REVIEW

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The Interrelationship Among Non-Alcoholic Fatty Liver Disease, Colonic Diverticulosis and Metabolic Syndrome

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ABSTRACT

Non-alcoholic fatty liver disease and colonic diverticulosis are widespread, obesity-related diseases. It has recently become clear that non-alcoholic fatty liver disease is a systemic disease and may play a key role in metabolic syndrome; therefore, the term metabolic-dysfunction-associated fatty liver disease has been introduced in the literature. Excess visceral adipose tissue is an important predictor of complications in both non-alcoholic fatty liver disease and colonic diverticulosis. Current evidence suggests that intestinal dysbiosis may be involved in the development of both non-alcoholic fatty liver disease and colonic diverticulosis, and that metabolic syndrome is a consequence rather than a cause of this complex relationship. In this review, our aim was to assess the current knowledge of the complex interplay between metabolic syndrome, non-alcoholic fatty liver disease, and colonic diverticulosis.

Key words: non-alcoholic fatty liver disease – diverticulosis – metabolic syndrome – metabolic-dysfunction-associated fatty liver disease.

Abbreviations: AD: acute diverticulitis; ADD: asymptomatic diverticular disease; BMI: body-mass index; CD: colonic diverticulosis; CDD: complicated diverticular disease; HTA: arterial hypertension; MAFLD: metabolic-dysfunction-associated fatty liver; MetS: metabolic syndrome; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; PCOS: polycystic ovaries syndrome; SAT: subcutaneous adipose tissue; SUDD: symptomatic uncomplicated diverticular disease; T2DM: type 2 diabetes mellitus; VAT: visceral adipose tissue.

INTRODUCTION

Metabolic syndrome (MetS) is characterized by abdominal obesity, insulin resistance, hypertension, and dyslipidemia [1]. Its prevalence has increased worldwide and it can be characterized as a growing epidemic with a significant impact on healthcare costs [2]. The relationship between MetS and a broad spectrum of different conditions has been widely investigated, particularly in the context of gastrointestinal and liver disorders.

Non-alcoholic fatty liver disease (NAFLD) used to be considered a hepatic manifestation of MetS. However, new insights indicate that NAFLD is a systemic disease closely associated with MetS, and it is considered both a cause and consequence of MetS. Non-alcoholic fatty liver disease often occurs together with cardiovascular diseases, chronic kidney disease, type 2 diabetes mellitus (T2DM), polycystic ovary syndrome, psoriasis, malignancies, osteoporosis, and central obesity. Indeed, its relationship with these conditions is more complex than previously thought [3, 4].

Extra-hepatic manifestations of NAFLD may be linked to the chronic low-grade inflammation observed in metabolic disorders [3]. Changes in gastrointestinal microbiota and accumulation of visceral adipose tissue (VAT) (responsible for increased production of both adipocytokines and classical cytokines) cause protracted inflammation in NAFLD. Emerging evidence suggests that the interleukin-1 family of cytokines, which are associated with pro- and anti-inflammatory effects, are the essential mediators in the so-called adipose tissue-liver crosstalk [4–6].

Metabolic-dysfunction-associated fatty liver disease (MAFLD) is defined as the presence of hepatic steatosis (confirmed by liver biopsy, imaging methods, or blood biomarkers) and is characterized by at least one of the following

three criteria: 1) being overweight or obese, 2) presence of T2DM, and 3) presence of metabolic dysregulation. The new definition of MAFLD omits the importance of alcohol consumption or other concomitant liver disease (Fig. 1) [7].

