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Review

Liver diseases and metabolic syndrome

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Emerging attention has been paid to metabolic syndrome, which comprises several metabolic disorders including visceral obesity, diabetes mellitus, dyslipidemia, and hypertension. Whether the severity of each disease is mild to moderate, the comorbidity of these metabolic disorders has a serious impact on the development of atherosclerosis. Nonalcoholic fatty liver disease (NAFLD) is the major hepatic disorder in patients with metabolic syndrome, and indeed it is the most common cause of abnormal liver function tests in the working population in industrialized countries. In recent years, it has become recognized that NAFLD is no longer just a trivial disease, and a rather considerable proportion of the patients develop liver cirrhosis. Furthermore, chronic infection of hepatitis C virus also develops a pathological feature of steatohepatitis, and extended hepatic steatosis has a serious impact not only on the progression of hepatic fibrosis but also on the antiviral efficacy of interferon therapy. Emerging lines of studies indicated that insulin resistance, abnormal lipid metabolism, and dysregulation of cytokines/adipokines (e.g., tumor necrosis factor-alpha, adiponectin, and leptin) are profoundly involved in the pathogenesis of NAFLD. This review aims to integrate the reported evidence and to provide the current point of view for comprehensive understanding of the pathophysiology of steatohepatitis.

Key words: metabolic syndrome, nonalcoholic fatty liver diseases, nonalcoholic steatohepatitis, chronic hepatitis C, pegylated interferon, ribavirin, sustained viral response

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Introduction

In Japan in recent years, the Western lifestyle has become common, and the morbidity rates of obesity, diabetes mellitus, dyslipidemia, and hypertension have gradually increased. Generally, the metabolic disorders, which are basically characterized by insulin resistance, have been recognized as risk factors for cardiovascular disease. Even if the severity of each disease is only moderate, it is most likely true that the comorbidity of these metabolic disorders has serious impacts on the development of atherosclerosis. From this point of view, metabolic syndrome has become a new hot topic, and suddenly many related papers have been published.[1,2] Moreover, it is a matter of interest that metabolic syndrome is closely associated with some gastrointestinal diseases as well.[3]

On the other hand, the liver is one of the most important organs associated with digestion, detoxification, production, and storage. Nonalcoholic fatty liver disease (NAFLD) has been noted as the most common cause of abnormal liver function,[4,5] and had, however, previously been recognized merely as a relatively benign disease mostly observed in some obese patients. In 1980, Ludwig et al. reported nonalcoholic steatohepatitis (NASH) as a novel liver disease entity, which is histologically characterized by zone 3-dominant hepatic steatosis with hepatocellular ballooning, lobular inflammation, zone 3 perisinusoidal fibrosis, and cirrhosis.[6] This notion indicated that NAFLD is no longer just a trivial disease, but rather potentially develops into liver cirrhosis.

At the same time, the number of obese patients steadily increased, and consequently obesity became one of the major causes of morbidity and mortality in the United States in the 1990s.[7,8] Also, obesity is also one of the most important risk factors for fatty liver disease. For this reason, the report of Ludwig et al. had a great impact on the management of patients with

NAFLD in the late 1990s. In Japan, the increase in the number of people with obesity caused the same health problems, following after the Western countries with a lag of a decade. Therefore, the metabolic abnormalities; so-called metabolic syndrome and fatty liver disease, have now become an important health issue in Japan as well.

Some recent studies have been trying to describe how liver diseases are closely associated with metabolic syndrome, because this is useful to elucidate the background and pathophysiology.[9–11] The aim of this review is to integrate the reported evidences of liver diseases and metabolic syndrome and find a way to establish a rational medical treatment of the metabolic disorders.

