.g. NrF2 and superoxide dismutase (Montesano et al. 2020). In addition, L-carnitine is useful in the management of T2DM. A meta-analysis that included 21 randomized clinical trials reported that a supplementation of one-gram daily carnitine could reduce body mass index and improve the glycemic and lipid profiles in T2DM patients (Mirrafiei et al. 2024). Preclinical studies demonstrated L-carnitine or its analogues could counteract the insulin resistance. A randomized controlled clinical trial showed supplementation of L-carnitine tartrate (500 mg twice daily for eight weeks) reduces the body mass index, fasting plasma glucose, insulin, and homeostatic model assessment of insulin resistance, when it is administered as monotherapy or in combination with synbiotics (Fallah and Mahdavi et al. 2023). In a systematic review and meta-analysis that included five studies, it was found that L-carnitine is a useful remedy to treat patients with insulin resistance (Xu et al. 2017). Therefore, L-carnitine does act as an AhR antagonist, but it minimizes the metabolic effects resulting from activation of hepatic AhR.

Anti-inflammatory effects

In an experimental animal model, TCDD-induced liver injury in the form of hepatic steatosis, significant deposition of lipid and neutrophil accumulation in the liver, elevated serum alanine aminotransferase enzyme, and interleukin 6 were observed (Olivero-Verbel et al. 2021). In another study, mice treated with TCDD for two weeks showed histopathological findings of liver fibrosis, which is associated with upregulation of the inflammatory biomarkers, including interleukin 1β and tumor necrosis factor-α (Pierre et al. 2014). Exposure to dioxin derivatives is associated with significant elevation of bilirubin and hepatic enzymes (ALT, AST, and alkaline phosphatase) (Kumar et al. 2014), accompanied by triggering to form and accumulate the lipid (i.e. *de novo* lipogenesis (Kawano and Cohen 2013; Geisler et al. 2017; Ipsen et al. 2018). Workers exposed to dioxins are at health risk for inflammation and liver diseases due to alterations in the lipid metabolism leading to high triglyceride deposits, ceramide, and sphingoid (Liang et al. 2021). In the preclinical studies, supplementation of L-carnitine reduces lipid accumulation, oxidative stress, hepatic fibrosis, and systemic inflammation, which is related to its effects on the expression of α-smooth muscle actin, peroxisome-activated receptor gamma, and nuclear factor kappa B (Mollica et al. 2020). Although L-carnitine did not antagonize the effect of dioxins at AhR, it specifically cancels the metabolic effects of dioxin at a molecular cell level (i.e. metabolic antagonist). It could be suggested that L-carnitine supplementation is useful to people exposed to dioxin and developed liver injury for the following reasons:

i. Dioxin is a persistent and continuous toxin that induces hepatic lipotoxicity;
ii. There is deprivation of the endogenous L-carnitine because it is synthesized in the liver;
iii. Continuous L-carnitine supplementation will support the liver against inflammation, apoptosis, and oxidative stress that followed or accompanied the dioxin-induced hepatic lipotoxicity.

Anti-apoptotic effects

It has been documented that dioxins induce cellular apoptosis in a dose-dependent manner, and it is associated with a generation of ROS and nitrative reactive species (NRS; e.g. nitric oxide) (Yang and Lee 2010). The apoptotic effect that is mediated by ROS and NRS can be blocked by using ROS or NRS inhibitors. On the other side, acetyl-L-carnitine provides an antiapoptotic effect via inhibition of the lipid peroxidation process and restoring the antioxidant activity of glutathione (Zidan et al. 2018). Another study demonstrated that L-carnitine protects the platelet count and function (aggregation and viability) during storage by the evidence of reducing the expression of apoptotic biomarkers (e.g. miR-326) (Norouzi et al. 2024). This indicates that acetyl-L-carnitine can act as a non-specific inhibitor of the dioxin that is mediated by blocking ROS production and not through blocking the AhR.

Anti-fibrosis

Preclinical studies demonstrated that dioxin accelerates the development of liver fibrosis in mice fed high-fat (45%) by the evidence of increasing hepatic collagen staining and a significant elevation of serum ALT and AST levels (Duval et al. 2017). Other studies demonstrated the association between liver fibrosis and inflammation upon subacute-chronic exposure to the dioxin, suggesting that due to the overproduction of ROS and depletion of superoxide anion dismutase, in parallel increasing levels of interleukin 1β and Tumor necrosis factor-α, as a result of activation of AhR (He et al. 2013; Pierre et al. 2014). Patients with chronic hepatitis who live in dioxin-contaminated areas are more likely to have the liver fibrosis stage with a significantly high aspartate aminotransferase (Pham et al. 2022). Recently, a preclinical study demonstrated that acetyl-L-carnitine significantly prevents the development of liver fibrosis induced by

propionic acid due to its anti-inflammatory and antioxidant properties (Alhusaini et al. 2023). Another clinical observational study of a small sample size demonstrated that a ten-week administration of L-carnitine significantly reduces the hepatic enzymes and improves the histopathological findings of NAFLD; it does not improve the scoring of hepatic steatosis or fibrosis (Lyu et al. 2024). These observations indicate that carnitine use is still in the preclinical studies for the management of MASLD.