Diverticulosis is defined as the presence of diverticula and is a common anatomical condition related to aging [8]. Colonic diverticulosis (CD) presents with a wide spectrum of clinical manifestations, ranging from asymptomatic disease to segmental colitis [9-11]. Although it is advised that use of the term "diverticular disease" should be avoided, for the purpose of this review (in order to achieve uniform presentation of the available data), the following terms will be used: asymptomatic diverticular disease (ADD), symptomatic uncomplicated diverticular disease (SUDD), and complicated diverticular disease (CDD). Patients in which diverticulosis is an accidental finding are considered to have ADD. On the other hand, patients who report chronic gastrointestinal symptoms, such as changes in bowel habits, abdominal cramping, and discomfort, are diagnosed with SUDD. Complicated diverticular disease is diagnosed in the presence of more severe clinical conditions, such as acute diverticulitis (AD), diverticular bleeding, abscess and/or fistula development [10, 11]. The role of VAT and subsequent, chronic, low-grade inflammation is important in both the pathogenesis of CD and its complications [12, 13], which has led many researchers to further investigate the possible complex connection of CD and MetS [14, 15]. Components of MetS, such as central obesity, dyslipidemia, and arterial hypertension (HTA), increase the risk of CDD. However, the exact impact of metabolic risk factors on the prevalence of CD has not been clearly defined [16–19].

Our aim was to synthetize the current understanding of this complex interplay between CD, NAFLD, and MetS, given the shared pathophysiological traits and scarcity of data regarding the interrelationship between these diseases.

THE IMPACT OF NAFLD AND COLONIC DIVERTICULOSIS ON METABOLIC SYNDROME

The incidence and prevalence of NAFLD is increasing, and currently, 24% of the world population is diagnosed with this disease. While almost one-third of the population in the Middle East and South America have NAFLD, its prevalence is slightly lower in Asia, USA, and Europe (27%, 24%, and 23%, respectively). Notably, its incidence and prevalence are the lowest in Africa (14%) [20]. Both NAFLD and CD are more severe in the elderly [8]. Additionally, the incidence of NAFLD has an 'inverted U-shape' distribution, with a decreasing rate

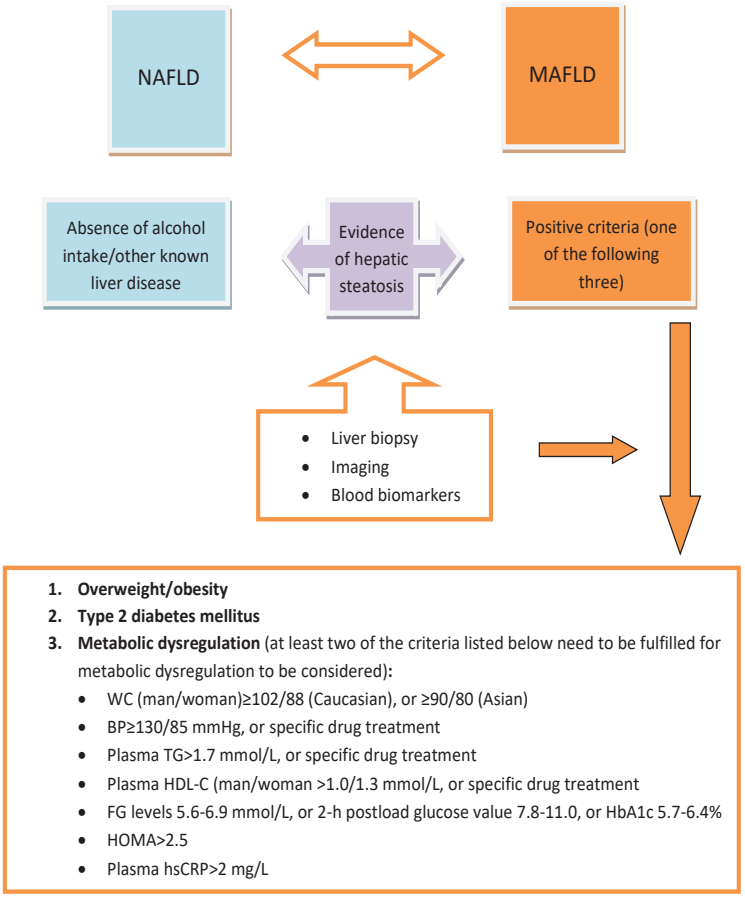

Fig. 1. Criteria for MAFLD diagnosis. BP: blood pressure; HDL-C: high-density lipoprotein; HOMA: Homeostatic Model Assessment for Insulin Resistance; hsCRP: high-sensitivity C-reactive protein; NAFLD: non-alcoholic fatty liver disease; MAFLD: metabolic-dysfunction-associated fatty liver disease; TG: triglycerides; FG: fasting glucose; WC: waist circumference.