Nonalcoholic steatohepatitis (NASH) and metabolic syndrome

Pathological features of NASH/NAFLD

Nonalcoholic steatohepatitis (NASH) is currently recognized as an important disease that potentially progresses to cirrhosis and liver-related death. In 1980, Ludwig et al. first reported liver biopsy findings that resemble alcohol-induced liver disease pathologically but develop in patients without alcohol abuse.[6] Since the 1970s, the number of people with obesity gradually increased at a steady state, and in the 1990s, some obesity-related diseases became a serious problem in Western countries. On that occasion, Day et al. hypothesized the "two hit theory" as the pathophysiology of steatohepatitis in 1998. The review article noted that fat accumulation in hepatocytes, induced by insulin resistance and some other factors, is the "first hit"; and after that, cell injury induced by oxidant stress and free fatty acids is the "second hit."[12] Additionally, the title of the review was so catchy that the "two hit theory" spread quickly through the world. In 1999, Brunt et al. proposed the grading (1–3) and staging (0–4) system of the histological lesions in patients with nonalcoholic steatohepatitis.[13] Although the system is only for NASH, it is a useful and semiquantitative evaluation that is now popular among pathologists and clinical physicians. About that time, Matteoni et al. evaluated the entire spectrum of NAFLD by using comparative analysis, pathologically: type 1, fatty liver alone; type 2, fat accumulation and lobular inflammation; type 3, fat accumulation and ballooning degeneration; and type 4, fat accumulation, ballooning degeneration, and either Mallory hyaline or fibrosis. In fact, the poor outcomes, including cirrhosis and liver-related death, were more frequent in patients in whom biopsies show ballooning degeneration and Mallory hyaline or fibrosis.[14] This pathological evaluation system is valuable because it is most likely true that there was a positive association between the types of the pathological classification and the outcome in the patients with NAFLD.

After these reports, as the more extended term, nonalcoholic fatty liver disease (NAFLD) acquired a new meaning and became accepted to cover the wide spectrum of metabolic fatty liver disorders.[15] More recently, a NAFLD activity score (NAS) was proposed for NAFLD and NASH with reasonable interrater reproducibility. Actually, the scoring system seems to be somewhat complicated and difficult to approach for some clinicians; however, it is useful to evaluate the semiquantitative and reproducible activity score, i.e., steatosis (0–3), lobular inflammation (0–2), hepatocellular ballooning (0–2), and fibrosis (0–4). An NAS greater than 5 is correlated with a diagnosis of NASH, and biopsies with scores of less than 3 were diagnosed as "not NASH."[16]

Clinical features of NAFLD/NASH and metabolic syndrome

Focused on the prevalence of NAFLD, a recent population-based cohort study revealed that 34% of the adult population; included an age range of 18–65 years in the United States, has fatty liver mostly without excessive alcohol abuse.[17] Furthermore, another population-based cohort study described the natural history of nonalcoholic fatty liver disease (NAFLD). It was shown that mortality among NAFLD patients was higher than the general population. Liver-related death was the third most common cause and accounting for 13% of all deaths; however, the absolute risk was low.[18] From the other point of view, the result of the study has still been controversial because of the inevitably implicated selection bias in the study. Even though, it could be believed that the report has a great impact on regarding NAFLD as a critical disease.

On the other hand, metabolic disorders such as obesity, hyperglycemia, hypertriglyceridemia, and hypertension were reported as risk factors for NAFLD/NASH.[18–22] Recently, a clinical study revealed the close relationships between Japanese patients with metabolic syndrome and NAFLD detected by abdominal ultrasonography.[23] The limitations of the report were insufficient examination to detect NAFLD and inappropriate estimation of central obesity to defined metabolic syndrome so far. Although the concept has become believed that NAFLD is a manifestation of metabolic syndrome, it seems obvious that the background of each entity is necessarily overlapped.

Experimental facts related to obesity, metabolic disturbances, and NASH

The experimental data indicated that ingestion of a high-fat diet promotes obesity and the development of metabolic disturbances in rodents.[24–26] A homozygous defect of obese gene in the mouse (ob/ob mouse) presents an obese phenotype as well.[27] Further, homozygous mutations of the leptin receptor gene have been identified both in mice (i.e., db/db mouse) and in rats [Zucker (fa/fa) rat], which are also associated with obesity.[28–30]

Pathophysiology of NASH: insulin resistance, free fatty acids, and cytokines

Although it is not yet fully understood what is the pivotal cause of whether simple hepatic steatosis or steatohepatitis occurs, it is most likely true that insulin resistance and increased free fatty acids in the liver are highly associated with NASH.[31,32] Insulin resistance leads to fat accumulation in hepatocytes by lipolysis and hyperinsulinemia.

