In prospective and retrospective DILI studies, the annual incidence has been reported as 2.7 per 100,000 people. Furthermore, in many countries, DILI has been associated with acute liver failure. The risk factors for DILI include numerous interrelated factors, such as advanced age, sex, drug dose, genetic factors, concomitant drugs, excessive alcohol consumption, nutrition, pre-existing liver disease, diabetes mellitus, human immunodeficiency virus infection, and kidney failure. Historically, DILI has been divided into two types. Type 1 is idiosyncratic, and type 2 results from idiosyncratic reaction. Type 2 is mostly dose-independent, and can be either allergic, immunemediated, or non-allergic, nonimmune-mediated. The diagnosis of DILI is determined by a temporal relationship between drug administration and increased levels of liver enzymes and/or alkaline phosphatase, exclusion of other causes of liver damage, and rarely repeated drug challenge. There is no standardized clinical test for this condition. Drug-induced cholestasis is induced when drugs disrupt bile acid transport by inhibiting liver transporters involved in bile flow. Cholestasis can be also found in severe metabolic dysfunction-associated fatty liver disease (MAFLD) stages, alcoholic hepatitis and alcoholic cirrhosis. Drug-induced cirrhosis is associated with drugs that cause fibrogenesis and production of extracellular matrix molecules.

MAFLD is a new concept, proposed in 2020, that has been suggested to replace the term nonalcoholic fatty liver disease because it does not require the exclusion of alcoholic liver disease or viral hepatitis. It is a more accurate term for people with fatty liver and those with dysmetabolism. MAFLD is well known as a highly prevalent disease affecting a quarter of the world’s adult population and is the main cause of chronic liver disease in Europe and USA. Besides, with the very high prevalence of MAFLD and alcohol abuse worldwide, the relationship among any present study population and real-world populations is of concern. The novel MAFLD criteria concentrate on the role of dysmetabolism in fat accumulation in the liver, that is the most frequent driver of fatty liver injury progression. When fatty liver injury progresses due to preexisting MAFLD in combination with drug administration, it is defined as a dual-etiologic fatty liver disease. Recently, two studies have recommended that the MAFLD criteria are more efficient and better for perceiving patients with a higher risk of fibrosis, in contrast with nonalcoholic fatty liver disease criteria. MAFLD is diagnosed in patients when they have the hepatic manifestation of metabolic syndrome, which is diagnosed when three or more of the following conditions are found: high glucose, hypertension, obesity, high triglyceride, and low high-density lipoprotein-cholesterol. There is a growing number of clinical reports proposing that certain drugs can be more hepatotoxic in overweight patients with MAFLD, in contrast with lean patients. DILI in MAFLD appears in two particular clinical situations. First, antibiotics such as piperacillin-tazobactam, telithromycin, and some analgesics and antipyretics, like
Acetaminophen, can induce more serious and common acute liver injury. It appears that some drugs, like amiodarone and statins, do not induce hepatotoxicity more often in MAFLD patients. Other drugs like antiretroviral agents, corticosteroids, and methotrexate appear to cause the alteration of simple fatty liver to nonalcoholic steatohepatitis or exacerbate necroinflammation, pre-existing steatosis, and fibrosis. Some drugs can cause more serious acute liver injury in MAFLD because this illness is connected with the various modified activities of metabolizing enzymes such as cytochromes P450. Regarding the above-mentioned information, MAFLD is frequently connected with increased CYP2E1 activity and decreased CYP3A4 activity as well as with higher glucuronide formation. These enzymes are responsible for metabolism of, e.g., lorazepam and acetaminophen. More in vitro and in vivo research is required because the mechanisms wherewith drugs and xenobiotics are more hepatotoxic in MAFLD are not well known and more studies are a necessary in ensuring success in dealing with this issue, especially considering the worldwide epidemic of obesity.