of newly diagnosed cases after the 6th decade in men and the 7th decade in women [21, 22]. Nevertheless, NASH and cirrhosis that result from chronic inflammation typically develop in advanced age [23]. Colonic diverticulosis is also more common in Western countries, underlying the impact of Western diet, lifestyle, obesity, and MetS on development of CD [9, 18, 22]. Consequently, it appears that dietary habits and aging significantly influence the occurrence and severity of NAFLD and CD.

Recent research shows that typically CD and NAFLD occur concomitantly. In a retrospective study investigating accompanying diseases in patients with NAFLD, Kempiński et al. [24] determined that CD is the second most frequent concomitant gastrointestinal disease, second only to gastroesophageal reflux disease. Colonic diverticulosis was significantly more prevalent in the study group than in the controls (23.7% vs. 15.8%; $p<0.005$) [24]. Bae et al. [19] evaluated risk factors associated with ADD. The overall prevalence of diverticulosis was 8.1%; alternatively, it was 69.7% among patients with fatty liver disease [19]. While the presence of T2DM, hyperlipidemia, smoking status, and alcohol consumption were similar in patients with CD and the control group, HTA was significantly more frequent in patients with ADD. This study reported that moderate and severe fatty liver disease, as well as waist-hip ratio, were risk factors for ADD, highlighting the possible role of central obesity and NAFLD in the pathogenesis of ADD [18]. Contrary to these findings, Sahin et al. [21] found that in elderly patients, diverticulosis is a negative predictor of liver steatosis. According to this study, diverticulosis could be an indirect sign of malnutrition in patients over 75 years of age, since higher values of albumin and triglycerides, were identified as independent predictors of liver steatosis [21]. The age difference between the patients included in these studies may be the reason for these conflicting findings.

GUT MICROBIOTA: A POSSIBLE KEY LINK BETWEEN NAFLD AND COLONIC DIVERTICULOSIS?

Altered gut microbiota has been identified as a possible shared factor in the pathogenesis of CD and NAFLD. Recent data have shown that specific microbial species, and the metabolites that they produce, can directly impact human metabolism [25].

It was not until recently that solid evidence emerged from controlled experimental trials that linked gut microbiome and NAFLD. Gut microbiota transplants to germ-free animal models could result in the transfer of the fatty liver disease phenotype [26]. Initial fecal microbiota transplantation from conventional mice to germ-free mice was linked to the transfer of the obesity phenotype [27] and demonstrated that transfer of gut microbiota from mice with NAFLD to germ-free mice resulted in the transfer of NAFLD features, including hyperglycemia and steatosis [26]. The same study showed that gut microbiota affects lipid metabolism in the liver, independent of obesity.

In animal models, it was shown that microbiota may be used for therapeutic purposes, since the transfer of this ecosystem from healthy, lean animals to a mouse model of NAFLD (high-fat diet-induced steatohepatitis) could induce a decrease in lipid accumulation in the liver, as well as serum transaminase levels [28]. Also, intestinal microbial dysbiosis has been reported in patients with NAFLD and non-alcoholic steatohepatitis (NASH) [29-32]. Disturbances in intestinal microbiota, accompanied by impaired gut permeability, can lead to enhanced hepatic exposure to both gut microbiota and its products, which may promote liver inflammation and subsequent fibrogenesis [33, 34]. Microbiota can produce various metabolites, including ethanol, which may contribute to the development of NAFLD, with a similar pathophysiology as described for alcoholic fatty liver disease. Notably, children with NASH have increased abundance of alcohol-producing bacteria and elevated blood-ethanol concentration [29].