Recently, the cytokine–adipokine interaction related to NAFLD is increasingly drawing great attention to elucidate the underlying mechanism. Insulin resistance is thought to be regulated by proinflammatory cytokines, such as TNF-α (tumor necrosis factor-alpha), and some adipokines, e.g., adiponectin and leptin.[33,34]

TNF-α and NAFLD/NASH

TNF-α is an important inflammatory cytokine that is overexpressed in the adipose tissues of rodent models of obesity.[35] Clinically, enhanced TNF-α expression was shown in patients with NASH compared with patients with simple steatosis.[36] Experimental data described that free fatty acids induced production of TNF-α through promoting hepatic lipotoxicity.[37] Moreover, it was shown that antibody-mediated neutralization of TNF-α improves NAFLD in ob/ob mice.[38] Taken together, these findings indicated that TNF-α is one of the critical factors for occurrence and progression of NAFLD/NASH.

Adiponectin and NASH

There is a noteworthy adipokine, adiponectin, which is one of the important properties for antiinflammation, insulin sensitization, and antiatherosclerosis. Adipose tissue is the major site of endogenous adiponectin production. It is well known that hypoadiponectinemia is observed in patients with visceral obesity and insulin resistance, especially NASH and atherosclerosis.[39–41] Furthermore, Hui et al. showed that hypoadiponectinemia is a feature of the NASH independent of insulin resistance.[42]

Additionally, the experimental data suggested that adiponectin and TNF-α suppressed each other's synthesis locally in adipose tissue and suppressed each other's function remotely in muscle in adiponectin-deficient mice.[43] These data indicated that adiponectin has a key role in neutralization of TNF-α. Interestingly, adiponectin considerably alleviated hepatomegaly, steatosis, and abnormal liver function in nonalcoholic obese ob/ob mice as well.[44]

Leptin and hepatic fibrosis

Leptin, an obese gene product mainly produced from adipocytes, is also a cytokine-type hormone that regulates food intake and fat metabolism through actions on the central nervous system.[27] Leptin receptors (Ob-R) have originally been shown in hypothalamic neurons, through which leptin regulates food intake and body weight.[45] In the late 1990s, Potter et al. described that the activated stellate cells in culture during hepatic fibrosis can express leptin.[46] The findings lead to the hypothesis that leptin plays a pivotal role in profibrogenic responses in the liver caused by hepatotoxic chemicals.

Endogenous leptin and hepatic fibrosis

First, we demonstrated that administration of recombinant leptin augments profibrogenic responses in the liver caused by xenobiotics [i.e., carbon tetrachloride, thioacetamide (TAA)] in mice.[47] After that, to investigate whether endogenous leptin promotes hepatic fibrogenesis, we utilized ob/ob mice; which lack leptin because of naturally occurring disruption of the leptin gene. Interestingly, ob/ob mice demonstrated extremely poor profibrogenic responses against xenobiotic treatment. It was shown that leptin appears to promote profibrogenic responses in the liver, in part, by upregulation of transforming growth factor-beta (TGF-β), suggesting that leptin is one of the key regulators of hepatic fibrogenesis.[48,49]

Second, we evaluated that role of Ob-R in hepatic fibrogenesis using Zucker rats, which lack functional Ob-R as a result of a missense mutation in the common, extracellular domain.[50] Zucker rats presented extremely poor profibrogenic responses in the liver caused by chronic thioacetamide (TAA) treatment as compared to their lean littermates, indicating that Ob-R is involved in the profibrogenic responses in the liver.

Leptin as a profibrogenic cytokine via MAPK and PI3K/AKT

Further, leptin increased TGF-β mRNA in isolated sinusoidal endothelial cells and Kupffer cells. From this point of view, it is suggested that leptin promotes hepatic fibrogenesis through upregulation of TGF-β in the liver. Moreover, leptin augmented PDGF-dependent proliferation of HSCs by enhancing downstream intracellular signaling pathways via mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3 kinase(PI3K)/Akt.[51] Collectively, it is postulated that leptin acts as a profibrogenic cytokine in the sinusoidal microenvironment. These findings indicated that leptin is one of the key regulators for inflammation and progression of fibrosis in various chronic liver diseases including NASH. In a similar hypothesis, Anania et al. indicated that leptin is profibrogenic in activated HSCs partly via the Jak-Stat pathway as well.[52]

Recently, several studies also identified that leptin upregulates collagen expression in HSCs; i.e., increased α2 (I) collagen gene expression in cultured rat hepatic stellate cells,[53] and enhanced α1 (I) collagen gene expression in LX-2 human hepatic stellate cells via JAK-mediated H_2O_2-dependent MAPK pathways.[54] Meanwhile, several studies described that leptin stimulates and increases tissue inhibitor of metalloproteinase I (TIMP-1) gene expression.[55–57] Moreover, ObR activation in HSCs leads to increased expression of proinflammatory and proangiogenic cytokines, indicating a complex role for leptin in the regulation of liver wound-healing responses.[58] Collectively, it is most likely true that these data support the hypotheses; profibrogenesis is markedly increased when hepatic stellate cells are activated, where leptin plays a pivotal role in hepatic fibrosis.

