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Review Article

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Fatty Liver, Developing Factors and the Outcomes

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Abstract

Fatty liver has grown increasingly in recent decades. Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in the United States with a prevalence of 30% and the leading cause of liver disease with a mortality rate of 25.2% in the world. Fatty liver is divided into two types, alcoholic and non-alcoholic. It has been reported that 44% of NAFLD patients progress to nonalcoholic steatohepatitis (NASH) at the second biopsy, and in several countries, hepatocellular carcinoma is the most common disease. Unfortunately, no absolute cure has yet been found. Finding out about related diseases, genetics, lifestyle, mechanisms, and signaling pathways may have a great impact on discovering the best ways to treat fatty liver. In this study, we tried to present the most important components in developing this disease.

Keywords: Fatty Liver, Nonalcoholic Fatty Liver Disease, Metabolic-Associated Fatty Liver Disease, Nonalcoholic Steatohepatitis

1. Introduction

Fatty liver is the concentration of fat, mainly triglyceride, in liver hepatocytes which contain more than 5% of total liver weight. In this process, multiple factors are linked to each other including lack of physical activity, genetic predisposition, high caloric intake, oxidative stress, inflammatory cytokines, gut infection, and impaired immune response [1]. Fatty liver is divided into alcoholic form and nonalcoholic [2]. Nonalcoholic fatty liver disease (NAFLD) was termed by Dr.Schaffer in 1986 for the first time. NAFLD is a general name that contains a wide spectrum of liver abnormalities from simple steatosis Nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH) with different stages of necrosis, inflammation, and cirrhosis in the end and it can progress to hepatocellular carcinoma [3, 4]. According to the guideline in 2014, NAFLD confirms through imaging or histopathological tests, characterized by macro vesicular steatosis [5]. Detecting the steatosis is possible by liver histology or non-invasive biomarkers or imaging, with at least one criterion, such as obesity, type 2 diabetes mellitus, or clinical evidence of metabolic dysfunction (increased waist circumference and abnormal lipid profile), [6]. NAFLD has three feature which includes: an intrahepatic accumulation of triacylglycerol, hepatocellular inflammation, and ballooning with collagen deposition, resulting in fibrosis, cirrhosis, and hepatocellular carcinoma [7]. These days NAFLD is known as the leading cause of chronic liver disease in the US with a prevalence of 30% [8], and the major cause of liver disease-related morbidity with a mortality rate of 25.2% in the world [9]. The rate in Africa is 13% and in Southeast Asia is 42% [10]. In a study by MC. Phereson et. al reported that 44% of NAFLD patients had progressed to NASH in the second biopsy [11] and also in several countries, hepatocellular carcinoma is the most common disease [12]. Recently, it has been suggested to term it metabolic-associated fatty liver disease (MAFLD). However, alcohol consumption and alcoholic liver disease (ALD) are omitted in the MAFLD definition [13]. The global prevalence of MAFLD among obese adults is 50.7% and 59% and 50% in men and women, respectively [14]. Up to now, there is no specific therapeutic approach [15]. To manage NAFLD, lifestyle intervention with healthy eating and regular physical activity can be effective [16]. By the way, many diseases such as diabetes, metabolic syndrome and deranged metabolites in serum concentration, a complex of diverse metabolic reactions, genetic, environmental interaction between gut microbiota and innate immunity and sex hormones, thyroid hormones, growth hormone, diseases such as chronic kidney disease, gallstone disease, and cardiovascular diseases, predispose to NAFLD and metabolic syndrome progress[17-20]. Finally, secondary liver diseases that supposed to lead to NASH, have been rising and liver transplantation is increasingly performed as the only treatment option in the United States [17].

1.1 Nonalcoholic Steatohepatitis (NASH) and the Mechanisms

The NAFLD pathogenesis is not completely understood but is explained with two hit theories [19]. The first hit is fat deposition in the liver, TG deposition in the liver leads to insulin resistance

