Adipokines in Non-Alcoholic Fatty Liver Disease

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Non-alcoholic fatty liver disease (NAFLD) has become the major cause of chronic hepatic illness and the leading indication for liver transplantation in the future decades. NAFLD is also commonly associated with other high-incident non-communicable diseases, such as cardiovascular complications, type 2 diabetes, and chronic kidney disease. Aggravating the socio-economic impact of this complex pathology, routinely feasible diagnostic methodologies and effective drugs for NAFLD management are unavailable. The pathophysiology of NAFLD, defined as metabolic associated fatty liver disease (MAFLD), is correlated with abnormal adipose tissue–liver axis communication because obesity-associated white adipose tissue (WAT) inflammation and metabolic dysfunction prompt hepatic insulin resistance (IR), lipid accumulation (steatosis), non-alcoholic steatohepatitis (NASH), and fibrosis. Accumulating evidence links adipokines, cytokine-like hormones secreted by adipose tissue that have immunometabolic activity, with NAFLD pathogenesis and progression.

Keywords: adipokines ; NAFLD ; liver ; steatosis ; fibrosis ; inflammation ; NASH ; leptin ; biomarkers ; therapy

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver abnormalities characterized by increased hepatic fat content (>5%)—steatosis—in the absence of secondary causes, namely excessive alcohol consumption (>20 g/day for women and >30 g/day in men), medications, viral hepatitis, or certain hereditable conditions. Histologically, NAFLD can be categorized into non-alcoholic fatty liver (NAFL), when there is only evidence of hepatic steatosis, and non-alcoholic steatohepatitis (NASH), when, apart from steatosis, lobular inflammation and hepatocyte ballooning with or without perisinusoidal fibrosis can be observed. NASH, especially in the fibrotic state, often presents worse prognoses and frequently progresses to more severe conditions, such as cirrhosis and hepatocellular carcinoma [1].

NAFLD has become the major cause of chronic hepatic illness in children and adults, as well as the leading indication for liver transplantation in the future decades, replacing chronic hepatitis C. This high-incident pathology is also associated with extra-hepatic complications, such as chronic kidney disease and cardiovascular disease, which is the leading cause of death among NAFLD patients [2]. Mainly asymptomatic, NAFLD is considered a major societal, clinical, and research challenge due to its increasingly high prevalence, difficulties in its diagnosis, the lack of approved therapies, and its complex pathophysiology.

The development and progression of NAFLD is induced by multiple factors in a “multiple parallel-hit” model, where numerous genetic and environmental determinants (“hits”) interplay on an individual basis. These factors encompass, but are not limited to, genetic alterations, inflammation, gut dysbiosis, and metabolic abnormalities. Indeed, almost 90% of NAFLD patients present at least one of the metabolic syndrome features (abdominal obesity, hypertriglyceridemia, low HDL-cholesterol, hypertension, and high fasting glucose), and about 33% fulfill the criteria for diagnosing metabolic syndrome [3]. Therefore, metabolic-associated fatty liver disease (MAFLD) was recently proposed as a more appropriate overarching term that recognizes the metabolic risk profile of patients as the master criterion for diagnosis and considers the disease activity grade to be a continuum, which better describes disease pathophysiology [4]. Therefore, it is not surprising that the worldwide prevalence of NAFLD is rising in parallel with obesity [2], the main driver of metabolic abnormalities. Stepping up the strict correlation between obesity and NAFLD, there is a dose-response between weight loss and histological disease improvement; a 7% weight loss reverts NASH in 65–90% of patients, and a ≥10% weight loss causes fibrosis relapse in 45% of patients [3].

