Association between non-alcoholic fatty liver disease and colorectal cancer

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REVIEW

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ABSTRACT

Introduction: Colorectal cancer (CRC) is a common malignancy, ranking fourth among the causes of cancer-related deaths globally. Its incidence has increased in recent decades, and now more than one million CRC patients are diagnosed and thousands die annually. The 5-year survival rate varies with the stage at diagnosis, are approximately 90% in the early stages of disease, and less than 10% in advanced disease. Non-alcoholic fatty liver disease (NAFLD), which is a major cause of chronic liver disease, and characterized by the accumulation of fat in hepatocytes, has also emerged as a risk factor for CRC, and to be related with the development of colorectal polyps.

Areas covered: The purpose of this current review is to summarize the main findings of studies that have investigated the role of NAFLD in development of CRC.

Expert opinion: Various molecular pathways are altered during the development of NAFLD, which are also important in CRC tumorigenesis. There is growing body of evidence showing the potential role of activation of pro-inflammatory, disruption of anti-inflammatory pathways, increasing the activity of pathways involved in cell proliferation/survival. Thus targeting these dysregulated pathways via novel inhibitors can be a potential therapy for CRC prevention in cases with NAFLD.

1. Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and ranks fourth among the causes of cancer-related deaths globally [1]. Recently, there has been a reported increase in the incidence of CRC [2]. It is expected that about 2.2 million new CRC cases are diagnosed annually with more than 1 million cancer deaths projected for 2030 [3]. The 5-year survival rate varies with the stage at which it diagnosed, being approximately 90% in early stage of disease, and less than 10% in advanced stage [4]. CRC carcinogenesis is a multistep process and usually takes 10–15 years to develop, initially as a noncancerous polyp [1]. Due to high costs associated with screening for CRC, individuals who do not show symptoms and are not at risk, do not usually undergo assessment. As a result, identifying a high-risk population has been an emergent issue [5]. Recently, one of the major causes of chronic liver disease, non-alcoholic fatty liver disease (NAFLD), has also emerged as a risk factor for CRC, and to be related to the development of colorectal polyp and also to the pathogenesis of CRC.

NAFLD is characterized by the accumulation of fat in the liver. The global prevalence of NAFLD is increasing worldwide [6]. NAFLD refers to a range of changes from initial steatohepatitis, and later to fibrosis and cirrhosis [7]. Among the causes of NAFLD

are over-nutrition and its complications, such as weight gain, central obesity, insulin resistance, glucose intolerance, dyslipidemia and arterial hypertension and metabolic syndrome (MetS), which are amplified in individuals with genetic predispositions [8]. The relationship between NAFLD and conventional metabolic conditions including diabetes mellitus, obesity and dyslipidemia had been established previously [9]. Finding of recent studies revealed that NAFLD as a new potential risk factor for extra-hepatic cancers [10]. The purpose of this current review was to summarize the main findings of studies investigated the role of NAFLD in development of CRC.

2. Non-alcoholic fatty liver disease overview

2.1. Epidemiology and clinical features

The term NAFLD covers a range of liver conditions from simple steatosis to non-alcoholic steatohepatitis (NASH), cirrhosis and even hepatocellular carcinoma (HCC). NAFLD [11–13]. NAFLD which is the most common chronic liver conditions worldwide, is identified by accumulation of fat in the liver in the absence of chronic alcohol consumption or drinking alcohol less than 40 g/day in the patient history [14]. The global prevalence of NAFLD in the adult population is evaluated to be about 24% [15,16]. Furthermore, 3–10% of children is reported to have

NAFLD [6]. The majority of NAFLD patients are asymptomatic. However, most of symptomatic patients have non-specific symptoms including feeling abdominal pain in right upper quadrant, fatigue and malaise [17].

2.2. Risk factors and pathogenesis

There are several risk factors for NAFLD that include: male gender, obesity, insulin resistance (IR), type 2 diabetes mellitus, dyslipidemia and MetS [17]. The pathogenesis of NAFLD involves several stages. In the first stage, steatosis, is likely triggered by insulin resistance. The second stage entails oxidative stress and cytokines alteration which worsen the condition. The relationship between NAFLD and reduced insulin sensitivity due to impaired insulin signaling has been discussed by several researchers. Free fatty acid (FFA) form fat in diet can be esterified with glycerol in to triglycerides (TG) and subsequently stored in adipocytes. Insulin resistant related metabolic abnormalities occur when accumulation of fat in liver lowers insulin stimulated glucose uptake [18]. Elevated concentrations of FFAs and consequential lipotoxicity, insulin resistance, peripheral adipose tissue dysfunction and gastrointestinal derived endotoxins jointly play a role in activating and maintaining the production and release of pro-inflammatory cytokines, both on a systemic level and in the liver. Two main inflammatory pathways, c-Jun N-terminal kinase (JNK)/activator protein-1 (AP-1) pathway and IκB kinase (IKK)/nuclear factor-kappa B (NF-κB) pathway, have crucial roles in the development of the chronic inflammatory state in NAFLD [19]. Connections have been made between hepatic FFAs flux, oxidative stress, response to endotoxins and cytokine production and activity, and individuals' genetic makeup, particularly as indicated by single nucleotide polymorphisms, for NAFLD development and progression [19].

2.3. Diagnosis and treatment

The gold-standard method for diagnosis of NAFLD is by liver biopsy. Nevertheless, besides histology analysis, an excessive fat accumulation in the liver can be established using noninvasive diagnostic tests including ultrasonography, magnetic resonance imaging (MRI), computed tomography (CT) and transient elastography (fibroscan) [20]. Although Laboratory testing is insufficient of NAFLD diagnosis and also may be normal, however, especially elevated serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are the most frequent abnormal biochemical tests. In most cases the AST-to-ALT ratio is less than 1 [17]. In addition, other biochemical tests consisting triglyceride level, gamma-glutamyltransferase and alkaline phosphatase may be increased. Regarding to the important effect of NAFLD on human health, and in order to prevent the progression of NAFLD to more severe liver disease, some diagnostic algorithms have been proposed. Although the importance of diagnosis of NAFLD is obvious, in some groups of patients these algorithms are not appropriate. A recently reported example of this is in the diabetic patients. The European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) algorithm may lead to many diabetic patients being referred to liver clinics. According to this algorithm, those patients in whom significant liver fibrosis has not been excluded should be referred to liver clinics for elastography. Hence, there remains a need for developing more specific markers of steatosis in specific patients including patients with type 2 diabetes [12]. The most widely accepted efficient therapeutic approach for NAFLD are dietary and lifestyle modification, increased physical activity and at least a 3% weight reduction [21].