and activates harmful cytokines and may progress to hepatic cirrhosis and cancer [20]. In the second part of this theory, the changes involving cellular and molecula1.1r mechanisms due to the factors containing oxidative stress and fatty acid oxidation, lipid peroxidation, energy hemostasis, hepatic iron, variation of extracellular matrix, and changes in the immune system [19]. Mitochondria have a pivotal role and normalize liver function in the early stages, in which mitochondrial respiration increases to adapt to consume higher substrate and provide more ATP [21]. Recently, a third hit is added to this theory, insufficient hepatocyte proliferation and replacement of dead hepatocytes are suppressed because of oxidative stress, also hepatic progenitor cells (HPC) stimulate fibrosis and cirrhosis, and ultimately hepatocellular carcinoma [22]. As a result of insulin resistance, mitochondria cannot oxidize fat and fat accumulation leads oxidative stress and low-grade chronic inflammation, which all end in liver damage [23, 24]. So, the JAK-STAT signaling pathway, one of the mitogen-activated apoptotic pro kinase (MAPK), activates to control chronic liver injury [25, 26]. This signaling pathway is stimulated by growth hormone, growth factors, cytokines, and viral status [27], and activates apoptotic proteins such as BAX, and caspase3 [26]. A murine model in chronic hepatic inflammation, demonstrated elevated NF-KB activity, through a higher level of TNF-α, IL-6, IL-1β, and activation of Kupfer cells [28]. A study demonstrated in NAFLD induced by a high-fat diet, Tyrosol, a polyphenolic compound, can be effective in liver function and reducing fat deposition. In addition, JAK1 and STAT3 were down-regulated by trysol to alleviate inflammatory response [29]. The hippo signaling pathway is tumor suppressive in mammals to control organ size by regulating cell proliferation, survival, and differentiation [30]. A central component involve in the hippo signaling pathway is YAP (yes associated protein)/ TAZ-TEAD(TEA- domain) which are up-regulated in the NASH model in mice and humans [31]. According to YAP function in cell proliferation, apoptosis inhibition, maintaining stem cell phenotype, and promoting epithelial transition; its activation ended in hepatomegaly whereas deletion ended in liver dysfunction [31]. Several genes are the hippo targets such as connective tissue growth factor 28, jng1, and Notch receptor2 (Notch2) [30]. In a study, liver inflammation in mice and humans regulates the level of YAP/TAZ/CYR61 to attract macrophages to improve liver fibrosis [32]. A higher level of TAZ resulted in transcription of Indian hedgehog (IHH) gene, and hepatic satellite cell activation (HSC), liver fibrosis and inflammation, and eventually cell death. Also, a study revealed that cholesterol increase TAZ in fibrosis, cholesterol has a role via a soluble adenylyl cyclase (SAC) - protein kinase A- Inositol triphosphate A receptor (PI3R) - calcium Rho A pathway to prevent TAZ destruction [33]. WNT/ β catenin is one of the central signaling pathways in liver prenatal development, postnatal growth regeneration, metabolic zonation, ammonia and drug detoxification, and hepatobiliary improvement [34]. SIRT1 protein manages cellular metabolism via NAD-dependent histone deacetylation and influence the transcription and mediate genes in glucose and lipid metabolism [35]. In a study, NAFLD induced in a rat model had shown that overexpression of SIRT1 improves HPC differentiation through activating the WNT/β catenin pathway and its knockdown, reducing HPC activation and WNT/β catenin pathway. Though, SIRT1 plays a central role in activating HPC to cure liver injury via WNT/β catenin pathway [36].

1.2 Alcoholic Liver Disease (ALD)

Alcoholic liver disease (ALD) is the second most common cause of death in the new world [37]. According to the 2021 world health organization statistics, around 2.3 billion people are current drinkers (who have consumed a drink containing alcohol in the last 12 months) [38]. ALD includes alcoholic hepatitis, steatohepatitis, liver fibrosis, cirrhosis, and liver cancer. However; there is an obvious relation between alcohol consumption and ALD development, other factors such as genetics, epigenetic factors, and environmental are cofactors in ALD development [38]. By heavy alcohol drinking, disturbance in lipoprotein synthesis and lipid metabolism has occurred and resulted in fatty liver [39]. Alcohol consumption produces a large amount of acetaldehyde in the body and this excess amount leads to reactive oxygen generation (ROS) and proinflammatory cytokine and immune system response increased and leads to hepatocyte damage [40, 41]. Due to the high level of ROS generation, mitochondrial DNA (mt DNA) damage and will result in mt DNA deletion on a large scale, this deletion, directs mitochondrial dysfunction, which accelerates ROS generation over and over. Ultimately with chronic alcohol consumption, the morphology, and function of mitochondria will be altered, which is the hallmark of ALD patients. In alcoholics, more FFA is released into the circulatory system, and TG levels rise, FFA is oxidized in the process of β-oxidation or incorporated into TG. With impaired mitochondrial function, TG accumulation in the liver, and circulation are exacerbated [42].

1.3 NAFLD and Hepatocellular Carcinoma

In a prospective study in Rochester County, Minnesota a study followed by 4772 patients for eight years and 90% of this population had a higher risk of malignancy, especially liver, endometrium, stomach, pancreas, and colon. As a result, obesity alone cannot increase the risk of malignancy; it supports the idea that people with safe storage space for fat remain healthy (obese and healthy). So authors suggested that the association between cancer and NAFLD is low but it can be a mediator to other diseases [43]. In other cohort analyses, in the last decade, the prevalence of NAFLD-HCC has quadrupled, compare to 2.5-fold hepatitis [44]. As a major global public health challenge, HCC is ranking sixth in disease and fourth in mortality [45]. The incidence rate in women and men is 7th and 5th, respectively [46]. It has a very poor prognosis of 5 years and its overall survival is 17% [44], 21-33% of steatotic patients develop severe liver fibrosis and HCC [47]. Unresolved inflammatory responses and necrosis can lead to tissue damage, regeneration, fibrosis, cirrhosis, and HCC in sequence. It has been shown that in the premalignant culture environment, immune cells, produce a lot of factors such as cytokines, chemokines, growth factors, and prostaglandins proangiogenic factors to support hepatocytes transformation and protect their survival during anti-apoptotic, neoangiogenesis activation, and inhibition of immune surveillance [48]. Therefore, the process of carcinogenesis takes place with the help of immune-related factors, in which chemokines, cell infiltration, and their receptors all contribute to the proliferation and survival of these

