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Introduction:

Although non-alcoholic fatty liver disease (NAFLD) is being replaced by metabolic dysfunction-associated fatty liver disease [1], studies concerning genetic and epigenetic factors in this new scenario are still scarce. This way, we will still adopt the nomenclature NALFD when discussing the studies in the context of this review.

NAFLD affects about 25% to 45% of the world's western population [2, 3]. The spectrum of the disease includes simple steatosis, steatohepatitis with or without fibrosis, leading to cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) [4]. NAFLD is currently the third indication for liver transplantation worldwide, and it will potentially be the leading indication in 2030 [3, 5].

Many cofactors have been recognized and related to the high prevalence and severity of NAFLD. Metabolic syndrome, obesity, and type 2 Diabetes Mellitus (T2DM) are the most relevant factors associated with progression from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) and fibrosis[6]. Patients with T2DM have a higher prevalence of NAFLD, with a high prevalence of NASH and advanced fibrosis [6-8]. Previous studies in a population of T2DM patients have shown a 69% prevalence of NAFLD. Of those, 78% presented NASH on hepatic biopsy, and 34 to 60% had advanced fibrosis [8]. In a bidirectional relation, NAFLD also increases up to 5.5 times the risk of future development of T2DM and could be considered an early predictor of the disease [9]. Ethnicity also influences the prevalence of NAFLD, with Hispanics presenting a higher prevalence than Caucasians and African Americans,

independently of metabolic factors. The differing genetic and environmental basis could be responsible for these findings in diverse ethnic groups [10]. Accordingly, the observation of familial clusters of NASH and cirrhosis suggests a substantial hereditary influence in NAFLD progression [11]. Data from diverse epidemiological, familial aggregation, and twin-cohorts studies, with a well-designed methodology, suggest that hepatic steatosis is highly heritable [12-17]. Some of these studies use magnetic resonance elastography to assess liver fibrosis or serum aminotransferase levels to infer hepatic steatosis [13, 15]. They demonstrated a high prevalence of NAFLD in family members of children with NAFLD, monozygotic and dizygotic twins, and first-degree family members of T2DM patients [14, 15]. So far, the risk of hepatic steatosis and more severe disease in family members and children of patients with NAFLD is not fully understood, as well as the pathogenetic pathways involved in this process.

Genome-wide association studies have demonstrated the association of single nucleotide polymorphisms (SNP) with NAFLD. Patatin-like phospholipase-domain-containing 3 (rs738409 C>G encoding for PNPLA3 I148M), also known as adiponutrin gene, is located at chromosome 22 and was the first SNP described [18]. Although this is the most robust variant linked to NAFLD, additional genetic variants have been identified subsequently: transmembrane 6 superfamily member 2 (TM6SF2) [19, 20], glucokinase regulator (GCKR) [21], membrane-bound O-acyltransferase domain-containing 7 (MBOAT7) [22, 23] and hydroxysteroid 17β-dehydrogenase (HSD17B13) [24-26] among others. Currently, these variants have been associated with multiple pleiotropic effects, including a protective effect for NAFLD as seems to occur with the HSD17B13 polymorphism [25]. The different phenotypes resulting from these

genes might partially explain the heritable component and metabolic profile of NAFLD patients and their offspring [12, 27].

Although our understanding of genetic influence has exponentially increased in the past few years, it cannot thoroughly explain the high prevalence of NAFLD in family members of patients with the disease. Experimental studies have investigated different pathways related to NAFLD development in the offspring [12, 28, 29]. In this context, environmental and epigenetic mechanisms play an essential role in the occurrence and progression of NAFLD. Epigenetic factors involve mechanisms that affect and regulate gene expression without changes in DNA sequences [30, 31]. Therefore, gene expression and cell phenotype related to NAFLD might depend on the genetic information encoded by DNA sequences and epigenetic factors [32]. This review aims to discuss the impact of genetic, epigenetic, and environment-related variables associated with NAFLD in the offspring of affected patients.