Medical therapies for targeting comorbidities of NAFLD, such as the use of insulin sensitizers such as metformin and thiazolidinedione in diabetic patients, lipid lowering agents like statin in dyslipidemia, antioxidants such as vitamin E and hepatoprotective agents like ursodeoxycholic acid (UDCA) may be useful in NAFLD treatment.

Despite the lack of randomized clinical trials, a recent expert panel has discussed the pharmacological treatment for NASH using pioglitazone, statins and ezetimibe in-combination or alone [22]. Among the other drugs reviewed were fibrates, simtuzumab and omega 3 fatty acids, that were considered to be drugs with equivocal effect on treatment of NAFLD [23]. An old and well known drug in this category is metformin. Metformin has the capacity to improve insulin resistance, and it has also been reported to be effective in treating NAFLD. Moreover, metformin can reduce the risk of developing HCC in those who have cirrhosis [24]. While there is an insufficient body of evidence available regarding the effect of metformin on the histopathological improvement in NAFLD liver, it seems that using this drug may improve the all-cause mortality of patients with NASH [25]. Besides improving liver function, it has been demonstrated that metformin can also decrease risk of colorectal malignancies in a dose dependent manner in diabetic patients [26,27]. Emricasan a pancaspase inhibitor has also been also used to treat NAFLD and liver fibrosis. However, the effect of such treatment on the development of colorectal tumors is not clearly established [28]. Although more research is needed it seems that other drugs including agonist of the farnesoid X receptor may have a role in improving liver inflammation and insulin sensitivity of diabetic patients and NAFLD as well as anti-proliferative effects on CRC cells by inducing cell cycle arrest [16,29]. While the possible link between NAFLD and CRC development is emerging, it is appears important that future trials evaluate the effect of such drugs on CRC development in NAFLD patients.

2.4. NAFLD and malignancies

NAFLD is one of the most common chronic liver disease and its relationship with insulin resistance, diabetes and some cancers will increase its importance. It has been shown that malignancies are one of the most common causes of death among NAFLD patients. The association between NAFLD and developing some cancers is not clearly understood. A recent study by Kim et al. demonstrated the association between NAFLD and the incidence of malignancies [30], showing that NAFLD patients have higher rates of all cancers including HCC. Moreover, male NAFLD patients are more likely to develop CRC while the female are more likely to develop breast cancer. Regardless of cancer type, it seems likely that obesity plays a major role in the development of these various cancers in NAFLD. Metabolic and hormonal dysregulation together with the NAFLD itself in obese patients has been related to development of various cancers including breast cancer [30]. As we will discuss later, the systemic inflammatory disturbance during the development of NAFLD development and progression may be the cornerstone of the most of dysregulation in body system and development of cancers, especially CRC that is the focus of the present review. In brief, inflammation occurring during the development of NAFLD can affect liver and other organs including the gut, blood vessels and adipose tissue. The effect of inflammation on altered gut microbiota has also been linked to the development of several gastrointestinal malignancies. Moreover, increased leptin and reduced adiponectin is found in individuals with NAFLD and this has been linked to the development of colorectal malignancies. Insulin resistance caused by release of adipokines and FFAs as well as abnormal deposition of fat in different tissues will enhance NAFLD progression and development of colorectal tumors [31]. Regardless of the cause or effect relation between NAFLD and CRC, it has been reported that CRC patients with pre-existing NAFLD have a worse prognosis [32]. All of these findings indicate the importance of reviewing the role of NAFLD in CRC and highlighting the possible way ahead for further studies in this area.

3. Colorectal cancer overview

3.1. Epidemiology and clinical features

CRC is the most prevalent gastrointestinal malignancy and ranks second among all cancer-related deaths in developed countries. Recently, there has been a significant elevation in the incidence of CRC [2]. Although both gender have been affected similarly but geographical differences have been observed in CRC incidence rate. Epidemiological studies have been indicated that more than 60% of new cases and CRC related deaths occur in high-income countries [3]. The highest incidence rates are reported from Australia and New Zealand, and European and North American countries. African and South-Central Asian countries show the lowest rates. Based on the degree of invasion, CRC is classified as early or advanced stage. In early stage CRC is ordinarily asymptomatic or exhibit with non-specific manifestations including change in bowel habit, loss of appetite, weight loss, anemia and abdominal pain. In more advance stages, tumor spreads by local invasion or distant metastasis and symptoms become more prominent.