2. Adipokines as Potential Therapeutic Targets for NAFLD

2.1. Leptin and Adiponectin

Leptin, the forerunner and best-characterized member of the adipokine family, plays a pivotal role in appetite and body-weight homeostasis by augmenting anorexigenic neuropeptides and suppressing orexigenic factors in the central nervous

system [5]. Likewise, leptin has been described as modulating several physiological processes, such as lipid and glucose metabolism, as well as both innate and adaptive immunity [5]. Most of the current knowledge about leptin's action arose from leptin-deficient *ob/ob* mice and leptin-receptor-deficient *db/db* mice. These murine models exhibited marked hepatic alterations, such as IR, accumulation of TG and lipids, and steatosis, which were partially reverted following leptin administration to *ob/ob* mice [6][7]. Although leptin acts as an anti-steatotic hormone preventing the accumulation of and promoting the mobilization of hepatic lipids, leptin resistance may cause the leptin inability to alleviate hepatic steatosis [6][7]. Furthermore, high leptin plasma levels derived from obese adipose tissue are associated with hepatic inflammatory and fibrogenic mechanisms and therefore, with NAFLD development [6][7].

On the contrary, adiponectin, an adipocyte-secreted hormone inversely correlated with obesity and with determining roles in insulin sensitivity, glucose levels, and lipid metabolism [8], has been reported to protect the liver from steatosis, inflammation, and fibrosis [9]. Adiponectin augments insulin's capacity to suppress glucose production, prevents hepatic DNL, suppresses FA synthesis in hepatocytes, and enhances FA β-oxidation [9], overall protecting the liver from steatosis. Adiponectin was also described as decreasing the production of inflammatory cytokines, such as IL-6 and TNF-α, through the modulation of toll-like receptor 4 (TLR4) signaling. By boosting the beneficial effects of adiponectin in NAFLD development, this adipokine was described to possess anti-fibrotic effects by preventing leptin profibrogenic signaling [9]. Therefore, strategies aiming to rescue the leptin–adiponectin balance, i.e., reverting the obesity-associated increased leptin levels and reduced adipokines levels, are of relevance for NAFLD treatment [9].

2.2. Ghrelin

Ghrelin stands out as one of the few peripheral peptide hormones with an orexigenic effect. Initially identified as a stomach-derived hormone, ghrelin is an endogenous ligand for the growth hormone secretagogue receptor 1a (GHSR1a). It stimulates food intake and adiposity and acts as a regulator of glucose metabolism, reward behavior, gut motility, or even hepatic lipid metabolism and the immune system [10][11]. This hormone circulates in blood in two forms, an acylated (AG) form and an unacylated form (UAG, also named DAG from desacyl ghrelin). This post-transcriptional modification is catalyzed by ghrelin O-acyltransferase (GOAT), and the producing AG is the active form that triggers the signaling of the cognate receptor GHSR1a. Initially thought to be an inactive form, it has been suggested that UAG to antagonizes AG activity on glucose metabolism and lipolysis and reduces food consumption and body weight [11][12]. Given its regulatory activity on metabolism and immune system, there is a growing interest on the role of ghrelin-GOAT system in the development and progression of NAFLD.

In murine models, the administration of ghrelin during or after diet-induced NAFLD development counteracts dysregulated hepatic lipid metabolism, oxidative stress, apoptosis, and inflammation [13][14]. Furthermore, the action mechanisms involved in the beneficial effects of ghrelin on NAFLD were investigated. The amelioration of liver injury by ghrelin was accompanied by the reestablishment of phosphoinositide 3-kinase (PI3K)/Akt and liver kinase B1 (LKB1)/AMP-activated protein kinase (AMPK) pathways [13]. Ghrelin also attenuates lipotoxicity by upregulating autophagy via AMPK/mTOR restoration and inhibiting nuclear factor kappa B (NF-κB) [14]. Recently, ghrelin was demonstrated to block the progression of NASH induced by lipopolysaccharide (LPS) in mice fed with a high-fat diet through the reduction of Kupffer cells' M1 polarization, which is mediated by GHSR1a [15]. In addition to these results demonstrating the beneficial effects of ghrelin, the genetic deletion of ghrelin in mice also significantly reduced age-associated hepatic steatosis, partly by downregulating diacylglycerol O-acyltransferase-1, one of the key enzymes of TG synthesis [16].