cancer cells. Lipotoxicity as a major cause of NAFLD leads to NASH/ fibrosis, cirrhosis, and even HCC development. Besides denovo lipogenesis, exogenous fatty acids protect HCC cell growth. In obesity; as a result of decreasing in carnitylpalmitoil transferase 2 (CPT2) activity, fatty acid oxidation is reduced, lipotoxicity happens and carcinogenesis will increase [46]. Also, oxidative stress is a primary factor in NAFLD which may contribute to HCC development [49]. Oxidative stress changes the regulatory mechanism of sterol binding protein transcription factor (SREBP) to regulate sterol and fatty acid biosynthesis and even interaction with tumor suppressor gene P53 [50]. However the mechanism of NAFLD- NASH- HCC remains vague, But lipid disorders have an important role in NAFLD-HCC development [51]. Francisco González-Romero et. al have shown that transcription factors E2F1 and E2F2 –carnitine palmitoyl transferase 2 axis has a role in hepatocarcinogenesis. In the mice with high-fat diet (HFD), and diethylnitrosamine (DEN) administration, the expression levels of E2F1 and E2F2 increased. Although E2f1−/− and E2f2−/− mice were resistant to DEN–HFD-induced hepatocarcinogenesis but lipids were accumulated. DEN–HFD, induces fatty acid oxidation and carnitine palmitoyl transferase 2 (CPT2), (the enzyme essential for fatty acid oxidation). The down-regulation of this enzyme was related to NAFLD-related hepatocarcinogenesis. Compared to the control group, E2F2 binding to the promoter of Cpt2 was increased in the group of DEN–HFD-administered mouse liver, so E2F2 directly repressed the transcription. Also, they found that in humans, CPT2 expression was inversely correlated with E2F1 and E2F2 expressions. Overall, they concluded that the axis of E2F1–E2F2–CPT2 produced a rich fat environment related to hepatocarcinogenesis [46]. It was suggested that Zinc finger and homeobox (ZHX2) (a tumor suppressor gene) mediate suppression of Alpha-fetoprotein, Glypican-3 (GPC3) transcription in HCC cell culture [51]. ZHX2 expression suppresses the uptake of exogenous lipids via suppressing transcription of lipoprotein lipase and delayed HCC cell proliferation, tumor growth, and lipid deposition. So; ZHX2 can have a protective role from lipid deposition in NAFLD and as a result inhibit HCC progress [52]. Another pathway in NASH-related hepatocarcinogenesis is an androgen receptor-driven oncogene, cell cycle-related kinase (CCRK), which interacts with obesity-induced proinflammatory signaling. A feed-forward loop fueled by CCRK, this made by inducing co-occupancy of STAT3-AR promoter and transcriptional up-regulation, promotes mTORC1/4E-BP1/S6K/SREBP1 cascades through GSK3β phosphorylation. Also in transgenic mice, induction of hepatic CCRK stimulates mTORC1-dependent G−CSF expression to increase polymorphonuclear myeloid-derived suppressor cell recruitment and tumorigenicity. Ultimately, in human NASH-associated HCCs, the STAT3-AR-CCRK-mTORC1 pathway components are concordantly over-expressed. It shows the dual roles of an inflammatory-CCRK circuitry in driving metabolic and immunosuppressive reprogramming by mTORC1 activation, therefore causing a pro-tumorigenic microenvironment for HCC progression [53]. Hepatic fibroblast growth factor 21 (FGF21) is a protein activated under metabolic stress such as starvation, hepatosteatosis, obesity, and diabetes. FGF21 controls lipolysis activity, it increases in steatohepatitis and decreases during HCC progress. FGF21 knocking down, in NASH and NASH-related HCC models, cause IL-17A upregulation in hepatocytes by TLR4 and NF-KB pathway. With the restoration of FGF 21, the NAFLD level decreases and the tumor size of HCC reduces by anti-IL-17. In the end, FGF21 plays a role as an inhibitor of TLR4-IL-17A signaling in the NASH-HCC model [54]. Another factor to control liver growth is neurofibromatosis (NF2) interacts with the YAP/TAZ protein which is the regulator of liver growth. NF2 also is a critical factor to control liver regeneration, by losing the NF2 function, YAP/TAZ activity becomes stable and results in the proliferation, and differentiation growth of cells which is advantageous to survival in oncogenic stress [55].