3.2. Risk factors and pathogenesis

Geographical differences in the incidence of CRC seems to be due to differences in dietary and environmental factors, interacting with genetics factors [2]. Beside age and the genetic factors, the presence of inflammatory bowel disease, familial adenomatous polyposis (FAP), Lynch syndrome and environmental factors including nutritional practices, physical activity, obesity, smoking, alcohol consumption and over-consumption of red meat constitute the major risk factors for CRC [22]. Links between MetS, CRC and colorectal neoplasia (CRN) which share common risk factors have been examined in development of CRN. Several studies have revealed that metabolic syndrome significantly increases the risk of CRC or CRN (26, 27). In transition from normal colorectal epithelium to cancerous forms in CRC carcinogenesis, a number of various factors and signaling pathways are involved [16,23–26]. It is estimated that during lifetime between one third to one half of all individuals develop at least one adenoma [27]. Adenocarcinomas with glandular tissue origins constitute roughly 96% CRC cases. Although less than 10% of adenomas progress to cancer, adenomas, also referred to as adenomatous polyps, carry a comparatively larger risk of becoming cancerous. Insulin has been suggested as an agent of carcinogenesis of CRC. Further, elevated levels of plasma insulin and glucose, glucose intolerance, obesity and physical inactivity have been shown to be correlated with CRC [28]. Most cases of CRC develop via the adenoma-carcinoma sequence. Adenomatous colorectal polyps are considered to be precursors of CRC. It has been reported that NAFLD, regardless of traditional CRC risk factors, is an important and independent risk factor for developing CRC [16]. Metabolic disturbances during NAFLD may act as a predisposing factor for developing cancer. This is expressed by alterations in several molecular and biological pathways. During development of NAFLD, some important molecular pathways in developing different cancers will be down or unregulated. Insulin resistance and metabolic syndrome has well-known changes in some molecular pathways, and are two common etiologies of NAFLD which are also considered to be important in developing different cancers such as CRC. The main trigger of developing neoplasms which are affected by these two conditions are initiated by a disruption in cellular microenvironment. Increased Insulin-like growth factor-1 (IGF-1) and insulin during insulin resistance will act as a precursor of developing CRC neoplasms mainly due to induction of cellular proliferation and inhibition of apoptosis [29]. Beside the role of insulin resistance in NAFLD, there is a low inflammatory state which is usually aggravated by proinflammatory cytokines produced by liver and other cytokines such as IL-6 and TNF-a [30]. Moreover, the effect of different adipokines are prominent in developing alteration in tissue metabolism and cellular environment. Adiponectines will modulate the inflammation process and induce tumorogenesis [31]. All of these factors lead to a suitable environment for angiogenesis and proliferative state with decreased apoptosis (Figure 1).

3.3. Diagnosis, staging, treatment and prognosis

Colonoscopy with biopsy of any suspicious areas is generally regarded as the first choice for CRC diagnosis [5]. Screening colonoscopy is widely believed to be the most
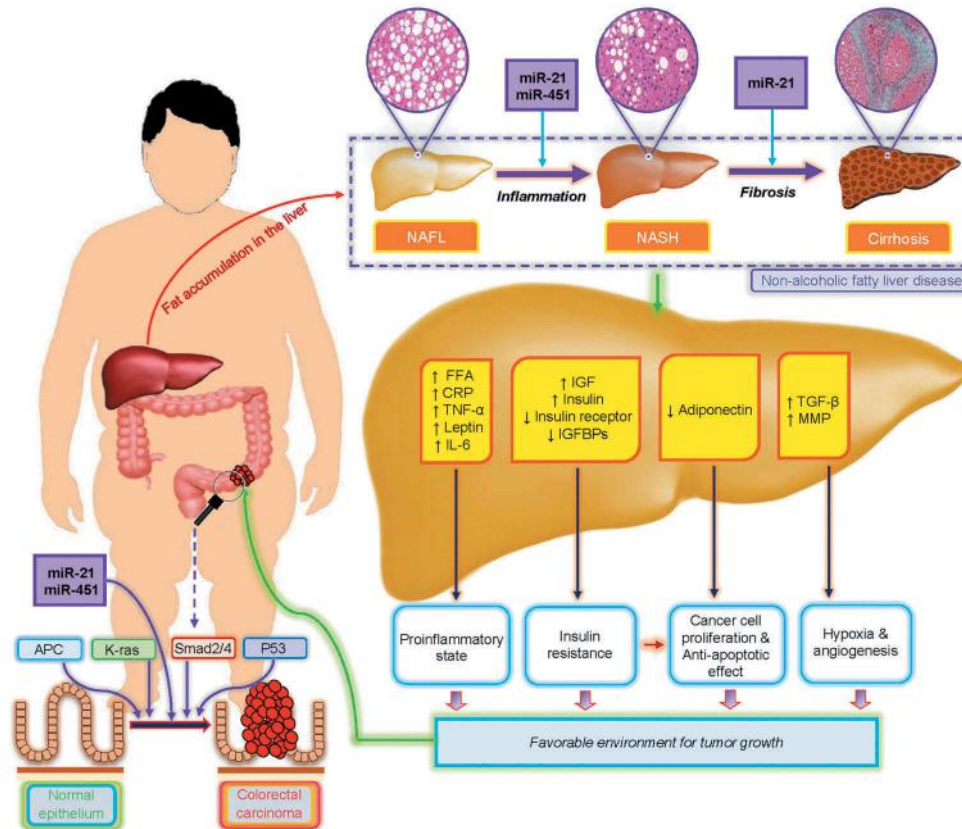
Figure 1. This schematic figure illustrates the possible relation between NAFLD and developing CRC. Accumulation of fat in liver results in gradual changes and development of NAFLD. There are many different factors suggested for these chronic changes. miR-21 and miR-451 are one of important mechanism which could be effective in pathogenesis of both NAFLD and CRC. During NAFLD alteration in different cellular pathways occur. Overproduction of many chemicals and inflammatory factors such as CRP and interleukins along with reduced production of other factors such as adiponectin provide a favorable environment for tumor growth including CRC.

effective method to reduce the incidence of CRC and CRC mortality by removing precancerous polyps [32,33]. In addition to physical examination, biochemical tests, and imaging such as CT scan, MRI, positron emission tomography (PET) scan could be beneficial in detection of CRC and its local or distant invasion. The stages of CRC are categorized as follows: (i) Stage I (CRC cells are limited in epithelial layer without invasion to deep layers of colorectal wall), (ii) Stage II (invasion of CRC cells into deep layers of colorectal wall), (iii) Stage III (invasion of CRC cells into regional lymph node) and (iv) Stage IV (distant metastasis). Treatment of CRC relies on disease stage and involves three main approaches: (i) surgery, (ii) chemotherapy and (iii) radiotherapy [1]. The most common protocol applied in chemotherapy is the FOLFOX protocol (including 5-Fluorouracil, Folinic Acid (Leucovorin) and Oxaliplatin) and CapeOx protocol (including capecitabine and oxaliplatin) [34]. In addition to conventional therapeutic approach, targeted therapeutic approaches may be used based on clinicopathological and molecular features of CRC tumors [1,23–25]. CRC stage at treatment is largely associated with survival. The 5-year survival rate for patients with CRC can be as high as 90% for cancers detected at the early stages or as low as 10% when cancer cells have formed distant metastasis [35].