Changes in gut motility can contribute to bacterial overgrowth and nutrient malabsorption [8]. Animal studies have suggested that a diet high in cholesterol, fructose, and especially fat can cause loss of up to 30% of enteric neurons, the main regulators of gut motility [8, 35]. However, it is unclear whether reduced gut motility contributes to the progression of NAFLD. Steatohepatitis and liver fibrosis have been associated with enteric neural loss, and morphometric analysis determined that CD is also associated with structural alterations of enteric neurons [34, 36]. In addition to diet, intestinal dysbiosis has a significant impact on gut motility. We are getting closer to identifying biological mechanisms involved in gut-liver axis in animal models; however, it remains unclear whether these processes independently, or more likely, jointly, initiate the pathophysiological cascade, and eventually create a "*circulus vitiosus*" responsible for the development of these disorders (Fig. 2).

One of the pioneering studies by Ley et al. [37] reported that obese subjects have fewer *Bacteroidetes* species and a greater abundance of *Firmicutes* species compared to healthy controls. Some of the subsequent studies could not confirm this finding; however, the *Firmicutes/Bacteroidetes* ratio remained a frequently studied marker for microbiota dysbiosis in relation to diabetes and metabolic diseases [38].

Mouzaki et al. [29] reported that patients with NASH had a decreased abundance of *Bacteroidetes* compared to patients with simple liver steatosis and healthy subjects. A higher abundance of fecal *Clostridium coccoides* (corresponding to the *Lachnospiraceae* family) [39] was found in patients with NASH compared to those with simple steatosis. However, after correction for fat intake and BMI, this difference was not significant [29]. Yet another study confirmed this trend and verified an increase in abundance of the phylum *Firmicutes*, including *Lactobacillus*, but also several genera within the *Lachnospiraceae* family (*Dorea*, *Roseburia*, and *Robinsoniella*) in patients with NAFLD compared to healthy subjects [31]. In addition, Loomba et al. [32] assessed gut microbiome compositions in patients with mild or moderate NAFLD and advanced fibrosis using whole-genome shotgun sequencing of DNA extracted from stool samples. They found a higher prevalence of *Firmicutes* in those with mild or moderate NAFLD, while *Proteobacteria* were the dominant microbiota in those with liver fibrosis [32]. Wang B et al. [30] investigated intestinal dysbiosis in non-obese patients with NAFLD. They reported opposite trends for the Bacteroidetes phylum, which

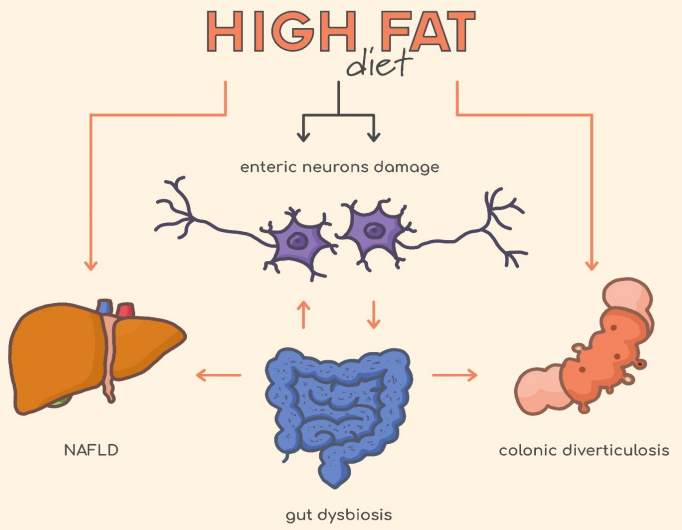

Fig. 2. Overlapping pathophysiological cascade of NAFLD and CD. NAFLD: non-alcoholic fatty liver disease.

was detected in up to 20% of patients with NALFD compared to lean individuals. In obese adults, the Firmicutes phylum, particularly the *Lachnospiraceae* family, were reduced in abundance compared to healthy, non-obese adults [30]. This was also true for the *Lactobacillaceae* family, and for bile acid dehydroxylating *Ruminococcaceae*. All these studies have linked impaired gut microbiota not only with the development of NAFLD, but also its progression and disease severity.