1.4 NAFLD and Autoimmune Disease

In the pathogenesis of NAFLD, inflammatory response and immune system (both adaptive and innate immunity) have a crucial role [56]. In obesity, adipokines and cytokines secretion increase from white adipose tissue, immune cells produce cytokines and provide low-grade chronic inflammation [57]. Accordingly, proinflammatory cytokines such as IL-6, TNF-α, and adipokines such as adiponectin and leptin have a beginner role in pathogenesis and worsening NAFLD by controlling metabolic energy balance and immune response [58]. Due to previous studies in rodents with a high-fat diet, liver steatosis was developed and as a result, B-cells accumulation increases proinflammatory cytokines gene expression and IL-6 and TNF-α will be released, therefore inflammation and fibrogenesis develop [59].

1.5 NAFLD and Thyroiditis

Hypothyroidism is a condition of high level of serum thyroid stimulating hormone (TSH) and a low level of serum thyroid hormone. In subclinical hypothyroidism, there are a normal level of free thyroxin (FT4) and normal clinical symptoms [60, 61]. Reduction in thyroid hormone release can terminate in metabolic changes such as reduction in resting energy expenditure, weight gain, increasing cholesterol level, reduced lipolysis, and reduced gluconeogenesis [62]. Primary hypothyroidism due to the hypothalamic-thyroid axis has an incidence of 0.3-3.7% in the USA population, and 0.2-5.3% in Europe [63]. Thyroid hormones act through leptin and adiponectin and stimulate β-oxidation and lipogenesis repression, as a result, increased fatty acid production, insulin sensitivity in hepatic tissue, and reduced hepatic gluconeogenesis [60, 64]. HMG-COA reductase is regulating enzyme in cholesterol biosynthesis which is under the control of sterol regulatory element binding protein (SREBP-2) that all of which are controlled by thyroid hormone [64]. Thyroid hormone receptor α is located on chromosome 19, which mediates a lot of functions in the heart and brown adipose tissues, while the isoform β is located on chromosome 3 and regulates TSH and thyroid hormone secretion as a hypothalamus-pituitary negative feedback loop [65]. Moreover, β-isoform is expressed in the liver under the regulation of T3, thus activates the LDL receptor gene, regulating HDL metabolism, activating lipoprotein lipase [66, 67]. The β isoform function was confirmed by an experiment in which THR-β was knocked out in mice. An increase in liver mass and hepatic lipid accumulation with reducing fatty acid oxidation and increasing lipogenic gene expression was demonstrated. Knocking out of THR α, resulted in lower fat content in white adipose tissue

and a decrease in lipogenesis, insulin resistance, and hepatic steatosis [67]. In hypothyroidism excess energy leads to lipid deposition in the liver, according to animal studies, T3 has a central role in liver microtubular networks, with a disrupted effective level of T3 in hypothyroidism, hepatic mitochondrial turnover, autophagy in NAFLD demonstrated [68]. In a Cohort data in the US population in 2021, to evaluate whether hypothyroidism is a risk factor for NAFLD or not, the results showed that, hypothyroidism is an independent risk factor for NAFLD, even though thyroid hormone therapy cannot be effective in risk reduction [69]. In the same study in Germany in 2021, both hypothyroidism and autoimmune thyroiditis have an association with a higher risk of NAFLD with the same rate in both sexes [70]. In the assessment between histopathology of NAFLD patients and their serum thyroid hormones levels, hypothyroidism in NASH patients is prevalent and it can be a risk factor for it, however, it is not associated with fibrosis and steatosis severity, which means that thyroid disruption, has a direct or indirect role, in NASH / NAFLD pathogenesis [68]. Another thyroid disease is autoimmune thyroiditis in which cells produce antibodies against thyroid peroxidase and thyroglobulin that reflect as biomarkers for autoimmune disease [71]. These autoantibodies lead to damage not only to the thyroid but also to other tissues. In previous studies, it was demonstrated that thyroid autoantibody participated in glucose, and lipid metabolism disease [56]. Moreover, the relationship between NAFLD and insulin resistance, obesity, and other risk factors such as autoimmunity problems can be involved. In 20-35% of NAFLD patients excluded autoimmune hepatitis, and one or more autoantibodies were presented. In a study of 388 patients in China who had proven NAFLD through the biopsied liver, various autoantibody was identified in their serum. 21.6% of patients had at least one antibody, and ANA antibody was found in 50% of patients. Also, Anti-U1RNP antibody (anti-U1RNP) or Perinuclear anti-neutrophilic cytoplasmic antibodies (P-ANCA) was identified in 2.3% and 1.5% of patients, respectively. Thus, serum autoantibody is an independent risk factor for NAFLD and advanced liver fibrosis patients [71]. In another study in China, patients were categorized into MAFLD and NON-MAFLD, and CRP level and thyroid autoantibodies were measured. The results showed, MAFLD has a relation with high TSH levels and alleviates with an increase of free T4, thyrotropin receptor antibodies (TRAb), anti-thyroglobulin antibodies (TgAb), and thyroid peroxidase antibodies (TPOAb) levels. Also, MAFLD can be associated with lower levels of thyroglobulin antibody, thyroperoxidase antibody, and higher CRP level [56].