4. Role of non-alcoholic fatty liver disease in development of colorectal polyps

Although several studies have attempted to identify a connection between colorectal adenomatous polyps and NAFLD, the results have not been in agreement. Still, most pointed to a positive correlation between NAFLD and colorectal adenomatous polyps [36]. Hwang et al. [37] were the first to try to investigate the link between NAFLD and colorectal adenomatous polyps. Analyzing 2917 patients who had undergone colonoscopy and assessing anthropometric measurements, biochemical tests for liver and metabolic function, and abdominal US, they showed that NAFLD was associated with colorectal adenomatous polyps. Further studies should be performed to confirm investigate NAFLD as a predictor for the development of colorectal adenomatous polyps and cancer [37]. In a retrospective cohort study of 5517 Korean women aged 35–80 years which diagnosed fatty liver diseases using abdominal US, Lee et al. [38] showed that NAFLD was significantly associated with an increased incidence of adenomatous polyps. Wong et al. [39] found that NAFLD is associated with increased prevalence of colorectal adenomatous polyps. Among the 29 patients in their study with advanced neoplasms, 13 had isolated lesions in the right-sided colon. Further, for the most part, increased risk of adenomatous

polyps was found in NASH subjects as opposed to those with simple steatosis. Wong et al. used proton magnetic resonance spectroscopy to diagnose NAFLD, in concert with liver biopsies for some patients. Stadlmayr et al. [40] explored the link between CRC and NAFLD in patients who had undergone colonoscopy, both male and female patients with NAFLD showed higher rate of adenomas. Also, tubular adenomas and adenomas of the rectum were observed to be more prevalent in men with NAFLD. For women with NAFLD however, more tubular adenomas with adenomas of the proximal colon were identified. In a retrospective assessment of patients who completed liver transplant evaluation Bhatt et al. [41] showed the higher prevalence of adenomatous polyps in NAFLD patient compared to patients with other forms of end stage liver disease. Furthermore, compared to patients who did not suffer NAFLD, NAFLD patients had a ~ 2.5-fold higher risk of polyps and a ~ 2-fold higher risk of adenomatous polyps. Huang et al. [42] compared patients who developed adenoma after an initial negative baseline colonoscopy (adenoma group) with those who had a second negative colonoscopy (non-adenoma group) and found NAFLD to be an independent risk factor for colorectal adenoma development following a negative baseline colonoscopy. The risk was higher in patients who suffered from NAFLD and other comorbidities, such as hypertension, smoking or MetS. In a study by Touzin et al. [43], the researchers compared patients who had previous biopsy had confirmed simple steatosis or NASH with the control group for whom sonographic imaging had not indicated fatty liver disease. They found a potential increased polyp burden for patients with fatty liver disease compared with the control.

5. Association between non-alcoholic fatty liver disease and colorectal cancer

Cigarette smoking, obesity and a high alcohol intake are indicated as factors causing increased risk of CRC in several guidelines for CRC screening. Accordingly, individuals who partake in such behavior are encouraged to undergo colonoscopy at younger age [44]. Obesity and MetS are associated with an increased cancer risk, and new evidence suggests an association between NAFLD and CRC. As a result, patients with NAFLD should also consider colonoscopy at an earlier age [36,45]. In their 2012 study, Lee et al. [38] analyzed Korean 5517 women and discovered a significant association between NAFLD and with an increased incidence of CRC among their subjects. All manifestations of the syndrome might be predictors of the development of colorectal neoplasms [38]. Wong et al. [39] found compared to healthy controls, NAFLD patients, diagnosed through magnetic resonance spectroscopy and liver biopsy, had significantly higher risk of colorectal adenomas and advanced colorectal neoplasm. Interestingly, patients with NAFLD and NASH usually develop colorectal adenomas and advanced neoplasms in the right sided colon. The association between NASH and colorectal neoplasm was observed independent of demographic and metabolic variables [39]. In a study conducted in Austria [40], CRC precursor lesions and early CRC were significantly more commonly seen in patients with NAFLD undergoing colonoscopy, in comparison with the control group. The increased risk was independent of other symptoms of IR. The investigators showed that in males, NAFLD increased the likelihood of CRC and lesions of rectum. In females, NAFLD increased the prevalence of lesions in proximal colon [40]. Lin et al. in a cohort study [44], found using colorectal biopsy and NAFLD, diagnosed though ultrasound imaging, a higher prevalence of CRMN in NAFLD patients. Similarly, sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in subjects with NAFLD. According to these findings, physicians should urge patients with NAFLD to undergo colorectal screening [44]. By examining routine abdominopelvic CT images taken for staging, Aktas et al. [46] investigated the relationship between NAFLD and CRC. Their retrospective study, involving 105 patients, found lower density on contrast abdominopelvic CT of CRC patients which agrees with a NAFLD diagnosis [46]. Basyigit et al. [28] evaluated the risk for CRC in patients with NAFLD in relation to IR. NAFLD was diagnosed by US. IR was assessed by the homeostatic model of assessment of IR. Employing multivariate logistic regression analysis, the researchers discovered a significant association between the presence of IR and the risk for colorectal adenoma and carcinoma. Moreover, the risk for CRC was significantly associated with the absence of NAFLD. A significant association between CRC risk and absence of NAFLD was also observed. Concurrent absence of NAFLD and presence of IR was also significantly associated with high risk of CRC. The authors showed that the absence of NAFLD in the presence of IR can predict CRC [28]. A study conducted by Kim et al. [47] showed that NAFLD was associated with higher incidence rates of cancer. Unadjusted, age-sex-adjusted, and multivariable adjusted analysis consistently showed that NAFLD was significantly associated with HCC, CRC in males, and breast cancer in females. The researchers used ultrasonographic imaging to diagnose hepatic steatosis in the absence of other known liver disease, including alcoholic or viral hepatitis [47]. Ahn et al. [16] investigated the risk of colorectal neoplasia in relation to the presence and severity of NAFLD. NAFLD was detected using US. The study revealed a close association between the presence and severity of NAFLD and colorectal neoplasia and advanced colorectal neoplasia which bring to attention the need for physicians to be aware of the increased risk of colorectal neoplasia in patients with NAFLD [16]. In a study with 1793 subjects divided into four groups based on the status of NAFLD and MetS, Pan et al. [5] utilized relative excess risks of interaction (RERI), attributable proportion (AP), and synergy index (SI) to measure additive interaction. The authors found that NAFLD and MetS were risk factors for colorectal neoplasm and CRC, respectively. MetS was associated with an increased risk of CRC in patients with NAFLD as well. It was thus suggested that patients with NAFLD and MetS undergo colonoscopic examination at regular intervals [5]. In another study, Yang et al. [48] recruited patients with both index and surveillance colonoscopy. This study demonstrated that in surveillance colonoscopies in patients with any adenoma at the index colonoscopy, NAFLD had little influence on the occurrence of CRN. This finding leads to the possibility that NAFLD is more closely linked to the initiation of CRN. Consequently, NAFLD can be seen an important risk factor in patients with negative index colonoscopy who demand surveillance colonoscopy [48]. In a meta-analysis of observational studies by Mantovani et al. [3], the investigators aimed to measure the extent of the association between NAFLD and risk of both colorectal adenomas and cancer in asymptomatic individuals undergoing screening colonoscopy.