Mitochondria abnormalities and NAFLD/NASH

Mitochondrial abnormalities were described in liver biopsy specimens of patients with NASH[59,60]; however, it is also unclear whether the observed mitochondria abnormalities are congenital or acquired. Mitochondrial defects are supposed to be one of the primary causes of steatosis because of impaired β-oxidation of fatty acids in humans.[61] Moreover, recent study has shown that anti-TNF antibody improves mitochondrial dysfunction in ob/ob mice.[62] Taken together, these findings indicated that inflammation derived from oxidative stress is one of the most important backgrounds in patients with NAFLD/NASH as well as metabolic syndrome.

Chronic hepatitis C, hepatic steatosis, and metabolic syndrome

Chronic hepatitis C virus (HCV) infection is a significant worldwide problem because approximately 170 million people are suffering from HCV infection. It is thought that about 80% of acute HCV infection becomes chronic, that 20% will develop liver cirrhosis, and that 1%–6% will develop hepatocellular carcinoma each year.[63] A new treatment strategy including the combination of pegylated interferon and ribavirin were developed; nevertheless, the overall efficacy of the treatment is not enough to overcome HCV infection at the moment, as only about 54%–63% respond.[64–66]

Hepatic steatosis is a common histological feature of chronic hepatitis C (CHC), which is observed in 40%–70% of the patients.[67] Hepatic steatosis occurs more frequently in patients with chronic hepatitis C than in the general population in the world.[68] First, focusing epidemiologically on host-related factors, overweight patients with chronic hepatitis C have increased circulating insulin levels.[69] At the same time, obesity and diabetes mellitus and/or insulin resistance are associated with hepatic steatosis in patients with chronic hepatitis C.[70–72] These clinical features are often observed in patients with metabolic syndrome. Therefore, it was supposed that multiple risk factors for metabolic disorders are closely correlated with the prevalence of hepatic steatosis in CHC patients. Second, focusing on virus-related factors, it was commonly shown that the HCV genotype 3 is significantly associated with hepatic steatosis.[73] Additionally, evaluation of paired (pre- and postantiviral therapy) liver biopsies demonstrated a marked decline in steatosis in HCV genotype 3 patients who achieved sustained viral response (SVR).[74] Although it is hypothesized that genotype 3 virus is more cytopathic and therefore steatogenic, the mechanisms underlying the genotype specific steatosis are still not fully elucidated. Moreover, transgenic mice expressing hepatitis C virus core protein develop hepatic steatosis and insulin resistance without gain in body weight at a young age.[75,76] Taken together, these findings suggested that multiple factors are closely associated with the occurrence of hepatic steatosis in patients with chronic hepatitis C, not only host-related metabolic disorders but also HCV itself.

Importantly, emerging lines of clinical data revealed that several metabolic disturbances; such as obesity, insulin resistance, and hepatic steatosis, are significant risk factors for decreased SVR to the interferon and ribavirin combination antiviral therapy in CHC patients[71,72,77–87] (Table 1). Underlying mechanisms of lesser efficacy of antiviral treatment are not well investigated; however, it is postulated that oxidant stress and

Table 1. Relationships between hepatic steatosis and response rate of antiviral therapy in patients with chronic hepatitis C