1.6 Genetic and Polymorphisms

As NAFLD is a multi-characterized disease which is an excess accumulation of fat in the liver and dysregulation in fat metabolism, gene polymorphisms also affect the predisposition of NAFLD [72]. Also in epidemiological studies, it was shown that individual differences and ethnicity describe the different prevalence of NAFLD all over the world for example Hispanic America has the highest prevalence of NAFLD while African Americans have the lowest prevalence [73-75]. Even the histological changes during NAFLD pathogenesis can associate with ethics, too in Asia where NAFLD starts with ballooning degeneration. To previous research, single polymorphism nucleotides (SNP) can influence gene expression which is involved in lipid metabolism [76]. Here we explain some of them.

1.7 Transmembrane 6 superfamily member 2 (TM6SF2)

Transmembrane superfamily 2 (TM6SF2) is located on chromosome 19 (19p12). A gene that encodes a protein with 200-350 amino acids that it's roles are not clear. This protein contains 7 to 10 transmembrane domains and has 2 isoforms by alternative splicing [77]. This gene has two gene variants PNPLA3& E167K which have a main role in NAFLD pathogenesis and development. The nonsynonymous variant of TM6SF2 is the E617K mutation t which causes misfolding protein and protein degradation and also affects cholesterol metabolism and VLDL content [78]. Besides, Population genetic studies demonstrated that this gene variant has an association with hepatic TG level and ALT [79]. Silencing TM6SF2/MBOAT, with a short palindromic repeat, in the HEPG2 cell line, results in increasing the risk of lipid accumulation and microvesicular lipid droplets. Due to deleting TM6SF7, endoplasmic reticulum stress, oxidative stress, and the number of mitochondria will be increased and it has been revealed that deleting genes, causes mitochondrial disability with a shift to anaerobic metabolism, inducing higher proliferation rate, reversed metabolism, and tumor genesis [80]. In addition, the knocking down of liver-specific TM6SF2 dysregulates VLDL secretion and promotes steatosis, fibrosis, and HCC progression [81]. So that TM6SF2E167K can be an independent risk factor for NAFLD [77]. Another study, indicated that over-expression of TM6SF2 can lower the hepatic accumulation, and by its down-regulation, the mutation of E167K stimulated and increase intracellular lipid accumulation. Acetyl COA carboxylase inhibitor (MK-4074) can be useful in reversing the lipid metabolism dysregulation and NAFLD phenotype, in TM6SF2 deficiency [78].

1.9 MICRORNA

MicroRNAs (MIRs) play a role as post-translational regulators in cellular pathways dysregulation of them can lead to NAFLD pathogenesis. Five MIR in NAFLD pathogenesis (MIR34a, MIR122, MIR191, MIR192, and MIR200a) was studied in a cross-sectional study. The results showed that MIR34a, MIR122, and MIR192 are associated with hepatic steatosis in different stages, for example, not showing pathologic features such as ballooning degeneration, or lobular inflammation, while MIR200a is the only MIR strongly associated with NAFLD. Though all of them are related to NAFLD with different stages and severity [82].

1.10 Patatin-Like Phospholipase Domain-Containing Protein 3 (PNPLA3)

PNPLA3 rs 738409 or 1148 M is gene variant function is still unclear, in-vitro studies have shown that it can have TG hydrolase, lysophosphatidic acyltransferase, and calcium-independent phospholipase A2 function, also it is responsible for retinyl palmitate hydrolase in the hepatic stellate cell. So it is associated with liver fat content and as a result fibrosis and cirrhosis. A transcription pathway in which PNPLA3 is involved is NF-KB which is an inflammatory pathway that up-regulates NAFLD [83]. In studies, it was shown that activation of lipid

metabolism by regulatory binding protein 1c regulates PNPLA3 expression [84]. In a cross-sectional study of Brazil's population, PNPLA3 CG increases the risk of NAFLD [85].

1.11 17β-Hydroxysteroid Dehydrogenase type 13 (HSD17B13)

HSD17B13 (SCD9) is a gene that has a 17 kb length and is located on chromosome 4q22 with 8 exons and 7 introns. With alternative splicing, it can code 9 different proteins which are isoforms of each other but their function remains unclear [86]. By encoding a liver-specific lipid droplet-associated protein, it has a role in lipid biogenesis and metabolism. Recently it has been reported that HSD17B13 has a function in retinoid metabolism regulation by activating retinol dehydrogenase [87]. Knocking this gene out, will not protect mice from steatotic damage induced by a high-fat diet or alcohol consumption [88].