Anti-ferroptosis

The main feature of ferroptosis is the accumulation of the byproducts of the lipid peroxidation process that is initiated by ROS. The precise link between ferroptosis and MASLD is still not well explored (Feng et al. 2022). Tong et al. (2023) reported that using liprostatin-1 (a ferroptosis inhibitor) alleviates most of the MASLD characteristics in mice, including reducing hepatic triglycerides, inhibiting lipid peroxidation products, e.g. MDA, and attenuating the metabolic derangements related to insulin resistance, mitochondrial dysfunction, and even liver fibrosis. An ex vivo experimental study showed a significant accumulation of MDA in the hearts of rats exposed to the TCDD, indicating that dioxin activates ferroptosis in the tissue (Mahdi et al. 2019). L-carnitine supplementation had no significant effect on malondialdehyde levels in patients with osteoarthritis (Baghban et al. 2021). It is interesting to mention herein that ROS play a major role in the activation of the lipid peroxidation process and ferroptosis, but neither dioxins nor carnitines showed specific effects on the ferroptosis process.

Clinical evidence of using carnitine as an effective antagonist against dioxin-induced hepatic toxicity

Table 2 shows that there is evidence that dioxins could cause fatty liver disease associated with metabolic derangement, e.g. insulin resistance and T2DM.

Table 2. Evidence of metabolic dysfunction associated steatotic liver disease induced by dioxins and ameliorated by carnitine

Drugs	Study design	Exposure/treatment	Evidences	Ref
Dioxins	Observational study	Dioxin contaminated area In Vietnam	Histopathology: comprised of hydropic degenerative hepatocytes, lymphocytes and polynuclear leukocytes; granular and lipoic degeneration; liver fibrosis ↑ Circulated TCDD levels, ↑TEQ-PCDD/Fs levels ↑ ALT and AST levels	Pham et al. 2022
	Observational metabolic study	Chinese workers exposed to Dioxins	The TEQ values range: from 29.49 to 765.35 pg/g lipid in higher-exposure persons ↓ Fatty acid β-oxidation	Liang et al. 2020
	Observational lipidomic study	Chinese male workers Exposed to dioxins	Circulating levels of accumulations of triglyceride, ceramide, and sphingoid Imbalance-free fatty acid metabolism	Liang et al. 2021
Carnitine	Controlled clinical trial	Patients with NAFLD	↑ Circulating mitochondrial DNA copy number ↓ Circulating ALT and AST	Li et al. 2023
	Meta-analysis Includes five studies	Insulin resistance	Improves the insulin-resistant	Xu et al. 2017
	Controlled clinical trial	Non-alcoholic steatohepatitis	↓ Total cholesterol, triglycerides, low-density lipoproteins, and insulin resistance Improves the clinical symptoms	Zakharova et al. 2023
	Controlled clinical trial	Hepatic steatosis and chronic hepatitis C	↓Total cholesterol, triglycerides ↓ ALT and AST levels	Romano et al. 2008
	Meta-analysis includes eight studies	NAFLD	↓ ALT and AST in adults but not in younger people ↓ Total cholesterol	Liu et al. 2023
	Meta-analysis includes five controlled studies	NAFLD	↓ ALT and AST ↓ Circulating triglyceride ↓ Insulin-resistant ↔ Body mass index, total cholesterol	Abolfathi et al. 2020
	Controlled clinical trial	NAFLD and Type 2 Diabetes	Normalised ALT level ↑ Ultrasound findings: liver attenuation index	Bae et al. 2015

Note: TCDD – 2,3,7,8 tetrachlorodibenzodioxin, TEQ – Toxic equivalency, PCDD/Fs – Polychlorinated dibenzo-p-dioxins and furans (PCDD/Fs), ALT – alanine aminotransferase, AST – aspartate aminotransferase, NAFLD – non-alcoholic fatty liver disease. ↑ – increase, ↓ – decrease, ↔ – no effect.

On the other side, meta-analysis studies and clinical trials reported significant effects of using carnitine in the management of non-alcoholic fatty liver disease with or without insulin resistance. The effects of carnitine on metabolic dysregulation showed variable results, which could be related to the optimum dose, the derivative of carnitine, the duration of treatment, and associated comorbidities. It could be useful to use acetyl-L-carnitine instead of L-carnitine because it crosses the blood-brain barrier and improves the cognitive dysfunction associated with hepatic steatosis.

Conclusions

Subclinical studies and epidemiological observational studies indicated that exposure to dioxins as persistent endocrine-disrupting chemicals is a cause of metabolic dysfunction associated with steatotic liver disease, as evidenced by hepatic steatosis and the presence of obesity, type 2 diabetes, and abnormal lipid profiles, which is due to the activation of hepatic aryl hydrocarbon receptor. Although carnitines have no antagonistic effects against aryl hydrocarbon receptors, they counteract most of the metabolic events resulting from the activation of aryl hydrocarbon receptors. Thus, carnitines' metabolic antagonist actions may be used to treat MASLD induced by dioxin, and it can be recommended as a preventive supplementary nutrient for workers exposed to dioxin or to people who live near the dioxin-contaminated areas.

Additional Information

Conflict of interest

The authors declare the absence of a conflict of interests.

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Data availability

All of the data that support the findings of this study are available in the main text.

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