Profiling studies of the microbiota in CD have highlighted that the overgrowth of the phylum Firmicutes (*Ruminococcus*, *Pseudobutyrivibrio*, and *Christensenellaceae* family) may be associated not only with SUDD, but also with AD occurrence [40, 41]. Indeed, diverticular pockets may represent unique niches that selectively promote the development of specific microbes, leading to inflammation and clinical manifestations of CD.

Barbara et al. [42] and Tursi et al. [43] investigated the difference in fecal microbiota between patients with uncomplicated CD and healthy individuals. They verified reduced abundance of *Akkermansia muciniphila* in the diverticular region compared with sites in the distal colon. They also observed a negative correlation between macrophage counts in CD and *Akkermansia* abundance [42]. Notably, patients with CD had significantly higher macrophage counts, which was negatively correlated with the abundance of the *Clostridium* cluster IV, which includes anti-inflammatory *Faecalibacterium Prausnitzii*. Therefore, it has been proposed that patients with CD lack anti-inflammatory microbiota species [42]. Indeed, a difference was noted in the microbiota of patients with SUDD and patients with ADD. Patients with SUDD had significantly reduced abundance of the phylum Firmicutes (*Clostridium* cluster IX, *Lactobacillaceae*) and *Fusobacterium* compared to asymptomatic individuals [43]. These findings are surprising, since increased abundance of *Fusobacterium* is a strong marker of various pathologies, including appendicitis [44] and colon cancer [45].

Patterns of microbiota dysbiosis assessed through metabolomics and gut microbiota diversity showed several pro-inflammatory (microbial) metabolites in patients with CD compared to controls. Barbara et al. [42] suggested that metabolome profiles associated with inflammatory pathways and bowel neuromotor disorders may distinguish patients with CD and healthy subjects. The results of the study by Tursi et al. [43] are not in line with the findings of Barbara et al. [43], as they only noted differences in fecal abundance of *Akkermasia muciniphila* in controls compared to patients with ADD and patients with SUDD.

In their attempt to highlight the significance of microbial metabolic output in relation to the pathogenesis of CD, Barbara et al. [42] showed that a combination of microbiological and metabolic profiling allows for separation between ADD and controls, mainly due to the change in *Akkermasia muciniphila* abundance. Indeed, *Akkermasia muciniphila* abundance is negatively correlated with levels of N-acetyl-glucosamine. Interestingly, microbiological and metabolic data allowed for separation between ADD and SUDD based on N-acetyl-glucosamine levels and several short-chain fatty acids [43]. In another study, profiles of microbiota were examined and compared between patients with SUDD who were previously diagnosed with AD and those who were not [41]. It was established that recurrent AD could be associated with a specific microbiota signature marked by the increased prevalence of *Pseudobutyrivibrio* and *Bifidobacterium* spp. and decreased prevalence of uncultured species belonging to the *Christensenellaceae* family and the Mollicutes order [41]. In this study, a correlation between symptoms, such as bloating and pain, and particular members of the gut microbiota was identified. The limitations of current studies are the small sample size, discrepancy between applied techniques, and scarce clinical assessment of CD, resulting in conflicting and/or inconsistent conclusions. Specifically, it seemed that the role of microbiota in the early phases of ADD is overlooked. Nevertheless, there was ample evidence that significant microbiota alterations are associated with complications of CD.

Since gut microbiota composition in NAFLD has also been linked to disease severity and progression [24], the aforementioned findings could indicate the potential for shared traits in the progression of both CD and NAFLD.

OBESITY IN NAFLD AND COLONIC DIVERTICULOSIS

Visceral adiposity, with associated pro-inflammatory effects, is a major risk factor for NAFLD and development of symptomatic CD [33, 46]. Several studies have reported a prevalence of NAFLD up to 90% in patients undergoing bariatric surgery for morbid obesity. Although simple hepatic steatosis of various degrees was the most common clinical finding, NASH was diagnosed in up to 50% of these patients [47–49].