1.12 Suppressor of Cytokine Signaling 1 (SOCS1)

A gene for suppressing cytokine signaling, which will be activated by external stimulation such as cytokines, growth factors, and toll-like receptors. The protein mediates inflammatory responses in immune cells and metabolic organs such as adipose tissue and the liver. Isoform 1 of this family can act as an inhibitor of journals kinase signal transductor and activate JAK/STAT transcription instead. According to Agnieszka Kempinska-Podhorodecka et. al SOCS1 gene polymorphisms have a relation with obesity and glucose metabolism. They found that serum liver enzymes were not significant with the variants of SOCS1 while TG level and insulin resistance and overweight in NAFLD patient was associated with the variants of SOCS [89].

1.13 Semaphorin 7A (SEMA7A)

Semaphorin is an extracellular signaling protein that can bind to plexin and integrin. This protein is known as the John Milton hage antigen or CD108, agylycosylphosphatidyl inositol anchored membrane with chemoattraction and compulsive function. The SEMA7A has a crucial role in axon growth, T cell activation, and other biological processes with the help of its receptor binding to integrin-β, plexin c1 [90]. Previous studies have shown that deficiency of this gene in the mouse can lead to reducing fatty acid oxidation, and oxidative phosphorylation, though SEMA7A has a regulatory role in lipid metabolism. To the finding of Nan Zhao. Et al research, SEMA7A heterozygote mutations increase the risk of NAFLD, NAFLD activity scores, and the severity of steatosis. The Sema7aR145W mutation (humanSEMA7A R148W), induces the accumulation of small lipid droplets in the liver of mice, compared to the livers of the wild-type mouse. The mutation of the Sema7aR145W, causes N-glycosylation increasing Sema7a and integrin β1 proteins (its receptor in the cell membrane), in the liver. Also, this mutation increases Sema7aR145W protein interaction with integrinβ1 and PKC-α, promoting PKC-α phosphorylation, which both of them annulled through silencing of integrin β1. In primary mouse hepatocytes, Induction of PKCα_WT, but not PKCα_dominant negative, overexpression, promote transcriptional factors Srebp1, Chrebp, and Lxr expression and their downstream Acc1, Fasn, and Cd36 expression. Overall, the mutation of SEMA7AR148W induces the accumulation of intrahepatic lipid and NAFLD in mice through increasing PKC-α–stimulated FA and FA uptake and triglyceride synthesis, therefore it is a strong genetic determinant of NAFLD [91].

1.14 Angiotensinogen Polymorphism rs699cc (AGT rs699cc)

Angiotensinogen gene polymorphism associated with HDL level, in patients with peripheral arterial diseases [92]. In addition, AGT M 235T genotype, is related to serum LDL and total cholesterol levels, although this polymorphism can increase the risk of overweight and obesity [93]. In Mengzhen Dong et al study, the AGTrs 2493132 T allele and AGT rs2493132 CT + TT genotype enhance the risk of CAD in the patients with NAFLD in the Chinese Han population [94].

1.15 Mitochondrial DNA

As mitochondria have an essential role in NAFLD pathogenesis and energy metabolism, scientists have shown that liver mitochondrial DNA in NAFLD patients has a higher mutation than in healthy people [95]. According to analysis, the mitochondrial DNA mutation site names OXPHOS (oxidative phosphorylation) is a primary target for the phenotype manifestation, the identified mutations are not only somatic but also in the whole body [96]. An uncoupling protein (UCP) is a mitochondrial inner membrane protein that is involved in energy hemostasis, insulin secretion, free fatty acid concentration, and lipid metabolism. It has been found in white adipose tissue, skeletal muscle, pancreatic islets, and CNS. UCP protects CNS from acute alcohol consumption and insulin resistance. In the study by Rezapour S et al, they investigated the UCP2 (25bp) insertion/ deletion mutation in NAFLD, in 72 patients with NAFLD and type 2 diabetes and 77 healthy control. It has been shown that insertion/insertion genotype mutation was observed in diabetic patients. Patients with NAFLD, with Delete/Delete, and Delete/Insertion genotypes, had higher alanine transferase (ALT), aspartate transferase (AST), triglyceride (TG), and lower high density lipoprotein (HDL) levels than healthy controls, [97]. Aaron M. Gusdon et al. showed that mitochondrial haplogroup G (a human mitochondrial DNA) is more significant in NAFLD patients compared with healthy controls. Also, the pathogenic rs738409 GG genotype is higher in patients with haplogroup A [98]. Ming Qiao et. al found that SNPs of rs2143571, rs3761472, and rs738491 of the SAMM50 gene, are associated with a higher risk of NAFLD vulnerability [99]. Sevastianova et al., have shown that the homozygous individuals of the PNPLA3 rs738409 G allele had a significant decrease in liver fat content when a 6-day hypo caloric- low carbohydrate diet was used [100].