The findings indicate that NAFLD is associated with a moderately elevated prevalence and occurrence of colorectal adenomas and cancer. It should be kept in mind that the observational design of the studies used does not permit the inference of causality, thus further investigation into the matter is required to shed light on the role hepatic contributors to increased risk of colorectal tumors for patients with NAFLD [3]. Ze et al. [49] evaluated the relationship between the fatty liver index, which predicts NAFLD, and the prevalence of colorectal adenomas. 2976 subjects over 40 years old who underwent routine checkups, including abdominal US and colonoscopy, were examined. The researchers found high fatty liver index could be a helpful predictor of colorectal adenoma [49]. Table 1 summarizes the studies that have investigated CRC in NAFLD patients. Regarding the evidence about the relationship between CRC and NAFLD, screening of patients with high risk of liver fibrosis, as suggested by Dyson et al. and Chalasani et al. seems a reasonable approach [63, 64]. Although there is insufficient evidence about CRC screening, we would suggest screening in at high-risk patients with NAFLD (Figure 2). Further studies are required regarding the cost-effectiveness of such screening.

6. Pathological mechanisms linking non-alcoholic fatty liver disease and colorectal cancer

Although the exact mechanism behind the association between NAFLD and developing colorectal neoplasm is not clear, a recent meta-analysis has suggested possible relationship between these two clinical conditions [50]. It has been proposed that the NAFLD alone cannot be the exact reason behind developing colorectal neoplasms and presence of other risk factors will be mandatory. Some researchers such as Yang et al. have proved the relation between NAFLD and colorectal neoplasm and also suggest that NAFLD should be considered as an important factor for determining the screening colonoscopy intervals [48]. There are some explanation about the link between NAFLD and developing cancer which can be categorized in to four main groups. The most studied

explanation is related to IR. The most likely mechanism associated with IR is due to Insulin-like growth factor-1 axis and hyperinsulinemic state which results in anti-apoptotic and proliferative effects [51]. The other explanation is related to adipose tissue dysfunction. As same as IR, the anti-apoptotic and proliferation effects are also seen with up-regulation of many pathways such as leptin/AMP-activated protein kinase (AMPK) and resistin/NF-kB or down regulation of adiponectin/caspase or tumor necrosis factor-α (TNF-α) activation [51]. It has been shown that NAFLD patients have decreased levels of adiponectin and increased level of leptin secreted by adipose tissue. In addition to the potentially carcinogenic effects of leptin, adiponectin will appears to have anti-cancerogenic effects by inducing caspase dependent endothelial cell apoptosis. Also, decrease in adiponectine level, the inhibitory effect on TNF-α is no longer available and tumor angiogenesis and proliferation will develop [51,52]. Inflammation and alteration in gut microbiota are the two other explanation which results in inflammation [51,53]. NAFLD and CRC patients mostly develop dysbiosis. Alteration gut microbiota will result in disruption bacterial metabolites and therefore inducement of activation of toll-like receptors (TLRs) which will further result in tumorigenesis [53]. By combining this evidence and by considering that NAFLD and visceral adipose tissue as the main component of central obesity axis, the explanation of the NAFLD effect of gastrointestinal neoplasms will become more evident. NAFLD itself and its dysbiosis as a low inflammatory state can build up an environment suitable for developing colorectal neoplasms as well as intrahepatic ones. This chronic inflammation alongside IR hyperinsulinemia will result in development of proliferation and anti-apoptotic effects necessary for developing different neoplasms. Disruption of adipokines, especially adiponectin, will further result in failure of anti-neoplastic effects and increase in pro-neoplastic effects of other adipokines such as leptin. Also recently, the role of different microRNAs (miRNA or miR) has been proposed in development of NAFLD. miRNAs are short single stranded

Table 1. Summary of the most relevant studies investigating role of non-alcoholic fatty liver disease in colorectal cancer.

Author and year	Country of population under study	Population	NAFLD detection method	Main findings	Ref.
Lee et al. (2011)	Korea	5517 female participants	US	Significant correlation between NAFLD and development of CRC	[38]
Wong et al. [39]	China	199 NAFLD and 111 without NAFLD	PMRS or biopsy	Higher risk developing colorectal adenomas and advanced neoplasm in NAFLD patients	[39]
Stadlmayr et al. [40]	Austria	1211 participants (632 NAFLD)	US	Significantly more CRC precursor lesions and were more likely to develop CRC in NAFLD patients	[40]
Lin et al. [44]	China	2315 participants (2052 NAFLD)	US	NAFLD was an independent risk factor for CRC	[44]
Aktas et al. [46]	Turkey	105 CRC	CT	Significantly higher prevalence of NAFLD in CRC patients	[46]
Basyigit et al. [28]	Turkey	127 NAFLD	US	Significantly correlation between absence of NAFLD and risk for CRC	[28]
Kim et al. [47]	Korea	25,947 participants	US	Strong association between NAFLD and development of CRC In male	[47]
Ahn et al. [16]	Korea	26,540 participants	US	Strong association between presence and severity of NAFLD and advanced colorectal neoplasia	[16]
Pan et al. [5]	China	1793 participants	US	NAFLD is among the risk factors for neoplasm and CRC. It also has an additive effect on the development of CRC	[5]
Yang et al. [48]	Korea	1023 participants	US or CT	Correlation between occurrence of colorectal neoplasia and NAFLD	[48]
Mantovani et al. [3]	Meta-analysis	11 studies including 91,124 participants	imaging or biopsy	NAFLD is independently correlated with a moderately elevation in incidence of colorectal adenomas and CRC	[3]
Ze et al. [49]	Korea	2976 patients	US	High fatty liver index can be used to predict colorectal adenoma	[49]