Drugs represent an alternative cause of fatty liver disease and the term that corresponds to this injury is drug-induced fatty liver disease (DIFLD). It is a specific form of DILI, characterized by intracellular lipid accumulation in hepatocytes with steatotic changes as the predominant histopathological pattern. Although this histopathological finding is required for the diagnosis, the finding is not specific. DIFLD is often accompanied by inflammation and oxidative stress, which leads to the development of drug-induced steatohepatitis (DISH). Chronic liver injury leads to hepatocyte death, followed by the activation of stellate cells which finally results in liver tissue fibrosis. In addition, there are numerous drugs which can cause progression of steatohepatitis. In 2015, Satapathy et al. have shown that tamoxifen, an anti-estrogen drug used in the treatment and prevention of breast cancer, was frequently associated with hepatic steatosis, although rarely with cirrhosis or steatohepatitis. Moreover, the authors emphasized that chronic exposure to amiodarone, 4, 4′-diethylaminoethoxyhexestrol and perhexiline maleate rarely led to cirrhosis. It is known that phospholipidosis develops after prolonged treatment with these drugs, in a dose-dependent manner. However, it does not lead to steatohepatitis. Further investigations are needed to elucidate mechanisms by which drug-induced steatosis leads to steatohepatitis and consequently to fibrosis.

Steatosis has been reported that amiodarone-induced acute and chronic liver injury without steatosis leads to necrosis and bridging fibrosis with early-stage cirrhosis. It is well known that amiodarone-induced hepatotoxicity has been characterized by histologic steatosis, phospholipidosis and fibrosis. However, in that case report, the histopathology showed an absence of steatosis and phospholipidosis, despite years of amiodarone ingestion. This suggests that lack of formerly accepted histopathologic findings, such as steatosis and phospholipidosis, should not exclude the disease. This conclusion, however, requires further study and confirmation. Various other studies have confirmed the role of amiodarone in the induction of liver cirrhosis, with possible fatal outcomes. Nevertheless, these adverse effects were found to be rare, with an incidence of 1–3%. A long-term surveillance for liver toxicity in high-risk patients using amiodarone has been suggested by numerous researchers.

Most drugs capable of causing steatosis and steatohepatitis are known to have cationic amphiphilic structure. These drugs are divided into three groups, including drugs that cause steatosis and steatohepatitis independently, such as amiodarone and perhexiline, drugs that can accelerate latent metabolic dysfunction-associated steatohepatitis (MASH), such as tamoxifen, and drugs that may cause sporadic events of steatosis/steatohepatitis, such as carbamazepine. More details over the effects of these drugs on liver tissue will be discussed in the sections below.

**Epidemiology of DIFLD**

Recently, reported annual incidences of DILI have varied widely in population-based studies, from 2.7 to 19.1 cases per 100,000. Accordingly, the true incidence of DIFLD in the general population remains unknown. However, drug-induced steatosis (DIS) or drug-induced steatohepatitis (DISH) are generally rare but well-documented forms of DILI. According to the Drug-Induced Liver Injury Network (DILIN), approximately 27% of DILI cases have some form of steatosis with histological injury. In the study of Kleiner et al., only one case was diagnosed with the predominant pattern of microvesicular steatosis, while the remaining cases showed a combination of macrovesicular steatosis with inflammation. Previously published descriptions of pathologic changes in DILI were used as the basis for the diagnostic classification in DILIN in the prospective study by Kleiner et al. To define patterns of injury, standard hepatopathological diagnostic criteria were used. Although this included a large proportion of DIFLD in DILI cases, the DILIN prevalence may be biased by the pre-existing presence of a fatty liver. The true data on DIFLD epidemiology might become clearer after eliminating diagnostic difficulties and deficiencies in systematic reporting.

**Histology of DIFLD**

DIFLD can present as pure macrovesicular or microvesicular steatosis or as DISH. Histologically, in macrovesicular steatosis, the accumulation of large lipid vesicles (mostly triglycerides) occurs in the hepatocyte, with the nucleus becoming consequently dislocated to the periphery of the cell. As in other causes of steatohepatitis, aminotransferases are increased production of reactive oxygen species (ROS) that mainly occur due to modification of the mitochondrial respiratory chain (MRC). Microvesicular steatosis (drug-induced) is frequently the result of drug-induced damage to mitochondria. This type of steatosis can start with small droplets of fat in the cytoplasm and then increase to macrovesicular steatosis characterized by large fat droplets that shifted the nucleus to the periphery. Frequently, macrovesicular steatosis can present with mixed large and small droplets. Depending on the particular pathogenic mechanism of each lipotoxic drug, DIS/DISH can present as micro- or macrovesicular steatosis/steatohepatitis, but most cases start acutely with microvesicular injury. The latency of DIFLD before clinical manifestations may vary.
For DIS/DISH diagnosis, liver biopsy is the standard means for confirmation of hepatic cell injury and liver inflammation.52