Heritage and Genetic factors

Studies in Familial Clusters and twin cohorts:

Several studies have shown a solid familial clustering of NAFLD, particularly in the setting of coexisting metabolic traits [14, 33-37]. Familial combined hyperlipidemia is the most frequent genetic dyslipidemia with a high risk of premature atherothrombotic cardiovascular disease. To assess whether liver steatosis is involved in the pathogenetic pathway of familial combined hyperlipidemia, Brouwers et al. studied family members with this disease and twenty spouses. Fatty liver diagnosed by ultrasound was significantly more prevalent in familial combined hyperlipidemia probands (40%) and relatives (35%) compared with their spouses [33]. Moreover, the authors evaluated the

correlations between indicators of fatty liver with plasma lipid levels. In all family members of those with familial combined hyperlipidemia, liver steatosis and alanine aminotransferase (ALT) levels correlated with triglyceride levels [33].

In the multigenerational Framingham Heart Study, a community-based study, individuals with at least one parent presenting hepatic steatosis had a two-fold increased odds of having liver steatosis themselves, compared to those without a parental history. Among participants without metabolic diseases, a higher proportion had liver steatosis if they had at least one parent with liver steatosis compared to those without any parent with steatosis. On the other hand, there was no difference in the prevalence of steatosis among patients with high cardiometabolic risk among participants with or without a parental history of liver steatosis. Based on these findings, this study suggested that a family history of liver steatosis was a significant risk factor for liver steatosis, but only in metabolically healthy participants [34]. This study goes against the previous one, which showed a higher prevalence of steatosis in those with familial hyperlipidemia. There was no investigation if the genetic aspects of those patients with familial hyperlipidemia could have influenced the higher prevalence of steatosis.

Schwimmer et al. evaluated 33 overweight children with biopsy-proven NAFLD and 11 overweight children without; NAFLD was significantly more observed in siblings and parents of the NAFLD children group. The correlation of liver fat fraction to body mass index (BMI) was more substantial in overweight children with NAFLD than without NAFLD, showing that there is likely an interaction between BMI and genetic factors on steatosis severity in families of children with NAFLD [14].

Similar to steatosis, hepatic fibrosis in NAFLD is also a heritable trait. Familial aggregation studies revealed a marked coexistence of advanced fibrosis or NAFLD cirrhosis among index patients and their first-degree relatives [35, 36]. A cross-sectional analysis demonstrated that first-degree relatives of probands with NAFLD cirrhosis present a 12 times higher risk of advanced fibrosis compared with the relatives of non-NAFLD controls [36]. Interestingly, in another recent cross-sectional study of a prospective cohort comprising 156 twins and their families, the same authors identified a metabolite (3-4-hydroxyphenyl lactate) related to the abundance of several gut microbiota species in individuals with advanced fibrosis. Then, in their conclusions, they propose a link between genetics and microbiota composition concerning NAFLD heritability [37].

The potential genetic link of NAFLD regarding steatosis and fibrosis inheritance triggered the development of studies in twins to evaluate if both steatosis and fibrosis had a significant shared gene. The first study in twins regarding NAFLD inheritance included 60 monozygotic and dizygotic twins [38]. Both liver steatosis and fibrosis were non-invasively quantified by magnetic resonance imaging [39] [39]. The presence of hepatic steatosis by proton-density fat fraction MRI and fibrosis by magnetic resonance elastography correlated between monozygotic twins but not between dizygotic twins, providing evidence that both hepatic steatosis and fibrosis might be heritable traits as well[38].