NAFLD, non-alcoholic fatty liver disease; CRC, colorectal cancer; US,ultrasonography; PMRS, proton magnetic resonance spectroscopy; CT, computed tomography; IR, insulin resistance
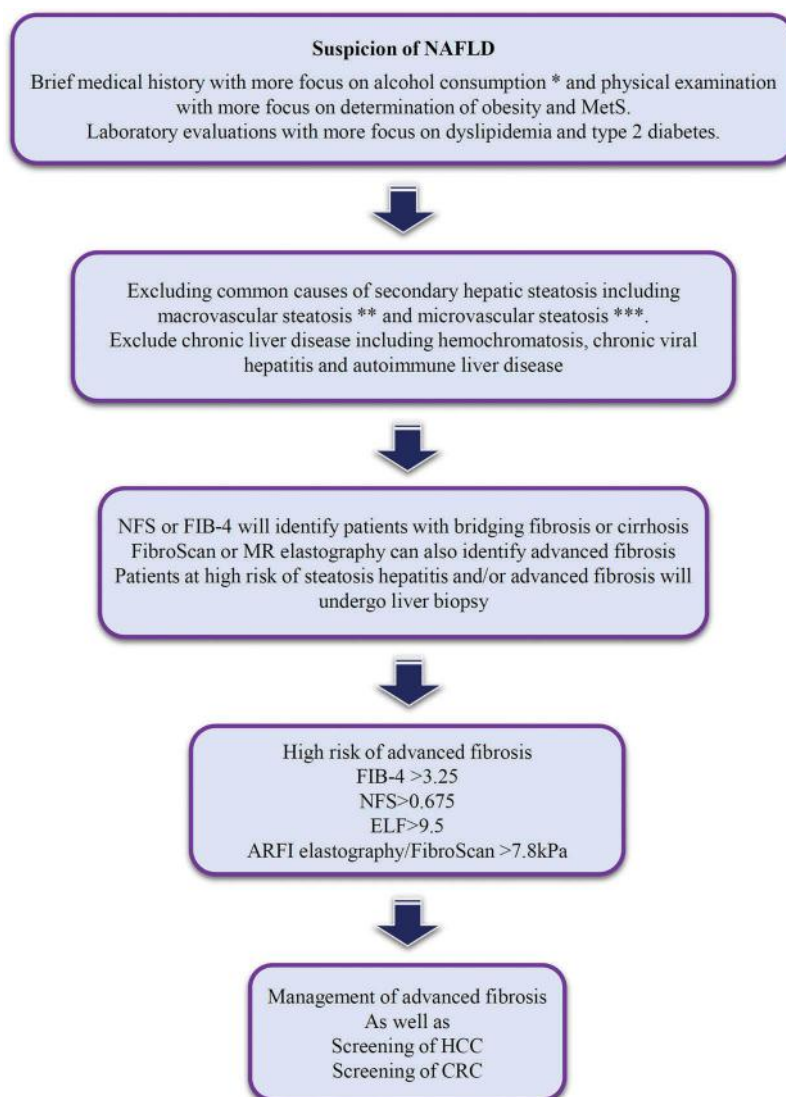
Figure 2. Patients under 65 years who were referred with abnormal liver function tests and ultrasound of liver may need screening for CRC in their possible NAFLD settings.

* The significant amount of alcohol consumption in NAFLD patients has not largely evaluated.
** Some well-known causes of macrovascular steatosis include: Wilson disease, lipodystrophy, abetalipoproteinemia and certain medications including tamoxifen, corticosteroids and etc.
*** Some well-known causes of microvascular include: inborn errors of metabolism, Reye's syndrome and certain medications including valproate and etc.
ARFI, acoustic radiation force impulse; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; NAFLD,non-alcoholic fatty liver disease; CRC, colorectal cancer

molecules composed about of ~22 nucleotides which can play different role cellular pathways and gene expression and especially in carcinogenesis [54]. miR-21 which is oncogene and miR-451 which act as tumor suppressor are two good examples of important micoRNAs which are seen during NAFLD development [55,56]. These two microRNAs are also reported to important in CRC pathogenesis. The possible effect of these shared microRNAs in NAFLD and CRC needs further studies to establish a cause effect relation.

7. Expert opinion

Various molecular/cellular mechanisms, including inflammatory, apoptotic and proliferation pathways, are altered during the development of NAFLD, which are also important in CRC tumorigenesis, suggesting that prevention of NAFLD development may be a rational approach in the prevention of CRC. Despite of recent

advances in molecular techniques for identifying the nature of various diseases, however still we are facing many gaps in our knowledge toward the understanding of the link between different diseases. Metabolic syndrome and obesity as well as NAFLD are considered as important role players in developing CRC and the link between these clinical conditions is now gathering as pieces of a puzzle in different researches. The most challenging issue for the researchers is gathering these pieces of puzzles in order to draw a conclusion regarding the exact effects of such clinical conditions. Beside this challenge, another which seems to be neglected is the effect of anti-cancer regimens for CRC patients who have NAFLD. Many of these drugs are metabolized in liver and in those who have liver dysfunction may face abnormal drug levels and inappropriate drug response. Chronic liver diseases such as NAFLD are now being considered as a possible risk factor for CRC. There is growing body of evidence showing the potential role of activation of pro-inflammatory, disruption of anti-

inflammatory pathways, increasing the activity of pathways involved in cell proliferation/survival, such as Akt/PI3K, Wnt, TGF-b pathways. Thus targeting these dysregulated pathways via novel inhibitors can be a potential therapy for CRC prevention in cases with NAFLD. Moreover parallel targeting of other pathway (e.g. NF-κB, TNF and JNK) are needed to prevent the possible feedback loop between these pathways. Combination therapy and parallel targeting of key dysregulated pathways (e.g. NF-κB, TNF, Wnt/PI3K pathways) in NAFLD cases for CRC prevention should be considered.