Concerning the effects of the ghrelin's isoforms, it was verified that plasma UAG levels were reduced after a sleeve gastrectomy and a Roux-en-Y gastric bypass in Wistar rats, whereas the AG:UAG ratio was augmented. Concomitantly, both surgeries diminished obesity-associated hepatic steatosis, inflammation, mitochondrial dysfunction, and endoplasmic reticulum stress. Moreover, AG has a similar effect in palmitate-treated hepatocytes, which suggests that the increased AG:UAG ratio after bariatric surgery might ameliorate obesity-associated NAFLD [17]. Possible underlying mechanisms are the reduction of lipogenesis and stimulation of mitochondrial FA β-oxidation, as well as hepatic autophagy, by relatively increased AG levels [18]. Nevertheless, in lean rats, the administration of exogenous AG induced hepatic IR and lipid accumulation, while the co-administration of UAG prevented the AG-induced effects [19]. Thus, further evaluation of the ghrelin-GOAT system and the effects of AG and UAG isoforms on NAFLD development is needed.

2.3. Resistin

Resistin (named for its ability to induce "resistance to insulin") is the founding member of resistin-like molecules (RELMs), a family of small, secreted cysteine-rich peptides with hormone-like and pro-inflammatory activities. It is mainly secreted by adipose tissue and inflammatory cells, and its action is thought to be mediated by the TLR4 receptor, although the receptors tyrosine kinase-like orphan receptor (ROR)-1, insulin-like growth factor type 1 receptor (IGF-1R), and adenylyl

cyclase-associated protein 1 (CAP1) have also emerged as potential candidate receptors [20]. Resistin has been shown to have pleiotropic effects, including the regulation of blood–glucose levels and lipid metabolism, as well as the induction of pro-inflammatory cytokines secretion or monocyte differentiation into macrophages [20]. In fact, resistin administration to C57BL/6J mice increased blood glucose, i.e., impaired glucose tolerance, due to the decreased insulin sensitivity, which was rescued after the administration of an anti-resistin antibody [21]. Similarly, the high-fat diet (HFD)-fed mice presented increased plasma resistin levels and severe IR, which is completely reversed after treatment with a resistin antisense oligonucleotide [22]. More recently, the mechanisms of action of resistin in a HFD-induced NAFLD model were disclosed [23]. Acute elevated resistin altered mitochondrial morphology and content, increased lipid accumulation, and up-regulated pro-inflammatory mediators in HFD-fed mice and palmitate-treated HepG2 cells. Furthermore, steatosis aggravation induced by resistin in mice is mediated by the AMPK/peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) pathway [23]. It was also reported that resistin treatment augments the suppressor of cytokine signaling 3 (SOCS3) expression, a suppressor of insulin signaling, in adipocytes [24].

Resistin-deficient mice demonstrated reduced hepatic glucose production and, consequently, their blood–glucose levels after fasting were low [25]. In addition, *ob/ob* mice and diet-induced obese mice, both lacking resistin, had reduced hepatic steatosis, since the expression of genes involved in hepatic lipogenesis and the secretion of very-low-density lipoprotein (VLDL) were decreased [26].