Kopylov et al. [19] demonstrated an association between obesity and CD; alternatively, Song et al. [50] determined that typically patients with CD have higher BMI. Furthermore, obesity expressed not only as BMI, but also as waist circumference and waist-to-hip ratio, has recently been highlighted as one of the strongest risk factors for CDD [12, 15]. In a Swedish cohort study with over 28-years of follow-up, which included subjects hospitalized for CDD, BMI was found to be a significant risk factor for CD [15]. Strate et al. [12] studied male health professionals with self-reported diverticulitis and diverticular disease (confirmed by assessment of the medical records) and reported that subjects with BMI>30 kg/m^2 had a relative risk of 1.78 (95% confidence interval (CI), 1.08-2.94) of developing diverticulitis, and 3.19 (95% CI, 1.45-7.00) of diverticular bleeding, compared to non-obese individuals.

Alfonso et al. [51] assessed both visceral and subcutaneous adipose tissue (SAT) via ultrasound, and further evaluated the association between SAT and CD. They reported that in addition to older age, VAT is an independent risk factor for CD. A few studies that used computed tomography also highlighted VAT, and not BMI, as an independent risk factor for left-sided CD [52, 53]. The significance of VAT as a risk factor for left-sided diverticulosis in Japan was reported in a study by Yamada et al. [54], indicating that patients with left-sided diverticulitis are more likely to develop diverticulitis when the VAT area is greater than 100 cm^2.

Similarly, Kim et al. [55] conducted a longitudinal study in adults who underwent abdominal ultrasonography, with a 4.4-year follow-up period, and suggested that larger areas of VAT at baseline are linked to higher NAFLD occurrence, with a hazard ratio of 2.23; additionally, an association with SAT was not identified. Interestingly, regression of NAFLD during the follow-up was noticed in subjects who had significantly higher baseline SAT areas, irrespective of the VAT area. Therefore, the authors proposed a possible beneficial effect of SAT on the disease course of NAFLD [55]. Additionally, the authors reported that an increase in VAT over time correlates with a higher probability of NAFLD development, independent of the baseline VAT area [56]. Conversely, a decrease in the VAT area had a protective effect on the disease course of NAFLD and led to disease regression [57]. Similar findings were reported by other authors who demonstrated that the VAT area is associated with both NASH and fibrosis development, with higher areas of VAT being associated with more severe disease [57].

Visceral adipose tissue is an important predictor of metabolic and intestinal complications in obesity-related disorders, including NAFLD and CD. The complex endocrine role of VAT includes the release of various hormones, including adiponectin and leptin. While leptin has pro-inflammatory activity, adiponectin acts as an anti-inflammatory agent [33, 46]. The role of adiponectin and leptin in obesity, insulin resistance, and NAFLD has been shown in several studies using human, animal, and in vitro models. However, studies addressing the specific role of these hormones in CD are scarce [33, 46, 58]. Tsochatzis et al. [59] suggested that both a reduction in adiponectin levels and increased leptin in obese individuals contribute to the development of hepatic steatosis, increased inflammation, and fibrogenesis of the liver tissue. Murray et al. [45] reported that adiponectin levels showed a negative correlation with VAT volume in patients with CD.

The exact role of abdominal obesity in the pathogenesis of CD remains unclear. The herniation of colonic mucosa due to an obesity-related increase in intraluminal pressure is also aggravated by methane gas production resulting from intestinal dysbiosis observed in obese individuals. Additionally, adipocytes produce pro-inflammatory cytokines that can influence colonic motility, which promotes diverticula formation [9, 20]. Studies investigating the specific role of obesity and metabolic factors in CD have shown varying results [14, 19, 53]. In a Southern-European prospective study, a positive association between increased waist circumference, blood pressure, hyperlipidemia, and CD was reported; also, there was no significant difference in the prevalence of T2DM and obesity between those who had CD and those who did not. Furthermore, multivariate analysis revealed that advanced age and greater waist circumference constitute independent risk factors for CD [14]. In a five-year longitudinal study by Kopylov et al. [19], the following factors were associated with increased risk of CD: age, male gender, BMI, obesity, systolic blood pressure, low-density lipoprotein cholesterol level, history of hypertension, ischemic heart disease, hypothyroidism, and absence of T2DM.