Following the same rationale, Cui et al. investigated a prospective cohort of community-dwelling monozygotic and dizygotic twin pairs living in Southern California, using non-invasive proton-density fat fraction MRI and magnetic resonance elastography to assess steatosis and fibrosis. They investigated if individuals prone to genetic susceptibilities to steatosis and fibrosis also had

genetic susceptibilities to metabolic variables such as arterial hypertension, dyslipidemia, insulin resistance, and diabetes mellitus. The authors have shown that both hepatic steatosis and fibrosis have statistically and clinically significant shared genetic determination, as well as metabolic traits such as high-density lipoprotein, triglycerides, insulin resistance, and glycosylated hemoglobin [13]. In another study, the same cohort of twins was evaluated regarding the metabolites of the gut microbiome and its effect on steatosis and liver fibrosis compared to a biopsy-proven NAFLD cohort. This proof of concept study provided evidence of a link between the gut-microbiome and 3-lactate that shared gene-effect with hepatic steatosis and fibrosis [37]. Hence, the heritage of NAFLD might have a contribution of multiple factors like a genetic inheritance that might directly affect steatosis and fibrosis but also heritable traits of the gut microbiome that might be inherited or even influenced by a shared lifestyle in the probands and its parents.

Genetic polymorphisms:

Genetic polymorphisms are involved in NAFLD expression regarding its relation with liver steatosis, advanced stages of fibrosis, and even with a possible protective effect for disease progression [12, 25, 40]. However, studies evaluating their impact on the offspring of patients with NAFLD are scarce.

As previously described, PNPLA3 rs738409 C>G variant is associated with hepatic steatosis and severity of NAFLD, progression to cirrhosis, and HCC, resulting in a worse prognosis [18, 41]. PNPLA3 encodes a triacylglycerol lipase, and this SNP promotes hepatic triglyceride accumulation by restricting substrate access to the catalytic dyad, thus inhibiting triglyceride hydrolysis in the cell [41, 42].

TM6SF2 function is related to the regulation of cholesterol synthesis and secretion of lipoproteins. Individuals who carry the variant rs58542926 C>T, which encodes the E167K amino acidic substitution, have a higher risk of NAFLD and histological disease severity, however, a protective effect on coronary artery disease was described [43]. On the other hand, opposite results highlighted that the T allele might be related to coronary artery disease as well, evidenced by myocardial infarction [44]. A large study with 60,801 patients with coronary artery disease compared to 123,504 healthy individuals described a protective effect of the T variant of TM6SF2 on this disease and found an equivalent although modest effect for the G variant of PNPLA3, that was more intense in the recessive model (genotype GG). At last, an exome study including more than 300,000 individuals showed that both TM6SF2 and PNPLA3 polymorphisms induce a protective effect on coronary artery disease and an increased risk of NAFLD [45]. So far, there is no study regarding the evaluation of the impact of TM6SF2 in the offspring of NAFLD patients.

In young adolescents, the rs1260326 C>T variant in GCKR was significantly associated with de novo lipogenesis in those with TT allele and a study demonstrated the additive impact of PNPLA-3 and GCKR risk alleles were related to NAFLD in obese youths [46, 47]. Another variant in GCKR, the rs780094 A>G, was associated with NAFLD in a meta-analysis involving 2,091 cases and 3,003 controls from 5 studies [48].

MBOAT7 was first studied in alcohol abusers and was related to a higher risk of cirrhosis. It encodes a protein involved in the re-acylation of phospholipids as a component of the phospholipid-remodeling pathway, known as the Land cycle. Subsequently, the rs641738 C>T variant in this gene was associated with increased hepatic fat, more severe liver damage, and fibrosis in NAFLD

individuals of European descent [49]. Moreover, it has been demonstrated that the T allele may predispose to HCC in patients without cirrhosis [50].

Recently, three polymorphisms have been identified as protective against advanced stages of NAFLD. Results from exome-sequence data from 46,455 individuals have shown an association between rs72613567:TA in HSD17B13, a variant with an adenine insertion, with lower levels of aminotransferases and reduced risk of chronic liver disease, including NASH [25]. Pirola et al. demonstrated the effect of this variant on a Hispanic population submitted to liver biopsy, investigating its association with histological parameters of NAFLD. They identified a lower risk of ballooning degeneration, lobular inflammation, and liver fibrosis, mediated by reduced enzyme activity in converting retinol to retinoic acid, suggesting a protective effect in inflammation and fibrosis [51]. Di Sessa et al. evaluated 685 obese children (mean age 10.56 ± 2.94 years) and demonstrated that carriers of the HSD17B13 A allele had a lower percentage of liver steatosis on ultrasound imaging and lower serum aminotransferases levels [52].