At the cellular level, resistin hampered glycogen synthase kinase 3β (GSK3β) phosphorylation in primary rat hepatocytes under hyperinsulinemic and hyperglycemic conditions, with further reduction of glycogen synthesis and hepatic insulin action [27]. Resistin also exerts pro-inflammatory activity by inducing the expression of cell adhesion molecules and pro-inflammatory cytokines in macrophages and mononuclear cells, contributing to the recruitment of leukocytes to inflammation sites [20]. Moreover, the secretion of resistin by infiltrated monocytes/macrophages is enhanced by pro-inflammatory mediators [20]. Of note, hepatic myeloid cells and T-lymphocytes from NAFLD patients showed a decreased response to resistin, which is associated with a failure to maintain redox homeostasis, which would be a risk factor for NAFLD severity [28]. It was also verified that resistin increased hepatic inflammation through mitogen-activated protein kinase (MAPK) signaling and the activation of a coagulation cascade in animal models [29]. Finally, resistin demonstrated profibrogenic effects by activating HSCs, which release IL8/CXCL8 and monocyte chemoattractant protein (MCP)-1/CCL2 via NF-κB, and increasing the transforming growth-factor beta (TGFβ) and collagen type I production in Kupffer cells [30] [31].

2.4. Retinol Binding Protein 4 (RBP4)

Distinct mouse models have been used to elucidate the RBP4 activity in metabolic diseases. In general, elevated circulating and adipose tissue RBP4 levels have been correlated with IR, dyslipidemia, and T2DM [32]. The possible RBP4-dependent mechanisms contributing to IR include impaired insulin signaling, the down-regulation of GLUT-4 translocation, and the induction of inflammatory and lipolytic pathways in adipose tissue, as well as the induction of phosphoenolpyruvate carboxykinase in the liver, thereby increasing glucose production [32].

In genetic and dietary mouse models of NAFLD, the results of hepatic expression of RBP4 are controversial. Liu et al. observed an abnormal hepatic RBP4 expression in apoE−/− mice fed with a high-fat and high-cholesterol (HFC) diet [33]. However, Saeed et al. described reduced hepatic RBP4 levels in C57BL/6J mice fed with a HFC diet and in *ob/ob* mice, while serum RBP4 levels were increased in both models [34]. Apart from that, transgenic mice overexpressing human RBP4 had increased hepatic lipid accumulation, cellular ballooning, and inflammation, which were exacerbated when mice were challenged with a high-fat diet, likely through RBP4-induced mitochondrial dysfunction [33][35]. Of note, recently, novel RBP4 antagonists were reported to reduce hepatic steatosis in transgenic mice with adipocyte-specific overexpression of RBP4 [36].

2.5. Visfatin

Nicotinamide phosphoribosiltransferase (NAMPT), also called pre-B cell colony-enhancing factor (PBEF) or visfatin, functions as an intracellular enzyme (iNAMPT) mediating the synthesis of nicotinamide adenine dinucleotide (NAD+) and as a cytokine-like soluble factor secreted into extracellular space (eNAMPT) [37]. Intracellular NAMPT regulates mitochondrial biogenesis, cellular metabolism, and survival, as well as the adaptive response to cell stress; it was described as modulating pancreatic β-cell function, likely regulating glucose homeostasis and IR [38]. On the other hand, extracellular NAMPT acts mainly as an inductor of pro-inflammatory cytokine production [37]. The NAMPT extracellular form has been associated with metabolic and inflammatory disorders, but its pathophysiological mechanisms are still ill-defined [37].

Administration of NAMPT to a methionine-choline-deficient (MCD)-diet-fed mouse model of NAFLD aggravated hepatic steatosis, increased inflammatory cell infiltration and inflammatory cytokines levels and exacerbated the expression of fibrotic markers in the liver, together with the induction of endoplasmic reticulum and oxidative stress [39]. In hepatocytes, NAMPT also induced the expression of inflammatory cytokines and diminished insulin signaling through a signal transducer and activator of transcription 3 (STAT3) and NF-κB activation [40]. These results support the adverse effects of NAMPT in hepatic steatosis, inflammation, and fibrosis. However, the pharmacologic inhibition or genetic ablation of NAMPT also showed deleterious effects. The intracellular NAMPT inhibitor FK866 promoted liver steatosis in HFD-fed mice and hepatic lipid accumulation in vitro via the sirtuin 1 (SIRT1)/sterol regulatory element-binding protein 1 (SREBP1)/fatty acid synthase (FASN) pathway [41]. Similarly, the knockdown of NAMPT in hepatocyte cells led to TG accumulation through the regulation of DNL via SIRT1/AMPK pathway [42]. Accordingly, the overexpression of NAMPT in hepatocyte cell lines mitigated lipid accumulation [41]. However, hepatocyte-specific NAMPT knockout mice on low-methionine and choline-free high-fat diet showed less TG accumulation than wild-type controls but had augmented histological scores for hepatic inflammation, necrosis, and fibrosis [43]. Of note, NAMPT KO mice on a control diet also showed liver injury, since they had decreased mitochondrial proteins and respiratory capacity and increased fibrosis due to low NAD+ levels [43]. Taken together, the present data suggest that the opposing activity of NAMPT in NAFLD pathophysiology could be derived from the different roles of extracellular and intracellular NAMPT, but further studies are needed.