In the next five years the incidence of CRC and NAFLD will be increased and more research interest will be aimed at these two topics. It seems that the 5-year survival rate of the CRC will be increased according to recent advances in possible therapeutic approaches. According to recent studies, there is rapid growing evidence about the possible molecular mechanisms linking chronic disease such as NAFLD to different cancers such as CRC.

Among various molecular mechanisms altered during development of NAFLD, some important in tumorigenesis. Alteration in inflammatory pathways and proliferation disruption as well as reduced apoptosis are considered as main effects during colorectal carcinogenesis. Further researches would be aimed on evaluating the effect of targeting theses pathways in controlling CRC. Prevention of NAFLD development by targeting these common pathways will be the reasonable approach in developing prevention strategies for CRC and further experimental research is warranted. Furthermore, the effect of some medications which are effective on treating NASH or can improve liver function on development of CRC is not clearly studied. It seems that studying the effect of such drugs, especially metformin on development of CRC in NAFLD patients can answer more questions about the widespread use of such drug in NAFLD patients.

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References

Papers of special note have been highlighted as:
* of interest
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1. Kuipers EJ, Grady WM, Lieberman D, et al. Colorectal cancer Review. Nat Rev Dis Primers. 2015;1(15065):65.
2. Sadeghi Gandomani H, Aghajani M, Mohammadian-Hafshejani A, et al. Colorectal cancer in the world: incidence, mortality and risk factors. Biomed Res Ther. 2017;4:10.
3. Mantovani A, Dauriz M, Byrne CD, et al. Association between non-alcoholic fatty liver disease and colorectal tumours in asymptomatic adults undergoing screening colonoscopy: a systematic review and meta-analysis. Metabolism. 2018;87:1–12.
4. Parizadeh SM, Esfehani RJ, Ghandehari M, et al. Epigenetic drug therapy in the treatment of colorectal cancer. Curr Pharm Des. 2018;24:2701–2709.
5. Pan S, Hong W, Wu W, et al. The relationship of nonalcoholic fatty liver disease and metabolic syndrome for colonoscopy colorectal neoplasm. 2017;96:2.
6. Stefan N, Häring H-U, Cusi K. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies. Lancet Diabetes Endocrinol. 2019 Apr;7(4):313-324.
7. Kleiner DE, Brunt EM. Nonalcoholic fatty liver disease: pathologic patterns and biopsy evaluation in clinical research. Seminars in liver disease; 2012;32(1):3-13.
8. Farrell G, Chitturi S, Lau G, et al. The Asia-Pacific Working Party on non-alcoholic fatty liver disease (NAFLD). Guidelines for the assessment and management of non-alcoholic fatty liver disease in the Asia-Pacific region: executive summary. J Gastroenterol Hepatol. 2007;22:775–777.
9. Perumpail BJ, Khan MA, Yoo ER, et al. Clinical epidemiology and disease burden of nonalcoholic fatty liver disease. World J Gastroenterol. 2017;23(47):8263.
10. Murphy N, Jenab M, Gunter MJ. Adiposity and gastrointestinal cancers: epidemiology, mechanisms and future directions. Nat Rev Gastroenterol Hepatol. 2018;15(11):659-670.
11. Lonardo A, Bellentani S, Argo CK, et al. Epidemiological modifiers of non-alcoholic fatty liver disease: focus on high-risk groups. Dig Liver Dis. 2015;47(12):997–1006.
12. Sberna A, Bouillet B, Rouland A, et al. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) clinical practice recommendations for the management of non-alcoholic fatty liver disease: evaluation of their application in people with Type 2 diabetes. Diabet Med. 2018;35(3):368–375.
13. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Clin Pract Gastroenterol Hepatol. 2018;15(1):11.
14. Dumitrascu DL, Neuman MG. Non-alcoholic fatty liver disease: an update on diagnosis. Clujul Med. 2018;91(2):147.
15. Younossi ZM, Blissett D, Blissett R, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. Hepatology. 2016;64(5):1577–1586.
16. Ahn J, Sinn D, Min Y, et al. Non-alcoholic fatty liver diseases and risk of colorectal neoplasia. Aliment Pharmacol Ther. 2017;45 (2):345–353.
17. Sweet PH, Khoo T, Nguyen S. Nonalcoholic fatty liver disease [Review]. Prim Care. 2017;44(4):599–607.
18. Hossain IA, Shah MMR, Rahman MK, et al. Gamma glutamyl transferase is an independent determinant for the association of insulin resistance with nonalcoholic fatty liver disease in Bangladeshi adults: association of GGT and HOMA-IR with NAFLD. Diabetes Metab Syndr. 2016;10(1):S25–S29.
19. Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism. 2016;65 (8):1038–1048.
20. Albhaisi S, Sanyal A. Recent advances in understanding and managing non-alcoholic fatty liver disease. F1000Research; 2018 Jun 11;7. pii: F1000 Faculty Rev-720.
21. Singh S, Osna NA, Kharbanda KK. Treatment options for alcoholic and non-alcoholic fatty liver disease: a review. World J Gastroenterol. 2017;23(36):6549.
22. Haggar FA, Boushey RP. Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. Clin Colon Rectal Surg. 2009;22 (4):191-197.

23. Bahrami A, Hassanian SM, ShahidSales S, et al. Targeting RAS signaling pathway as a potential therapeutic target in the treatment of colorectal cancer. J Cell Physiol. 2018;233 (3):2058–2066.

24. Moradi Marjaneh R, Hassanian SM, Ghobadi N, et al. Targeting the death receptor signaling pathway as a potential therapeutic target in the treatment of colorectal cancer. J Cell Physiol. 2018;233 (10):6538-6549.