Petta et al. evaluated the role of irisin, a myokine encoded by the fibronectin type III domain-containing protein 5 gene (FNDC5), in NAFLD patients. The variant rs3480 A>G was not associated with the severity of steatosis and NASH but was correlated with a lower prevalence of clinically significant fibrosis (F2-F4), showing a protective effect against fibrosis. They also found that irisin is expressed in human activated hepatic stellate cells, where promotes profibrogenic actions and collagen synthesis. Thus, the FNDC5 genotype might affect hepatic fibrogenesis by modulating irisin secretion [53].

Another variant in the interferon lambda 4 (IFNL4, previously known as interleukin 28B), the rs368234815 TT>λG, was studied in NAFLD patients of European ancestry. TT genotype determines the production of the alternative

IFNL3 transcript, modulating the activation of innate immunity and necroinflammation. The T allele was independently associated with severe fibrosis (F3-F4) and severe lobular necroinflammation (grade 2-3). So, this variant TT>λG was considered protective against liver fibrosis. This effect on liver damage was confirmed in non-obese individuals, but not in obese patients, probably because the role of metabolic factors overcame IFNL4 genetic background [54]. The genetic polymorphisms associated with NAFLD, their functions, and their effects are summarized in table 1.

Concerning NAFLD and family inheritance, the PNPLA3 polymorphism was the only one studied, Overweight and obese children with NAFLD confirmed by histology were evaluated regarding the role of lifetime exposures in association with a genetic predisposition, parental obesity, economic income, programming during fetal life, being breastfed or not, and later biomarkers of dietary habits and lifestyle, correlating with fibrosis. In this study, 75% of the children had fibrosis, independently associated with PNPLA3- GG genotype, parental obesity, not being breastfed, vitamin D levels (<20 mg/dL), and fructose consumption. Notably, a high socioeconomic maternal occupation was related to less severe fibrosis [55]. These findings reinforce the multifactorial impact of NAFLD inheritance. Recently, Jain et al studied 51 patients with NAFLD and their parents compared to 50 individuals without NAFLD and their parents as a control group and they observed that parents of the NAFLD group had a higher frequency of GG allele when compared to parents of those without NAFLD (15% vs 5%)[56]In this study no other factors except for PNPLA3 polymorphism was evaluated.

Environmental and Epigenetic Factors

In addition to the genetic information encoded by DNA sequences, epigenetic modifications increase or inhibit the expression of specific genes and affect chromatin structure without modifying nucleotide sequence. Epigenetics implies inheritable changes in the expression of genes, but they can also be acquired and may occur in response to environmental factors, such as nutrition, contributing to disease risk and severity [57]. These alterations can be transferred to the next generation and, in this way, may modify metabolic and NAFLD risk in the offspring. As epigenetic changes can be inheritable and modulated by environmental stimuli, they are considered reversible and could offer new individualized prevention and therapy [57]. So far, the impact of maternal and/or paternal risk factors on the clinical phenotypes of the offspring and the underlying epigenetic mechanisms has not been fully elucidated [58].