2.6. Chemerin

Chemerin, also named tazarotene-induced gene 2 (TIG2) and retinoic acid responder 2 (RARRES2), is secreted as inactive precursor, which is activated by proteases of the coagulation cascade, neutrophil-derived proteases (elastase and cathepsin G), bacterial proteases, and mast cell products (tryptase) [44]. This chemotactic adipokine binds to the G protein-coupled receptor chemokine-like receptor 1 (CMKLR1), which is expressed in dendritic cells, macrophages, and natural killer (NK) cells and may serve as bridge between innate and adaptive immunity [45]. Although the C-C chemokine receptor-like 2 (CCRL2) and the G protein-coupled receptor 1 (GPR1)/CMKLR2 were also described as chemerin receptors, their physiological activity is still uncertain. Chemerin and its receptor CMKLR1 are both expressed in adipose tissue [46], and they have been reported to be augmented in obesity and IR states (T2DM), decreasing after weight loss [47]. This adipokine also seems to regulate adipocyte differentiation, glucose and lipid homeostasis, and insulin sensitivity [44].

In addition to its ability to regulate glucose metabolism, IR, and inflammation, the role of chemerin in NAFLD is still unclear. The administration of recombinant chemerin ameliorate HFD-induced NASH in mice, as well as IR, leptin resistance, and liver lesions, by alleviating oxidative stress and promoting autophagy, at least in part, due to chemerin/CMKLR1-dependent activation of janus kinase 2 (JAK2)-STAT3 pathway [48]. On the contrary, the administration of a chemerin-derived C15 peptide did not affect hepatic TG accumulation, inflammation, or fibrotic gene expression in atherogenic diet-induced murine NASH [49]. Moreover, PI3K inhibition mitigated liver steatosis and KC-mediated inflammation due to the down-regulation of the chemerin receptor CMKLR1 in the liver [49]. Nevertheless, whole-body *Cmklr1*-gene abrogation in mice did not affect either the hepatic lipid accumulation, inflammation, fibrotic gene expression, NAS, or the IR [50]. Inconsistencies in the current data could be related to the differential modulation of hepatic chemerin in distinct murine models of NAFLD [51].

2.7. Adipocyte Fatty Acid-Binding Protein (AFABP)

There is strong evidence correlating elevated AFABP with IR and adipose tissue lipolysis in obesity and metabolic syndrome [52]. Interestingly, a recent research pointed out that AFABP as a metabolic/functional marker regulating macrophage functions likely having a determining role in pathophysiology [53]. Concerning to NAFLD, AFABP expression was elevated in Kupffer cells in both LPS-induced acute liver injury and diet-induced NAFLD [54]. In these NAFLD mice models, the pharmacological inhibition of AFABP ameliorated hepatic steatosis, macrophage infiltration, and hepatocellular ballooning [54]. Genetic ablation and the pharmacological inhibition of AFABP also attenuated bile-duct-ligation- and carbon-tetrachloride-induced liver fibrosis in mice through the reduction of collagen accumulation, liver sinusoidal endothelial cells (LSEC) capillarization, and HSC activation [55]. Mechanistically, elevated AFABP promotes LSEC capillarization, an early event of NAFLD pathogenesis, and LSEC-derived AFABP activate HSCs that augments TGFβ production and further extracellular matrix accumulation and fibrosis [55]. Furthermore, AFABP could promote hepatic inflammation through Kupffer cell activation [54]. Altogether, these findings suggest pharmacological inhibition of AFABP as a promising therapeutic strategy for NAFLD.