ARTERIAL HYPERTENSION AS A RISK FACTOR IN NAFLD AND COLONIC DIVERTICULOSIS

Almost half of the patients with HTA develop NAFLD. Several studies have indicated a strong association between increased blood pressure and NAFLD in both hypertensive and normotensive patients [60–62]. However, most of these studies were cross-sectional; therefore, it is not possible to determine the causal relationship between NAFLD and HTA.

The study by Ma et al. [63] highlighted the mutual relationship between NAFLD and HTA, emphasizing its bi-directional nature, and suggested that NAFLD could be both a cause and consequence of HTA. Several studies have addressed the interaction between elevated blood pressure and the development of CD. One of the first studies regarding this association, conducted by Yeo et al. [64], concluded that patients with HTA had a higher probability of developing ADD. This study further emphasized that inadequately regulated HTA is a significant risk factor for the development of ADD. A positive correlation between HTA and CD has been previously reported [14, 17]. Indeed, the atherogenic potential of HTA is well known. Considering that diverticula most commonly

occur in vulnerable spots of the colonic wall (the site where vasa recta passes through the circular muscular layer), it is possible to conclude that HTA, especially when inadequately regulated, may lead to structural changes in the bowel wall over time by damaging blood vessels and further reducing blood supply in vulnerable anatomical areas. Interestingly, the use of calcium channel blockers for the treatment of HTA appears to have a protective effect against CD [8].

THE IMPACT OF DIABETES MELLITUS TYPE 2 ON NAFLD AND COLONIC DIVERTICULOSIS

The reciprocity of NAFLD and metabolic disorders, including T2DM, has recently become an area of interest for both clinicians and researches. Changes in liver structure in NAFLD can contribute to the development of T2DM in predisposed individuals via hepatic insulin resistance. Hepatic ceramides and diacylglycerols are identified as the most important mediators of insulin resistance and play a major role in induction of lipotoxicity in numerous metabolic disorders. It has been suggested that the inhibition of their synthesis could lead to improvement of NAFLD, and consequently, insulin resistance, thereby preventing insufficiency of pancreatic beta cells [65]. Insulin resistance, as a central mechanism for the development of both NAFLD and T2DM, could be mediated by the production of a microbial metabolite, imidazole-propionate [66]. Imidazole-propionate is produced from the amino acid histidine by specific components of the microbiota, and this microbial metabolite can impair insulin signaling at the level of the insulin receptor (through activation of p38γ MAPK) [66]. Interestingly, the drug most prescribed in insulin resistance treatment, metformin, has been shown to influence colonic microbiota composition [67]. A recent study demonstrated that imidazole-propionate inhibits metformin activity through imidazole-propionate-activated p38γ [68]. Metformin has recently been used in various animal and human studies, and it reportedly has an anti-inflammatory role in CD [69, 70].

Type 2 diabetes mellitus, NAFLD, and CD are linked in a number of ways. Several studies have indicated that a low-fiber diet is associated with both T2DM [71] and cardiovascular disease development [72,73]. As previously stated, the following factors are associated with an increased risk for CD: advanced age, male gender, obesity, history of hypothyroidism, and absence of T2DM [19]. However, T2DM may play a role in the occurrence of diverticular bleeding [74]. Long-lasting T2DM is associated with numerous complications, including disruption of mucosal integrity, which may also be considered as a contributing factor to diverticular bleeding. A recently conducted meta-analysis assessed cohort studies on the relationship between CD and the following factors: age, gender, BMI, HTA, smoking, finger prick test glucose levels, HbA1c levels, and C-reactive protein levels [75]. It concluded that diabetes is an important risk factor for both CD and the development of diverticular bleeding. Patients with diabetes had approximately a 1.25-fold higher risk for diverticulosis, and approximately a 2.3-fold higher risk of colectomy, which was the only therapeutic option for diverticular bleeding. The main limitation of this meta-analysis is that only several prospective and randomized cohort studies were included, and that both patients with type 1 and type 2 diabetes mellitus were jointly analyzed [75]. Therefore, it may be possible to decrease the risk of recurrent and potentially life-threatening diverticular bleeding by providing the patient with adequate glucose regulation.