Epigenetic phenomena include four regulatory mechanisms, described as modification in DNA methylation, covalent histone modification, chromatin remodeling, and RNA-based mechanisms such as non-coding RNA. Among them, DNA methylation is the most studied [32, 59],

Experimental studies:

Some experimental studies, most of them in mice, tried to elucidate the mechanisms involved in the inheritance of NAFLD and the external factors that could modulate NAFLD development in the offspring through epigenetic factors. The mechanism behind the epigenetic modification in response to these factors is not always known. It has been shown that many factors during pregnancy may activate lipogenic and inflammatory pathways leading to NAFLD in the progeny [28]. Maternal obesity, high-carbohydrate, and high-fat diet during pregnancy, maternal malnutrition, alcohol, and caffeine ingestion may be related to this outcome. However, in addition to maternal profile or

lactation, in animal models, it is also evident that variables such as fructose and high digestion carbohydrate ingestion substantially impact NAFLD development after birth.

Many authors have studied the impact of breastfeeding, maternal obesity, and diet before or during pregnancy in animal models. Oben et al. demonstrated that maternal obesity and lactation could be linked to dysmetabolism in the offspring in female mice fed by an obesogenic diet before and throughout pregnancy and during lactation [28]. They compared the offspring of obese and lean dams and showed a dysmetabolic pattern in the first ones, including insulin resistance and NAFLD phenotype. Moreover, the offspring of lean dams fed by obese dams developed a dysmetabolic pattern, with increased body weight and higher levels of insulin and noticeably with cytokines such as leptin, interleukin-6, and tumor necrosis factor-alpha (TNF-a). Raised levels of leptin were also observed in the breast milk of obese mice compared to lean ones. They concluded that the mechanism that induced the dysmetabolic profile in the early postnatal period could be related to a modified pathway over hypothalamic appetite nuclei signaling by maternal breast milk and neonatal adipose tissue-derived leptin [28].

Considering the hypothesis that diet during and after pregnancy might also be involved in NAFLD in the post-weaning period, Pruis et al. observed that the male offspring exposed to prenatal and post-weaning western-style diet presented hepatomegaly, with high hepatic cholesterol and triglycerides content associated with the up-regulation of de novo lipogenesis, inflammation, and an abnormal lipid storage mechanism. This way, they concluded that a maternal western-type diet during pregnancy could stimulate a metabolic programming or phenotype induction that could lead to NAFLD development [60].

Not only the type of diet but also the components of the diet like carbohydrate content during pregnancy may impact the development of NAFLD in the progeny. In a study that fed pregnant mice either with a high fat-slow digestive diet or a rapid digestive diet, the offspring of the high fat-rapid digestive diet showed an abnormal liver lipid profile. However, it was not observed in their counterparts born from high fat-slow digestive diet fed-mice. This study suggested that just modifying the diet during pregnancy could bring benefits to the offspring preventing a disrupted liver lipid profile [61].

The relation of obesity in pregnancy and circadian cycle deregulation might affect metabolic pathways related to NAFLD in adults [29]. Mouralidarane et al suggested that in addition to an obesogenic post-weaning diet, obesity in the mother might lead to NAFLD as well by disrupting the liver's canonical metabolic rhythmicity gene expression. It implicates the role of abnormal circadian rhythm in the genesis of NAFLD, and alterations in this system during critical developmental periods might be responsible for the onset of the disease later in adulthood [29].

Another issue that might be considered regarding further development of NAFLD after birth in experimental studies in ethanol exposure. [62]. Shen et al developed a rat model of intrauterine growth retardation by prenatal ethanol exposure. These models were fed with normal and high-fat diets. Enhanced liver expression of the insulin growth factor -1 pathway, gluconeogenesis, lipid synthesis, and diminished expression of lipid output was accompanied in prenatal ethanol exposure female offspring fed with a high-fat diet.