3. Adipokines in NAFLD: Evidence from Clinical Studies

3.1. Ghrelin

Clinical studies have demonstrated that obese patients with IR or metabolic syndrome had lower UAG and total ghrelin levels, while the AG:UAG ratio was elevated [56][57]. Moreover, the AG:UAG ratio was positively correlated with IR in both obese children and adults [56][58]. After the proof about the influence of ghrelin on insulin sensitivity, some research focused on ghrelin's role in NAFLD, but the evidence is scarce, and not all studies take into consideration the concentrations of total ghrelin and its isoforms, AG and UAG.

Ghrelin levels were associated negatively with body mass index (BMI) in obese NAFLD patients diagnosed by ultrasonography [59] or biopsy [60]. Compared to matched healthy controls, patients with NAFLD showed reduced ghrelin levels, which correlated with IR [61]. However, in a study with NAFLD biopsy-proven patients that underwent bariatric surgery, UAG levels were increased in NASH patients compared to non-NASH subjects, while similar levels of AG were observed. Additionally, higher levels of AG, but not UAG, were observed in higher stages of fibrosis [62]. Further evidencing the role of ghrelin in NAFLD, recent case-control retrospective studies of biopsy-proven NAFLD patients suggested that the Leu72Met (rs696217 G > T) polymorphism and the "GG" genotype of rs26802 variant in the ghrelin gene have a protective effect against NAFLD [63][64].

3.2. Resistin

As described above, the positive correlation between resistin and IR, steatosis, and inflammation is well stablished in murine and cellular models, but data in human NAFLD are conflicting. A systematic research of Bekaert et al. found 12 studies reporting resistin levels in biopsy-proven NAFLD patients, of which 6 reported statistically significant results [65]. Circulating resistin levels were positively correlated with hepatic steatosis, portal inflammation, and NAFLD ACTIVITY SCORES in non-diabetic NAFLD patients [66][67][68][69]. Of relevance, Aller et al. found that resistin association with the steatosis grade was lost when the homeostatic model assessment of insulin resistance (HOMA-IR) parameter was included in the multivariate logistic analysis, indicating that resistin is a surrogate marker of IR [67]. Supporting the relevance of resistin in NAFLD, a predicting diagnostic biomarker panel for histological NASH in obese subjects included the serum levels of resistin together with adiponectin and cytokeratin 18 (marker of cell death) [70]. However, resistin was not included in the predicting algorithm for NASH or NASH-related fibrosis in a more recent study by the same group [71]. In contrast, a study described a negative correlation between circulating resistin levels and the steatosis grade in severely obese NAFLD patients [72]. The remaining studies included in the cited meta-analysis did not demonstrate an association of resistin with liver histological parameters in obese and non-obese NAFLD patients [73][74][75][76]. It is worth mentioning that, in this meta-analysis, 4 out of the 12 studies did not adjust their results for confounding factors, and the potential association between resistin and IR was conflicting among the studies [65]. More recently, the determination of serum resistin levels in severe obese NAFLD patients found no correlation with steatohepatitis or fibrosis severity [77]. Similarly, resistin circulating levels did not associate with steatosis grade, NASH diagnosis, hepatic ballooning, or lobular inflammation grade, but they did correlate with fibrosis stage in obese NAFLD patients [78].