Risk factors for occurrence of DIFLD

Some drugs cause progression of MAFLD to MASH or cirrhosis, and may also worsen the prognosis in patients with fatty liver.17 This conversion to MASH appears to involve genetic and environmental factors.17 MAFLD and obesity may enhance the risk of hepatotoxicity of various drugs.18 The possible mechanisms by which certain drugs are able to accelerate progression of MAFLD include induction of oxidative stress, diminished mtFAO, increased de novo lipogenesis, and damaged egress of VLDL from liver cells.53

Most often, DIFLD is a product of direct impact of drugs on the liver, mostly associated with the extended intake of medications. For example, long-term administration of drugs, such as amiodarone, perhexiline and diethylamino-nethoxyhexestrol, can lead to DISH. Furthermore, patients with additional risk factors, like obesity and cardiometabolic risks, are more prone to exacerbation of steatosis or steatohepatitis when irinotecan, tamoxifen and methotrexate are added to their therapy. Insulin resistance and hypertriglyceridemia in combination with antiepileptic drugs and steroids can also lead to steatohepatitis, MASH or DIFLD.27

Fatty liver injury progression is related to factors such as insulin resistance, adipose tissue dysfunction, lipid aggregation, and oxidative and endoplasmic reticulum stress. Also, increased gut permeability and increased plasma endotoxin levels can be associated with fatty liver.54-56

Besides environmental risk factors, genetics also plays a significant role in the progression of simple steatosis.57 Among patients with similar risk factors, large interindividual variability in phenotypic penetrance exists.57 Various genetic, epidemiological and twin studies have shown a strong heritability of predisposition to MAFLD.57 Apart from drugs, intrinsic (sex, age, ethnicity, liver, and renal condition) and other extrinsic (environmental chemicals, alcohol, diet, and drug-drug interactions) risk factors must be considered in any clinical algorithm associated with the fatty liver.58 There is growing evidence for a genetic contribution to the development of MASH, even though environmental risk factors play a main role in the development of simple steatosis. In various (twin, epidemiological, and familial) studies, a large variability exists in phenotypic penetrance among people with related risk factors, and a powerful heritability of sensitivity to MAFLD has been noticed.57 Studies on the role of genetics in DIFLD are still in the early phases, and more studies are needed to augment understanding of genetic variants and other risk factors in the progression of DIFLD and MAFLD.

Influence of pharmacogenetics on the risk for developing DIFLD

Alterations in genes involved in pharmacokinetics and pharmacodynamics are partially responsible for variations in drug response.58 Part of an individual’s predisposition for the development of side effects with high doses of certain drugs, like methotrexate or tamoxifen, can be explained by the patient’s genetic makeup as well as pharmacogenetics. As mentioned before, methotrexate and tamoxifen are some of the drugs that can cause macrovesicular hepatic steatosis linked to DIFLD. In the context of high-dose methotrexate toxicity, it is important to emphasize that it is unpredictable, and interindividual variability is significant. The results from the previous studies on the pharmacogenetics of high doses of methotrexate differ, and are sometimes contradictory. This can be partly explained by significant differences in the pharmacogenetics of various populations.39,59 Several genotypes have been associated with a higher risk of methotrexate toxicity, such as MTHFR 677TT (reduced activity of methylenetetrahydrofolate reductase which leads to diminished elimination of methotrexate), RFC-1 80G>A (reduced folate carrier 1, which is responsible for methotrexate entrance into the cells), and ABCB1 C3435TT (ATP binding cassette subfamily B member 1; reduced action of MDR1 and, therefore, slower elimination of methotrexate).60 The metabolisms of 5-fluorouracil depends on the enzymatic activity of dihydropyrimidine dehydrogenase. Instead, variants *2A or *13 of this enzyme are related to reduced metabolism of 5-fluorouracil, which can lead to serious side effects.61 Genetic alterations in the patatin-like phospholipase 3 gene (PNPLA3) affect the plasma levels of hepatic enzymes and risk for MAFLD development,62,63 including predisposition for fibrosis progression.54,65 The above-mentioned polymorphism is a powerful predictor of inflammation, steatosis and fibrosis66 but the role of PNPLA3 in DIFLD pathogenesis remains obscure.27 Polymorphisms of PNPLA3 are strongly associated with ethnic and interindividual variations in liver fat content.57 Hispanics were found to have a higher tendency to develop liver steatosis, unlike African-Americans.57 In addition, twin studies suggest that about 60% of alanine transaminase variability may be ascribed to genetic factors.68 Slow metabolizers for perhexiline, such as Caucasians, are at the greater danger of neuropathy and steatohepatitis. Perhexiline is catabolized by cytochrome P450 isozyme 2D6 and has a long half-life due to the slow liver clearance in slow metabolizers.69

In recent years, the genetic factors of steatosis have been studied utilizing genome-wide association techniques. Further research in the area of pharmacogenomics is needed to better understand numerous possible gene polymorphisms that might be responsible for increasing risk of DIFLD development.