1.16 Other SNPs

RETN produces human hormone of resistin, which contain 108 amino acid and cysteine-rich protein. Resistin hormone is produced by adipose tissue and inflammatory cell such as macrophages and monocyte.and causes IL-6, IL-12, and TNF-a secretion. There is a correlation between the RETN gene variant and obesity, T2DM, and hypertension. Tabeian et al, showed that the variant of RETN rs 3745367 gene variant does not have any significant relation with NAFLD means that this gene polymorphism does not increase the risk of NAFLD [101]. Fibronectin type 3 domain-containing protein 5 (FNDC5) is a membrane protein expressed in skeletal muscle and cleaved and released as irisin. FNDC5 rs 3480 G variant affect sarcopenia, and sarcopenia is completely associated with liver fibrosis and insulin resistance [102]. APO E as plasma lipoprotein, which plays a role in dyslipidemia by transferring TG, cholesterol

metabolites, has three gene alleles (E2, E3. E4). The E4 allele has a role in liver disease development. In a study in the Chinese population, the E4 allele had a higher prevalence in NAFLD patients than in healthy control, also E3/E3 has a higher risk of NAFLD development, while E3/E4 is a protective factor against NAFLD development [103].

1.17 Membrane-bound O-acyltransferase (MBOAT7)

MBOAT7, is a protein that is involved in the phosphatidylinositol pathway, in hepatocyte sinusoidal cells and hepatic satellite cells of the liver. The MBOAT7 gene is located on chromosom19. Scientists have shown that the rs641738 C > T MBOAT7/TMC4 variants are involved in developing NAFLD. MBOAT7 rs641738 T allele is related to lower expression of MBOAT7 and possibly predisposes to HCC in patients without cirrhosis. MBOAT7 along with PNPLA3 and TM6SF2 known as being involved in lipid metabolic processes and dysfunctional lipid turnover, therefore they can be identified to develop NAFLD [104, 105].

1.18 Life Style

Metabolic disease is the complex of obesity, diabetes, and other complaints such as hypertension and hyperlipidemia and are associated with HCC. NAFLD has three stages that are started by fat deposition and metabolic stress known as NAFL, the second stage is improved by higher fat deposition and liver inflammation leading to NASH. Constant inflammation, will be formed fibrosis in hepatic tissue and hepatic satellite cells will be activated, in the last stage, hepatocytes are replaced by fibrosis and ended in cirrhosis and liver failure [106, 107].

1.19 Obesity

Obesity is caused by not only the imbalance between caloric intake and energy expenditure but involves a complex of biological processes and psychological factors [108, 109]. Having an active life results in decreased lipid disorder, blood pressure, type 2 diabetes, and many metabolic diseases such as metabolic syndrome. As most NAFLD patients have low physical activity, 3-5 sessions (150-200minutes) per week of moderate physical activity have been shown to decrease NAFLD progression [110]. Research by Musso et al demonstrated weight loss of more than 7% results in better status in histological examination and cardiometabolic profile [111]. Due to guidelines, energy restrictions for women should be limited to 1200-1500 calorie daily, and for men 1500-1800 calories that are adjusted with body weight [112]. A higher level of fat infiltration and increased hepatic lipid accumulation and an increase of denovo lipogenesis lead to a reduction in hepatic lipid clearance, free fatty acid oxidation and VLDL excretion [113]. Liver hepatocytes and adipocytes have a close relation with HSC, Kupfer cells, and endothelial in the biochemical signaling pathway IKK B/NF-KB activated by obesity or a high-fat diet and all of them results in chronic inflammation [114]. As linoleic acid and arachidonic acid have a central role in inflammation, so reducing these fatty acids in the diet, inhibit progression to a more severe stage [115]. In obesity, different organs send signals to the liver, and activate related factors, so insulin resistance will start in the brain. When excess fat and glycerol deliver to the liver, lipolysis in white adipose tissue increases and direct to gluconeogenesis and triglyceride synthesis in hepatocytes [116]. In many animal studies, enriched fruit and vegetable diets, alleviate inflammation and NAFLD in the liver. It has been proven that flavonoids in animal models have a protective effect on NAFLD prevention by reducing body weight and fat deposition [79].