Although there are ambiguous data on circulating resistin levels in NAFLD patients, the existing results on its hepatic expression are more consistent. Augmented hepatic resistin mRNA levels were reported in patients with NASH compared to steatosis or control subjects and in steatosis patients compared to control individuals [79]. Moreover, a positive association between hepatic resistin mRNA levels and hepatic steatosis, inflammation, or fibrosis was reported in several studies [79][80]. Additionally, a positive correlation between hepatic resistin protein expression and NAS, aspartate aminotransferase (AST), alanine aminotransferase (ALT), BMI, glucose, insulin, HOMA-IR, gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), TG, and glycated haemoglobin was verified in obese NAFLD patients [81]. The resistin mRNA expression in subcutaneous adipose tissue was also verified to be increased in non-obese NAFLD patients, but no correlation with liver histological parameters was observed [68]. Interestingly, the immuno–histological assessment of hepatic samples of NAFLD patients revealed a resistin distribution predominantly in perisinusoidal cells (Kupffer cells and HSCs) [79], histiocytes of inflammatory infiltrate, and histiocytes surrounding the hepatocytes with steatosis [81]. Finally, a significant association was observed between resistin rs1862513 polymorphism and NAFLD [82], which supports the significance of resistin in the development of NAFLD.

3.3. Retinol Binding Protein 4 (RBP4)

Several clinical studies showed that elevated circulating RBP4 levels were associated with insulin-resistance states, namely obesity and T2DM [32]. In addition, decreased levels of RBP4 were correlated with recovering insulin sensitivity after weight loss or lifestyle intervention in obese adult or children populations [83][84]. Given the close association of

NAFLD pathogenesis and IR, NAFLD is assumed to be correlated with increased levels of serum RBP4; however, inconsistent findings were observed. In studies without histological confirmation, serum RBP4 levels seemed to be positively correlated with liver fat [85] and were found to be higher in NAFLD patients than controls, in adult and pediatric subjects [86][87]. Nevertheless, a systematic research reported that only three out of seven studies verified a positive correlation between serum RBP4 levels and liver histology among patients with biopsy-proven NAFLD [65]. Similarly, a meta-analysis research did not find any significant differences between NAFLD, NASH, or SS patients compared to controls, neither between NASH nor SS patients [88]. The researchers highlighted the heterogeneity across patient populations or the lack of adjustment for confounding factors in the analyzed research, which challenges comparisons between studies and limits the conclusions that can be drawn about the associations between adipokines levels and NAFLD. More recently, a 3-year follow-up study in a Chinese cohort of NAFLD patients diagnosed by abdominal ultrasonography verified that baseline serum RBP4 concentrations are positively associated with NAFLD development and inversely correlated with NAFLD regression [89]. Moreover, higher serum RBP4 levels were associated with an increased risk for prediabetes and metabolic syndrome in obese patients with NAFLD [90].

3.4. Visfatin

Several studies have evaluated the levels of visfatin in histologically confirmed NAFLD patients as well as the possible correlations with hepatic steatosis, inflammation, and fibrosis; but, current data are limited and inconclusive, as verified by two systematic research [65][91]. Most data reported similar serum visfatin levels in NAFLD [92], simple steatosis (SS) [93], or NASH patients [93][94] compared to control subjects, as well as in NASH compared to SS patients [93][95]. Likewise, similar hepatic visfatin expression was found in NASH and SS patients [96]. However, some studies also verified the augmented levels of serum visfatin in NAFLD compared to controls [97] or the decreased visfatin levels in NAFLD [98], SS, or NASH patients versus controls [70][95]. Of note, increased serum visfatin levels were associated with a reduced hepatic DNL index in women with ultrasound-diagnosed NAFLD, while in men it was correlated with augmented hepatic fat but not with DNL index, which suggests a sex-dependent interpretation for the serum visfatin levels in NAFLD prognosis [99].