Drugs that cause DIFLD

Drugs shown to cause macrovesicular liver steatosis are glucocorticoids, amiodarone, methotrexate, estrogens, tamoxifen, nonsteroidal anti-inflammatory drugs, paracetamol, 5-fluorouracil, and metoprolol.39,70-72 Drugs associated with microvesicular steatosis are valproic acid, tetracycline, aspirin, ibuprofen, zidovudine, and gluccorticoids.24,44 Drugs associated with DISH are valproic acid, tamoxifen, perhexiline, amiodarone, and propylcol.44,73 It is important to recognize the particular drugs that could cause acute liver damage on a fatty liver background or that could increase the danger of serious chronic liver disease. The hepatic accumulation of fat is not necessarily stable and DIS/DISH are reversible.74 In many cases, it is difficult to elucidate whether the fatty liver disease is a direct result of an effect on hepatic cells or a consequence of a weight gain caused by the drugs such as antidepressants or antipsychotics. Pharmaceuticals that could induce the progression or exacerbate pre-existing fatty liver to MASH and fibrosis are shown in Table 1.75

Mechanisms of DIFLD development

The main mechanisms in the development of DIFLD are thought to include lipogenesis and generation of free radicals leading to oxidative stress induction in hepatocytes.44,75 Kim et al.76 showed that amiodarone caused an increase in short, medium- and long-chain acylcarnitines in the livers of
rats, with the highest increases involving levels of acetylcar- nitine. The most probable cause of these disturbances in liv- er tissue is the effect of amiodarone on mtFAO by blocking the activity of the carnitine palmitoyltransferase-1 enzyme, thereby directly inhibiting the mitochondrial β-oxidation of acyl-CoA to acetyl-CoA and by inhibiting complexes I and II of the MRC.15,77 Another proven mechanism of amiodar- one-induced DIFLD is triggering of de novo lipogenesis by augmenting the expression of genes sterol regulatory ele-
ment-binding protein 1, thyroid hormone-inducible hepatic protein, ATP-citrate synthase, fatty acid synthase, and acyl-
CoA desaturase, which are all involved in the process of lipo-
genesis.79 Additionally, Anthérieu et al.79 demonstrated in vitro that amiodarone administration led to overexpression of genes involved in formation of lipid droplets, namely per-
ilipin-4 and adipose differentiation-related protein. Tamox-
ifen, like amiodarone, is a cationic amphiphilic compound that accumulates in liver tissue, causing liver injury.80 Its toxic effect is also achieved by impairing the mtFAO and in-
duction of de novo lipogenesis.79 A possible mechanism for the induction of hepatic steatosis includes the upregulation of SREBP-1c and its downstream lipogenesis target genes.24 Accumulation of triglycerides stimulates microsomal triglyc-
eride transfer protein expression associated with VLDL as-
sembly and secretion.80 Several in vivo studies confirmed the role of oxidative stress in tamoxifen hepatotoxicity. Like amiodarone, it causes a reduction in liver glutathione lev-
els, accumulation of oxidized form of glutathione, and lipid peroxidation.79,80 Methotrexate and especially its polyglutamated me-
tabolite are both stored in hepatocytes and exert hepatoto-
xic effects.82 Several mechanisms are proposed for the hepatotoxic effect of methotrexate, including hampering of folate entry to mitochondria, which leads to mitochondrial
peroxisome proliferator-activated receptor alpha, carnitine palmitoyltransferase-1, and fatty acid-binding protein 1), and enhancement of ROS genera-
tion by activation of the transcription factor ATF4 (which up-regulates CYP2E1; specifically, by doxycycline and mi-
nocyline).34,41,88,89 Nucleoside reverse transcriptase inhibi-
tors, such as zidovudine, didanosine, stavudine, tenofovir and abacavir, are capable of inhibiting human DNA polymer-
ase γ, leading to the decrease in mitochondrial DNA replica-
tion.90,91 Consequently, oxidative stress and accumulation of fat occur.90,91 All the above-mentioned mechanisms in-
volved in DIFLD development are summarized in Table 2.