25. Moradi-Marjaneh R, Hassanian SM, Fiuji H, et al. Toll like receptor signaling pathway as a potential therapeutic target in colorectal cancer. J Cell Physiol. 2018;233(8):5613–5622.

26. Rahmani F, Avan A, Hashemy SI, et al. Role of Wnt/β-catenin signaling regulatory microRNAs in the pathogenesis of colorectal cancer. J Cell Physiol. 2018;233(2):811–817.

27. Al-Jashamy K, Benayed SH, Hussain SM, et al. Trends of incidence and mortality with pathological description of colorectal cancer. Am Educ Res J. 2015;3:239–248.

28. Basyigit S, Uzman M, Kefeli A, et al. Absence of non-alcoholic fatty liver disease in the presence of insulin resistance is a strong predictor for colorectal carcinoma. Int J Clin Exp Med. 2015;8 (10):18601-10.

29. Alam S, Mustafa G, Alam M, et al. Insulin resistance in development and progression of nonalcoholic fatty liver disease. World J Gastrointest Pathophysiol. 2016;7(2):211.

30. Kim S, Keku TO, Martin C, et al. Circulating levels of inflammatory cytokines and risk of colorectal adenomas. Cancer Res. 2008;68 (1):323–328.

31. Jarrar M, Baranova A, Collantes R, et al. Adipokines and cytokines in non-alcoholic fatty liver disease. Aliment Pharmacol Ther. 2008;27 (5):412–421.

32. Zauber AG, Winawer SJ, O'brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med. 2012;366(8):687–696.

33. Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med. 2013;369(12):1095–1105.

34. Shinagawa T, Tanaka T, Nozawa H, et al. Comparison of the guidelines for colorectal cancer in Japan, the USA and Europe. Ann Gastroenterol Surg. 2018;2(1):6–12.

35. Lee K-C, Chung K-C, Chen -H-H, et al. Short-term postoperative outcomes of colorectal cancer among patients with chronic liver disease: a national population-based study. BMJ Open. 2018;8(7): e020511.

36. Mikolasevic I, Orlic L, Stimac D, et al. Non-alcoholic fatty liver disease and colorectal cancer. Postgrad Med J. 2017 Mar;93 (1097):153-158.

37. Hwang ST, Cho YK, Park JH, et al. Relationship of non-alcoholic fatty liver disease to colorectal adenomatous polyps. J Gastroenterol Hepatol. 2010;25(3):562–567.

38. Lee YI, Lim YS, Hs P, et al. Colorectal neoplasms in relation to non-alcoholic fatty liver disease in Korean women: a retrospective cohort study. J Gastroenterol Hepatol. 2012;27(1):91–95.

39. Wong VW-S, Wong GL-H, Tsang SW-C, et al. High prevalence of colorectal neoplasm in patients with non-alcoholic steatohepatitis. Gut. 2011;60(6):829–836.

40. Stadlmayr A, Aigner E, Steger B, et al. Nonalcoholic fatty liver disease: an independent risk factor for colorectal neoplasia. J Intern Med. 2011;270(1):41–49.

41. Bhatt BD, Lukose T, Siegel AB, et al. Increased risk of colorectal polyps in patients with non-alcoholic fatty liver disease undergoing liver transplant evaluation. J Gastrointest Oncol. 2015;6(5):459.

42. Huang KW, Leu HB, Wang YJ, et al. Patients with nonalcoholic fatty liver disease have higher risk of colorectal adenoma after negative baseline colonoscopy. Colorectal Dis. 2013;15(7):830–835.

43. Touzin NT, Bush KN, Williams CD, et al. Prevalence of colonic adenomas in patients with nonalcoholic fatty liver disease. Therap Adv Gastroenterol. 2011;4(3):169–176.

44. Lin X-F, Shi K-Q, You J, et al. Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study. Mol Biol Rep. 2014;41(5):2989–2997.

45. Muhidin SO, Magan AA, Osman KA, et al. The relationship between nonalcoholic fatty liver disease and colorectal cancer: the future challenges and outcomes of the metabolic syndrome. J Obes. 2012;2012:637538.

46. Aktas E, Uzman M, Yildirim O, et al. Assessment of hepatic steatosis on contrast enhanced computed tomography in patients with colorectal cancer. Int J Clin Exp Med. 2014;7(11):4342.

47. Kim G-A, Lee HC, Choe J, et al. Association between non-alcoholic fatty liver disease and cancer incidence rate. J Hepatol. 2018;68 (1):140–146.

48. Yang YJ, Bang CS, Shin SP, et al. Clinical impact of non-alcoholic fatty liver disease on the occurrence of colorectal neoplasm: propensity score matching analysis. PLoS One. 2017;12(8):e0182014.

49. Ze EY, Kim BJ, Jun DH, et al. The fatty liver index: a simple and accurate predictor of colorectal adenoma in an average-risk population. Dis Colon Rectum. 2018;61(1):36.

50. Shen H, Lipka S, Kumar A, et al. Association between nonalcoholic fatty liver disease and colorectal adenoma: a systemic review and meta-analysis. J Gastrointest Oncol. 2014;5(6):440.

51. Sanna C, Rosso C, Marietti M, et al. Non-alcoholic fatty liver disease and extra-hepatic cancers. Int J Mol Sci. 2016;17(5):717.

52. Endo H, Hosono K, Uchiyama T, et al. Leptin acts as a growth factor for colorectal tumours at stages subsequent to tumour initiation in murine colon carcinogenesis. Gut. 2011;60(10):1363–1371.

53. Louis P, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. Nature Rev Microbiol. 2014;12(10):661.

54. Parizadeh SM, Ferns GA, Ghandehari M, et al. The diagnostic and prognostic value of circulating microRNAs in coronary artery disease: a novel approach to disease diagnosis of stable CAD and acute coronary syndrome. J Cell Physiol. 2018;233(9):6418–6424.

55. Schetter AJ, Okayama H, Harris CC. The role of microRNAs in colorectal cancer. Cancer J. 2012;18(3):244.

56. Baffy G. MicroRNAs in nonalcoholic fatty liver disease. J Clin Med. 2015;4(12):1977–1988.