Oliveira et al. hypothesized that maternal high-fat diet might intensify the fructose impact in adolescent male rat offspring by changing the response of mechanisms involved in liver injury. The study was performed in Wistar rats fed by a standard diet and a high-fat diet. The offspring were fed with a standard

diet and then with a high fructose diet. Those born from mice fed with a standard diet were not affected by changes in liver morphology, as did the offspring of high-fat-fed rats. Therefore, the study concluded that fructose intake during adolescence hastens NAFLD onset and reveals a differentiated hepatic response to metabolic insult, depending on the maternal diet [63]. Notwithstanding, Nicolas-Toledo et al. evaluated the combination of fructose and maternal malnutrition in the development of NAFLD, showing that sucrose intake in adulthood increases fat content only in female rat offspring of dams fed with a low-protein diet during pregnancy, reinforcing the influence of maternal diet in the offspring [64]. Overall, these studies did not mention if epigenetic modifications were involved in the genesis of NAFLD, but could clearly show the impact of environmental factors through modification of diet, breastfeeding maternal and obesity pre, during, and after birth on the development of NAFLD. Of note, regarding specific epigenetic mechanisms, Suter et al. have described that epigenetic changes to histones may act as a molecular memory of intrauterine exposure, rendering the risk of adult disease. They investigated mice heterozygous for the Glut4 gene (insulin-sensitive glucose transporter) born to wild-type mothers demonstrating exacerbated metabolic syndrome when exposed to a high-fat diet in utero. The genome-wide epigenetic modifications in the fetal liver of susceptible offspring were analyzed, concluding that a maternal high fat diet is associated with functional alterations to fetal hepatic histones, some of which may persist up to five weeks of age [65].

Another study by Wei et al connected NAFLD with epigenetic methylation of specific genes in fathers. They have shown that even paternal diet patterns and prediabetes increase the risk of diabetes in the offspring through gametic epigenetic alterations. In their analysis, certain genes were differentially

methylated in the sperm of prediabetic fathers. These methylation changes in sperm-inherited genes can be transmitted from gametes to embryos, across generations [66].

All these experimental studies in animal models have revealed that maternal obesity and parental diet during pregnancy or lactation may significantly influence NAFLD and lipid dysmetabolism in the offspring either by environmental factors or through epigenetic factors, some yet to be better specified, mainly concerning environmental factors. Hence, cofactors as alcohol, caffeine ingestion, fructose intake, among others not yet identified, may activate pathways that can lead to NAFLD in the offspring.

Studies in mothers and newborns:

Animal studies confirmed that disruptions during early development stages could lead to increased susceptibility to metabolic dysfunctions later in life. Likewise, human data support that metabolic dysfunction, and its contribution to NAFLD can be closely related to genetic and environmental predisposing factors. However, the precise mechanisms that link changes in pre-and postnatal environments with NAFLD development risk in adolescence and adulthood remain poorly understood. These mechanisms involve shifts in lipid metabolism, mitochondrial dysfunction, altered gut microbiota, macrophage programming, and activation of epigenetic changes.

In prior studies, it was demonstrated that low birth weight babies exhibit an altered postnatal metabolism after developing an adaptative response to a suboptimal fetal environment [67, 68]. Although the mechanism is not completely understood, exposure to excessive and deficient nutrition during the prenatal period may induce a nutritional mismatch between metabolic efficiency and energy expenditure, increasing the risk of future cardiometabolic

diseases. If confirmed, an early and simple nutritional intervention might prevent the further development of metabolic diseases in adulthood.

Modi et al. evaluated 105 healthy mother-neonate pairs [69]. They measured neonatal adipose tissue content by whole-body MRI and intrahepatic lipid content by a proton magnetic resonance spectroscopy. They have demonstrated that infant adiposity, particularly abdominal adipose tissue and intra hepatocellular lipid correlated with increased maternal body mass index [69]. Recently, Bedogni et al. studied the prevalence and risk factors associated with bright liver in 391 1-year-old toddlers born from healthy mothers. The PNPLA3 I148M variant and maternal weight gain during pregnancy were related to the presence of bright liver in the ultrasonography [70]. Thus, interestingly, the authors suggested a potential gene-environment interchange between PNPLA3 and maternal environmental factors contributing to the risk of fatty liver disease at this earlier age, reinforcing the multifactorial inheritance of NAFLD.