**Current and future directions in the treatment of DI-
FLD**

A fairly common recommendation for the management of DILI and potential manifestation of DIFLD is the with-
drawal of the potential offending agent. Timely exclusion of the problematic drugs can lead to full recovery; up to 95% of patients show improvement but a few will still de-
vlop chronic liver disease.92 Criteria of withdrawal of the drugs causing DILI were published in 2009 by the Food and Drug Administration93 and are summarized in the following guidelines as follows: alanine aminotransferase or aspartate aminotransferase are >8 upper limit of normal (ULN), >5 ULN (for the period of 2 weeks), >3 ULN combined with international normalized ratio >1.5 and total bilirubin >2 ULN or levels of alanine aminotransferase/aspartate ami-
notransferase higher than 3, but followed with nausea, fe-
virulent fatigue, vomiting, rash, tenderness or pain (right upper abdominal quadrant) and potential eosinophilia.92 If there is no adequate replacement for the hepatotoxic drug, then the dose should be adjusted in order to manage the primary disease, especially in intrinsic DILI.92

Glucocorticoids are used sometimes to treat DILI and DI-
FLD, but only after a serious risk-benefit assessment. They are beneficial in patients who show notable signs of auto-
immunity or hypersensitivity, even after drug withdrawal.92 Ursodeoxycholic acid (UDCA) has a hepatoprotective effect (including for cholangiocytes), stimulatory effect on hepa-
tobiliary secretion, and prevents cellular apoptosis, as de-
scribed in 15 DILI patients.94 The effectiveness of UDCA in DILI cases lies in its improvement of the liver function abnormalities and relieving symptoms such as fatigue, pru-
ritus and jaundice.95–97 Significantly improving liver tests98 and possibly delaying liver transplantation99,100 Beneficial effects of UDCA have been shown in cohort studies and case reports after administration of the following drugs that cause liver injury, namely chlorpromazine, cyclosporine, amoxicillin-clavulanate, ticlopidine, fluoxacinill, parquat, and methotrexate.97,101–105 Rarely, individual case reports have supported the therapeutic properties of UDCA. One of those is a pediatric report of amoxicillin/clavulanic acid toxicity 4 years after the liver transplantation. Amelioration

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**Table 1. Drugs specifically hepatotoxic in DIFLD, MAFLD and obesity**

| Acute liver injury | Exacerbating pre-existing fatty liver or MASH | Promoting the transition of pre-existing fatty liver into MASH, fibrosis, or cirrhosis |
|-------------------|--------------------------------------------|-------------------------------------------------------------------------------------|
| Drugs             | Androgenic steroids, Benzobromarone, Corticosteroids, Irinotecan, Methotrexate, Tamoxifen, NRTIs, Pentoxifylline, Phenobarbital, Rosiglitazone, Tetracycline | Androgenic steroids, Benzobromarone, Corticosteroids, Irinotecan, Methotrexate, Tamoxifen |

**Note**: NRTIs, nucleoside reverse transcriptase inhibitors. Data from: Allard J et al.17 Drug-induced liver injury in obesity and nonalcoholic fatty liver disease, EASL Clinical Practice Guidelines: Drug-induced liver injury.
of the amiodarone-induced hepatotoxic effect was achieved with antioxidants such as N-acetyl-cysteine and vitamins C and E.75 Further clinical trials on humans are needed to confirm these observations.

Conclusions

DIFLD remains a great challenge for researchers and clinicians because of the lack of adequate diagnostic tools and numerous underlying pathophysiologic mechanisms involved. Therefore, many cases of DIFLD are unrecognized or confirmation of diagnosis occurs in later irreversible stages of liver disease. Elucidation of various pathways by which specific drugs cause DIFLD represents a step forward in the development of appropriate therapy. It is important to emphasize that drug withdrawal or dose adjustment are so far the best therapeutic recommendation when it comes to DILI/DIFLD cases. Nevertheless, some treatments, such as UDCA for cholestasis, have shown benefit in the early stages.98 However, the field needs more studies, especially in the use of pharmacogenetics to predict and avoid DILI, and in identifying individuals who may benefit from pharmacological interventions.

Author contributions

Conceived of and designed the article, and critically revised the manuscript (MS, TOK, VN), obtained funding, and provided administrative, technical and material support (MS), performed literature searches and wrote the manuscript (VN, LK, KD, KB), updated the text of the manuscript (TOK, NNL, SV, GYW), performed figure generation (TOK), and performed critical revision of the intellectual content (MS, GYW).

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