Reference		Patient numbers (study design)	Treatment	Genotype (%)			Fatty liver (%)	SVR rate (%)		
				1	2	3		Overall	Fatty liver (+)	Fatty liver (–)
Poynard et al.[79] Hepatology 2003	Western countries	1428 (retrospective)	48W IFN α-2b or 48W pegIFN α-2b plus Riba	68	15	15	65	54	35	57
Sanyal et al.[80] Am J Gastroenterol 2003	USA	137 (retrospective)	IFN plus Riba or PegIFN alone or plus Riba	90	4	3	47 48	25	14	35
Romero-Gomez et al.[81] Gastroenterology 2005	Spain	159 (prospective)	Peg IFN plus Riba	71	23	6	No data	52	18	53.7
Harrison et al.[82] Clin Gastroenterol Hepatol 2005	USA	315 (retrospective)	IFN or pegIFN plus Riba	76	24		100	40	28 (>33% steatosis)	44 (<33% steatosis)
Thomopoulos et al.[83] J Gastroenterol Hepatol 2005	Greece	116 (retrospective)	IFN or pegIFN plus Riba	41	8	34	45	52	39	66
D'Souza et al.[84] Am J Gastroenterol 2005	UK (White/Asian)	59 (prospective)	Peg IFN 2α plus Riba	63 genotype 1 and 2		37	83	55	55	56
Camma et al.[71] Hepatology 2006	Italy	291 (prospective)	Peg IFN plus Riba	100			57	36	25 (>1% steatosis)	50 (<1% steatosis)
Yaginuma et al.[85] Hepatol Res 2006	Japan	80 (retrospective)	24W IFNα-2b plus Riba	84	16		66	50	30 (>33% steatosis)	58 (<33% steatosis)
Jian et al.[86] Liver Int 2006	China	98 (prospective)	24W or 48W pegIFN α-2a plus Riba	39	45	13	14	58	29	62
Soresi et al.[87] Liver Int 2006	Italy	112 (prospective)	48W pegIFN α-2a plus Riba	72	14	13	64	41	33	55

IFN, interferon; pegIFN, pegylated interferon; Riba, ribavirin; SVR, sustained viral response; 48W, 48 weeks

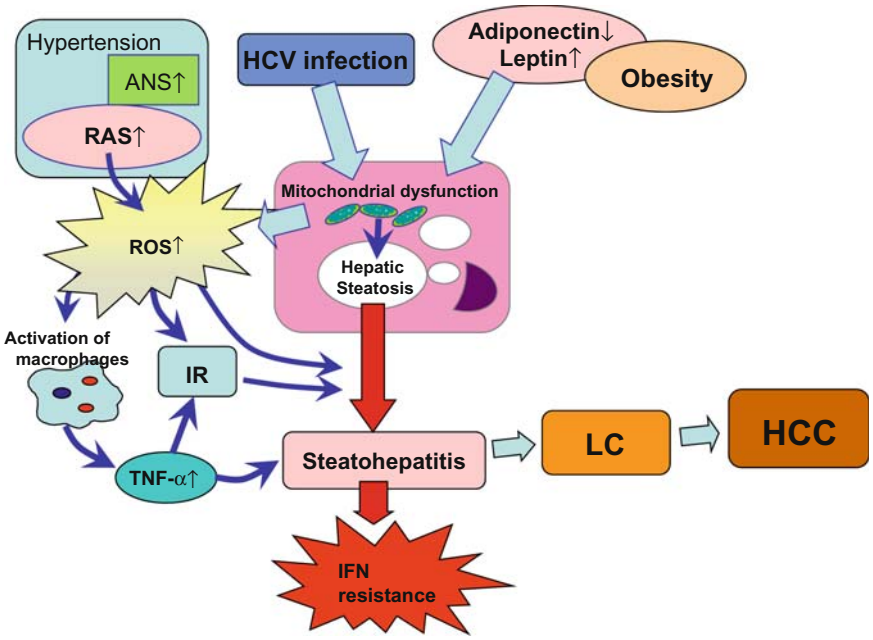

Fig. 1. Working hypothesis of the underlying mechanisms of the interaction between liver diseases including HCV infection and metabolic syndrome. (*i*) Underlying mechanisms of lesser efficacy of antiviral treatment are not well investigated; however, it is postulated that oxidant stress and proinflammatory cytokines are closely associated with interferon resistance. (*ii*) Etanercept, which is a chimerical protein that binds to and inactivates TNF-α in the liver and mononuclear cells, has been reported to improve the efficacy of antiviral treatment in patients with chronic hepatitis C. (*iii*) Furthermore, hepatic steatosis is a risk factor for HCC in patients with chronic HCV infection. *HCV*, hepatitis C virus; *ROS*, reactive oxygen species; *TNF-α*, tumor necrosis factor-alpha; *IFN*, interferon; *IR*, insulin resistance; *RAS*, renin-angiotensin system; *ANS*, autonomic nervous system; *HCC*, hepatocellular carcinoma

proinflammatory cytokines are closely associated with interferon resistance.[88,89] Indeed, Etanercept, which is a chimerical protein that binds to and inactivates TNF-α in the liver and mononuclear cells, has been reported to improve the efficacy of antiviral treatment in patients with chronic hepatitis C[90] (Fig. 1).