In a large study, Ayonrinde et al. investigated the relation of maternal factors and infant nutrition with the future development of NAFLD in adolescents aged 17 years. They concluded that average pre-gestational body mass index, breastfeeding for at least 6 months, and avoiding early supplementary formula milk feeding reduces the risk of NAFLD diagnosis by liver ultrasound [71]. Additionally, more extended maintenance of breastfeeding resulted in multiple benefits on maternal metabolism and a lower risk of NAFLD in mid-life [72-74]. The Healthy Start study examined a cohort of 951 mothers from different ethnicities [75]. Similar to others, they found that maternal body mass index was correlated to increased neonatal adiposity. It has also been demonstrated that increased maternal insulin resistance and fasting glucose levels are relevant elements contributing to this association. Excessive insulin resistance

during pregnancy activates placental inflammatory pathways and affects the fetus indirectly by increasing placental nutrient transfer capacity [76].

Still, regarding insulin-glucose metabolism, elevated blood glucose and insulin concentrations exacerbate de novo lipogenesis, resulting in increased intrahepatic lipids. Additionally, reduced glucose and pyruvate consumption in parallel with increased triglyceride concentrations and excess fatty acids incompletely oxidized can impair mitochondrial function and gene expression, limiting mitochondrial biogenesis and leading to NAFLD [76].

Peroxisome proliferator-activated receptor γ coactivator 1 (PGC1) gene is a transcriptional coactivator that participates in mitochondrial biogenesis and function, and hypermethylation PGC1 promoter was associated with decreased mitochondrial DNA content and insulin resistance in NAFLD patients [77, 78]. In a cross-sectional analysis, Gemma et al. noticed a positive correlation between maternal BMI and methylation of the PGC1 gene in the umbilical cord of their babies [79]. Based on their findings, the authors speculated that PGC1 might be a promising candidate gene involved in metabolic programming by epigenetic regulation [79]. DNA methylation in regulatory regions of different genes participates in NAFLD development and progression. Other epigenetic mechanisms affecting NAFLD pathogenesis include histone modification and microRNA (miRNA)-mediated processes. Notably, circulating miRNAs have been associated with the presence and heritability of NAFLD in a population study in 40 pairs of twins. Serum miR-331-3p and miR-30c were identified among the 21 miRs that were different between NAFLD and non-NAFLD individuals. These miRNAs are highly inheritable and correlate with each other suggesting a common pathway related to NAFLD [80].

Although shreds of evidence support that high pre-pregnancy body mass index in the mothers may lead to significant modifications in the infant gut

microbiome [81], few studies link maternal obesity and infant dysbiosis with NAFLD risk in later life. The neonatal gut microbiome can be essential for later homeostasis, and disruption of this early process may increase the risk of future metabolic diseases [82]. Emerging data provides evidence that the gut-liver axis is a fundamental element in the onset and progression of NAFLD. Gut microbiota dysbiosis may contribute to NAFLD by increasing concentrations of bacteria-derived endotoxins, pro-inflammatory cytokines, amino-acid metabolites, short-chain fatty acids, and bile acids, all of which might exert effects that promote macrophage programming and activation, favoring liver injury [83].

Conclusions:

NAFLD has an explicit component of inheritance through multiple genetic and epigenetic mechanisms that are not entirely understood. Epigenetic and environmental changes interact with inherited risk factors to determine an individual's susceptibility to NAFLD. Current evidence points to genetic polymorphisms as pleiotropic tools that lead to diverse traits and diverse phenotypes, including typical metabolic profiles in parents and their offspring. Importantly, epigenetic markers can also be transferred to successors by transgenerational epigenetic inheritance. Studies evaluating the interplay of genetic, epigenetic, and environmental effects in mothers and their offspring, although still small, show a direct effect of these factors and its related outcome, NAFLD. Either over the liver with steatosis or an abnormal metabolic profile Future studies may clarify what interventions are essential for preventing this complex disease in the perinatal or postnatal period aiming to reach better liver and metabolic-related outcomes in the upcoming adult population.