CONCLUSIONS

This review highlights the complex interrelationship and shared traits between NAFLD, CD, and MetS (Fig. 3, Table I). In the past, MetS was believed to be the cause of several clinical conditions traditionally associated with

Table I. Summary of CD and NAFLD meeting points.

Reference	Colonic diverticulosis	Meeting points	Non-alcoholic fatty liver disease	Reference
41	Deficiency of anti-inflammatory gut microbiota components	Dysbiosis	Impaired gut microbiota linked with hepatic fat deposition, progression of NAFLD and with the disease severity	25, 26, 27, 28, 29, 30, 31
39, 40	Correlation between gut microbiota signature and the disease severity		Pro-inflammatory effect	32, 33
11, 13, 14, 45, 50, 53	Risk factor for CD development and its complications	Visceral adiposity	Risk factor for NAFLD development and more advanced disease course	32, 54, 55, 56
18,49	High prevalence of CD in obese subjects			
13,16	Positive correlation between HTA and CD	Arterial hypertension	NAFLD is associated with an independent risk of identifying HTA	59,62
63	HTA is increasing the risk of asymptomatic CD development		HTA is an independent risk factor for NAFLD development	60, 62, 63
			HTA correlates with liver fat content	61
74	T2DM increases the risk of complicated CD	Type 2 diabetes mellitus	Insulin resistance as a pathogenic mechanism described in both NAFLD and T2DM	64
			Insulin resistance is related to higher incidence of fatty liver	60, 62

CD: colonic diverticulosis; HTA: arterial hypertension; NAFLD: nonalcoholic liver disease; T2DM: type 2 diabetes mellitus.

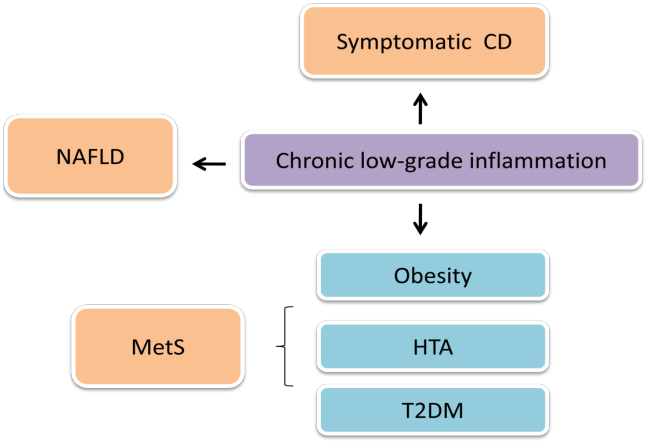

Fig. 3. The relationship between NAFLD, MetS and CD. CD: colonic diverticulosis; NAFLD: non-alcoholic fatty liver disease; MetS: metabolic syndrome; HTA: arterial hypertension; T2DM: type 2 diabetes mellitus.

metabolic abnormalities. Herein, we provide a different perspective by analyzing evidence of the reverse sequence of pathophysiological events by considering disturbances in gut microbiota as the cause of NAFLD and CD (especially symptomatic forms of the disease). Alternatively, MetS is considered a consequence of NAFLD and CD, rather than the cause of these conditions. Currently, it remains difficult to establish a strict pathophysiological timeline and define the underlying causative mechanisms of NAFLD. Nevertheless, the bi-directional relationship between these three diseases (NAFLD, CD, and MetS) implies that further studies are needed to develop novel therapeutic approaches and efficient treatment strategies.

Conflicts of interest: None to declare.

Authors' contribution: T.M., I.P., S.D., S.L., I.D., M.R.S. conceived the study and searched the relevant literature. I.P., S.D., S.L., I.D., M.R.S. drafted the manuscript. T.M., I.P., S.D., S.L., I.D., M.R.S. revised the paper. T.M supervised the study. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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