Collectively, it is most likely true that intensive adjustment of metabolic imbalance before the induction of antiviral therapy is favorable for the complete eradication of HCV infection.

Metabolic syndrome and progression of fibrosis, occurring as hepatocellular carcinoma (HCC) in chronic hepatitis

Progression of hepatic fibrosis is an important aspect in patients with chronic liver disease, such as NASH and chronic hepatitis C, because liver cirrhosis is one of the critical risk factors for liver-related death, including liver failure and hepatocellular carcinoma.

Recently, it has become apparent that hepatic fibrosis is associated with obesity, insulin resistance, and hepatic steatosis.[91,92] It is reported that NASH can progress to cirrhosis in up to 20% of the patients.[93] Therefore, it is suggested that metabolic abnormalities are closely associated with progression of fibrosis as well.

As a malignant disease, HCC is one of the most important diseases in patients with chronic liver disease. Recently, some epidemiological studies have reported that obesity and diabetes mellitus are a risk factor for hepatocellular carcinoma (HCC), respectively.[94–96] Furthermore, hepatic steatosis is a risk factor for HCC in patients with chronic HCV infection as well[97] (Fig. 1).

In the meantime, experimental data suggested that *PTEN* deficiency leads to steatohepatitis and hepatocellular carcinoma.[98] *PTEN* is a ubiquitously expressed tumor suppressor gene[99] that is mutated in many human sporadic cancers as well as in tumorigenic hereditary disorders. It is postulated that controlled blocking of molecules acting downstream of PI3K might provide significant therapeutic benefit to patients predisposed to NASH and hepatocellular carcinoma.

Hepatic steatosis, atherosclerosis, and hypertension

Metabolic syndrome, which is characterized by insulin resistance, is associated with atherosclerosis and hypertension and is recognized as an inflammatory disease.[100,101] It is a serious disease because the mortality rate of cardiovascular disease is increasing, especially in Asia.[102]

As with liver disease, it was reported that hypoadiponectinemia is observed in patients with coronary artery disease and is associated with the incidence of cardiovascular death.[103,104] Experimental data demonstrated that adenovirus-mediated increase of plasma adiponectin significantly suppressed the progression of atherosclerotic lesions in apolipoprotein E-deficient mice.[105]

Recently, the PROactive study (PROspective pioglitAzone Clinical Trial In macroVascular Events) has shown that pioglitazone; agonists of peroxisome proliferators-activated receptor γ (PPAR-γ), which is a thiazolidinedione that ameliorates insulin resistance

and improves glucose and lipid metabolism in type 2 diabetes, reduces the composite of all-cause mortality, nonfatal myocardial infarction, and stroke in patients with type 2 diabetes who have a high risk of macrovascular events.[106]

Hepatic steatosis is also increasingly recognized as one of the important risk factors for atherosclerosis and cardiovascular disease[107–109] (Fig. 1). Interestingly, a recent prospective study has shown that histological features in patients with NASH; including hepatic steatosis, ballooning necrosis, and inflammation, are improved by administrating pioglitazone as compared with placebo.[110] However, fatigue and mild lower-extremity edema developed in 1 of 55 subjects who received pioglitazone. Therefore, we have to find the appropriate dose of pioglitazone and be careful about the adverse effects.

Taken together, there seem to be close relationships among hepatic steatosis, atherosclerosis, and hypertension as metabolic disorders. From this point of view, we would be able to investigate the aspects of both liver and cardiovascular-related diseases.

Conclusions

In this review, we described the current understanding of relationships between liver diseases and metabolic syndrome. As we noted, there are so many intricate factors of causing hepatic inflammation, steatosis/steatohepatitis, fibrosis, and carcinoma in patients with chronic liver diseases in conjunction with metabolic syndrome. We should pay a critical attention to "liver diseases," because there must be a clue to elucidate the pathophysiology of so-called metabolic syndrome.

Necessarily, to avoid developing fatal diseases in the end, we have to establish a radical treatment strategy not only by ordinary diet and exercise therapy but also developing a sure remedy against liver diseases and metabolic syndrome.

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