Concerning histological parameters, most data did not report any correlation between serum visfatin and hepatic steatosis, inflammation, or fibrosis [92][93]. However, Aller et al. reported that circulating visfatin levels may predict portal inflammation, but not steatosis or fibrosis, in non-diabetic obese NAFLD patients [100]. In addition, Kukla et al. found a positive correlation between hepatic visfatin expression and the fibrosis stage but not hepatic steatosis and inflammation in morbidly obese NAFLD patients [96], while Gaddipati et al. reported a positive correlation between visfatin expression in visceral adipose tissue and steatosis degree in non-diabetic NAFLD patients [98].

Interestingly, visfatin was recently proposed as a potential serum biomarker related to the degree of hepatic steatosis and fibrosis among pediatric obese patients diagnosed by non-invasive methods (abdominal ultrasound and transient elastography with liver stiffness and controlled attenuation parameter) [101]. Moreover, a 10-year follow-up study verified no association between serum visfatin levels and leukocyte infiltration in fatty liver at the baseline, but visfatin serum levels were significantly increased during the follow-up, likely due to the combined effects of augmented BMI and diabetes prevalence [102]. However, this had certain limitations, in particular, the use of ultrasonography as the NAFLD diagnosis method, without confirmation by hepatic biopsy, and the measurement of visfatin levels in all samples (basal and 10-years after) at the end of the study, which likely affects the visfatin concentrations due to different storage times.

Thus, the different methodological strategies used to study visfatin levels in human NAFLD likely determine the inconsistencies among the current data, and future research is still needed.

3.5. Chemerin

Since chemerin regulates insulin signaling and chronic inflammation, it is reasonable to hypothesize that this adipokine may be related to NAFLD development. In fact, elevated serum chemerin levels were identified as a risk factor for NAFLD development in T2DM patients [103] and were pointed out as a novel non-invasive serum marker predicting liver steatosis in obese children [104]. A recent meta-analysis [105] further explored the correlations between serum chemerin levels and NAFLD (steatosis and/or NASH) and its specific hepatic histologic lesions (liver steatosis, lobular and portal inflammation, and fibrosis). Overall, circulating chemerin levels were consistently higher in patients with NAFLD and steatosis compared to controls, although no significant difference was verified between NASH patients and controls. Moreover, data on serum chemerin levels and specific liver lesions are inconsistent, and no correlations were verified [65][105].

It was found that chemerin expression in visceral adipose tissue was negatively correlated with the steatosis score and NAFLD ACTIVITY SCORES of obese NAFLD patients, likely through the modulation of IR and, thus, NAFLD [106]. Data on hepatic chemerin mRNA expression are contradictory; its levels were found to be negatively associated with inflammation,

fibrosis, and NAS, but not with steatosis, in non-obese NAFLD patients [107], while other studies verified an increased hepatic chemerin mRNA expression, as well as hepatic CMKLR1 expression, that correlated with hepatic steatosis, hepatocyte ballooning, and the NAFLD activity score in obese NAFLD patients [108][109]. Of note, the hepatic expression of both chemerin and CMKLR1 was associated with obesity [109], which can partially explain the inconsistency of the results.

3.6. Adipocyte Fatty Acid-Binding Protein (AFABP)

In ultrasound-diagnosed NAFLD patients, serum AFABP levels were higher in NAFLD patients compared with non-NAFLD group [110][111]. The same was observed in biopsy-proven NAFLD patients, where serum AFABP had an independent positive correlation with lobular inflammation and hepatocyte ballooning, even after adjusting for confounding factors [112] [113]. Milner et al. also reported higher serum AFABP levels in NASH patients compared with SS and correlated AFABP with IR, adiposity, and the fibrosis stage [112]. Nevertheless, other studies did not verify an association between AFABP and fibrosis, or that this adipokine was able to distinguish NASH from non-NASH patients [94]. In summary, serum AFABP levels are elevated in NAFLD, but its correlation with NASH, and particular fibrosis, is still unclear.

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