1.20 Insulin Resistance and Diabetes type2

At the cellular level, insulin binds to its receptor, a tetramer containing 2 alpha chains and 2 beta chains on the cell membrane surface. Insulin binds to the alpha chain and starts the signaling cascade and activates glucose transport, glycogen synthesis, lipogenesis, cell proliferation, cell differentiation, cell survival, and downregulation of gluconeogenesis and lipolysis. Insulin signaling has several steps; it started with the autophosphorylation beta chains receptor, by activation of IRS1/2 (insulin receptor substrate), signaling pathways will triggered: PI3K/AKT- TSC1/2- mTOR. Changes in each part of these signaling pathways can lead to insulin resistance. Inhibiting of IKK-B, JNK-1, and PKc that improve serine phosphorylation of IRs and reduce glucose uptake, glycogen synthesis, and also phosphorylation of FOXO, ended in hepatic gluconeogenesis [117]. In addition, some lipid species such as diacylglycerol, ceramide, and free fatty acids like palmitate and acyl-CoA are related to hepatic insulin resistance. So all body organs are influenced by hepatic lipid metabolism, and NAFLD will be developed [118].

1.21 Smoking

The relationship between NAFLD and smoking is controversial. It is proven that smoking increases the risk of cardiovascular diseases, diabetes, cancer, and respiratory diseases by increasing the production of reactive oxygen species (ROS) and lipid peroxidation. Despite the increasing levels of ROS and lipid peroxidation, the association between NAFLD and smoking has not been clear yet. The involving factors such as cytotoxic chemicals in cigarettes may stimulate fibroblast cell proliferation and growth that causes scar in liver tissue. In addition, nicotine has a strong association with hepatic injury by activating of acetylcholine receptor [19, 119]. Ebenezer T Oni et. al, in a study conducted on 6354 healthy subjects, found that smoking significantly increases oxidative stress as measured by gamma-glutamyl transferase (GGT). Their results showed that GGT levels are significantly higher in smokers with NAFLD. They performed a multivariate adjustment and demonstrated that current smoking was associated with higher GGT levels (about 4.65 IU/L) compared to non-smokers. These adjustments when made by NAFLD, showed that the association was greater in subjects with NAFLD. They concluded that GGT is an important oxidative stress marker in identifying the interaction between smoking and NAFLD [119]. Although smoking can be an enhancer factor in liver fibrosis, it has shown that advanced liver fibrosis was higher in diabetic smokers than healthy ones [120]. Karn Wijarnpreecha in a Cross-sectional study of 11205 participants, concluded that mortality from smoking was increased two-fold among the US population. Although the magnitude was not a significant difference in non-NAFLD individuals, however, smoking was a long-term determinant for the outcomes of NAFLD [121].

1.22 Sex

Although recent research has shown that NASH is a new

trend among women, men are more susceptible to NAFLD than women in premenopausal status [122]. These differences originate from hormonal differences. lipotoxicity is a hallmark in NAFLD development to NASH, also related to an inflammatory and fibrotic response. Estradiol inhibits the liver from lipid accumulation, inflammation, and fibrosis. Estrogen mediates its effects through two main pathways: genomic (canonical) and nongenomic (non-canonical). Estrogens, in the genomic pathway, bind two nuclear receptor isotypes, estrogen receptor α (ERα) and estrogen receptor β (ERβ), and activate them. These bindings of estrogen with ERs, cause homo- or hetero dimerization of ERs, then the complex of estrogen and ERs move to the nucleus and bind to specific DNA sequences, (EREs), and the transcription of target genes, like ATP binding cassette subfamily A member 3 (ABCA3) and regulate genes expression. In the non-genomic pathway, several signaling pathways activate without direct interaction with DNA. Estrogen rapidly enhances the level of cyclic adenosine monophosphate (cAMP) with activating adenylyl cyclase and intercede intracellular signaling transduction, like the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways. Estrogens on the other hand bind to G-protein coupled estrogen receptor (GPER) at the plasma membrane and causes extracellular signal-regulated kinase (Erk) activation. The expression levels of ERs differ according to the cell types, for example, ERβ is more plentiful than ERα in breast cancer cells, while ERα is more found than ERβ in hepatocytes [123]. In a cohort study it is investigated that the risk of diabetes type 2 is increased by the severity of NAFLD, a higher risk of NAFLD in postmenopausal women is shown therefore diabetes type 2 has greater development in women than men. [124]. After menopause, the prevalence of NAFLD in men and women is the same, that is reflected the estrogen hormone importance. Estrogen-related receptor alpha (ERRα) which is a nuclear receptor has a regulatory role in the lipid metabolism pathway and mitochondrial oxidative phosphorylation. This receptor mediates TG synthesis and VLDL secretion by controlling related genes. In ERRα- knockout mice that had more severe steatohepatitis, estrogen receptor alpha differently worked in lipid metabolism and VLDL secretion in different sexes [125].

2. Conclusion

Several constituents are involved in developing fatty liver, among which lifestyle can be the most preventable element for this disease. Regulating physical activity, food eating, and avoiding smoking and alcohol consumption are the ways to prevent fatty liver. For non-preventable factors such as genetics and thyroid disease, more studies are needed to develop the best therapeutic drugs.

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