World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v6.i5.306

World J Hepatol 2014 May 27; 6(5): 306-314
ISSN 1948-5182 (online)

REVIEW

Metabolic syndrome and non-alcoholic fatty liver disease in liver surgery: The new scourges?

François Cauchy, David Fuks, Alban Zarzavadjian Le Bian, Jacques Belghiti, Renato Costi

François Cauchy, David Fuks, Jacques Belghiti, Service de Chirurgie Hépato-Bilio-Pancréatique et Transplantation Hépatique, Hôpital Beaujon, Assistance Publique - Hôpitaux de Paris, 92110 Clichy, France
Alban Zarzavadjian Le Bian, Laboratoire de Recherche en Ethique Médicale et Médecine Légale, Université de Paris 5 Descartes, 75006 Paris, France
Renato Costi, Dipartimento di Scienze Chirurgiche, Università degli Studi di Parma, Azienda Ospedaliero-Universitaria di Parma, 43100 Parma, Italy
Author contributions: Cauchy F and Costi R designed the research; Cauchy F and Fuks D performed the research; Cauchy F, Fuks D and Zarzavadjian Le Bian A analyzed the data; Cauchy F wrote the paper; Fuks D, Zarzavadjian Le Bian A, Belghiti J and Costi R gave an important intellectual contribution; Belghiti J and Costi R supervised.
Correspondence to: Renato Costi, MD, PhD, FACS, Dipartimento di Scienze Chirurgiche, Università degli Studi di Parma, Azienda Ospedaliero-Universitaria di Parma, Via Gramsci 14, 43100 Parma, Italy. renatocosti@hotmail.com
Telephone: +39-335-8234285 Fax: +39-521-940125
Received: November 9, 2013 Revised: January 1, 2014
Accepted: January 17, 2014
Published online: May 27, 2014

Abstract

The aim of this topic highlight is to review relevant evidence regarding the influence of the metabolic syndrome (MS) and its associated liver manifestation, non-alcoholic fatty liver disease (NAFLD), on the development of liver cancer as well as their impact on the results of major liver surgery. MS and NAFLD, whose incidences are significantly increasing in Western countries, are leading to a changing profile of the patients undergoing liver surgery. A MEDLINE search was performed for relevant articles using the key words "metabolic syndrome", "liver resection", "liver transplantation", "non alcoholic fatty liver disease", "non-alcoholic steatohepatitis" and "liver cancer". On one hand, the MS favors the development of primary liver malignancies (hepatocellular carcinoma and cholangiocarcinoma) either through NAFLD liver parenchymal alterations (steatosis, steatohepatitis, fibrosis) or in the absence of significant underlying liver parenchyma changes. Also, the existence of NAFLD may have a specific impact on colorectal liver metastases recurrence. On the other hand, the postoperative period following partial liver resection and liver transplantation is at increased risk of both postoperative complications and mortality. These deleterious effects seem to be related to the existence of liver specific complications but also higher cardio-vascular sensitivity in a setting of MS/NAFLD. Finally, the long-term prognosis after curative surgery joins that of patients operated on with other types of underlying liver diseases. An increased rate of patients with MS/NAFLD referred to hepatobiliary units has to be expected. The higher operative risk observed in this subset of patients will require specific improvements in their perioperative management.

Key words: Metabolic syndrome; Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Neoplasia; Hepatocarcinoma; Liver surgery; Complications; Morbidity

Core tip: The metabolic syndrome (MS) and its hepatic manifestations, non-alcoholic fatty liver disease (NAFLD), are increasingly observed in Western countries. Both MS and NAFLD could favor the development of primary liver malignancies and may also lead to end-stage liver disease. These patients are at higher operative risk because of underestimated postoperative liver related complications but also specific increase in cardio-vascular complications. Specific improvements in the perioperative management of these patients are required in order to improve the operative results.

Cauchy F, Fuks D, Zarzavadjian Le Bian A, Belghiti J, Costi R. Metabolic syndrome and non-alcoholic fatty liver disease in liver surgery: The new scourges? *World J Hepatol* 2014; 6(5): 306-314

Available from: URL: http://www.wjgnet.com/1948-5182/full/v6/i5/306.htm DOI: http://dx.doi.org/10.4254/wjh.v6.i5.306

INTRODUCTION

The prevalence of the metabolic syndrome (MS) is reaching epidemic levels in Western Europe and Northern America, where it is reported to be as high as 25% in the general population[1]. The MS is a constellation of clinicobiological features closely related to insulin-resistance and includes dyslipidemia, hypertension, glucose intolerance and central obesity[1]. Non-alcoholic fatty liver disease (NAFLD) represents the hepatic manifestation of the MS. NAFLD pathological alterations, which range from simple steatosis to steatohepatitis, may lead to fibrosis and end stage liver disease[2]. As its incidence parallels that of the MS, NAFLD is currently becoming one of the first chronic liver diseases in Western countries and therefore has a major health impact[3]. Also, both MS and NAFLD have been suggested to be directly or indirectly associated with the development of primary liver malignancies[4-7]. For all these reasons, it is likely that more and more of these patients will be referred to hepatobiliary (HPB) and liver transplant units in upcoming years[8].

The increasing prevalence of MS/NAFLD and MS/NAFLD-related liver tumors is not the only issue related to these disorders. Despite numerous advances in the fields of hepatology, perioperative management and liver surgery, the impact of both MS and NAFLD on the postoperative course of patients undergoing liver surgery has long been neglected. As a matter of fact, it is only recently that evidence suggesting a specific and underestimated risk regarding postoperative morbidity and mortality in the setting of liver surgery has been released[8-13]. In that sense, it seems crucial that gastroenterologists and surgeons should be fully aware of the existence of MS and NAFLD as well as their negative impact on the postoperative course in order to optimize the perioperative management of concerned patients and to prevent any avoidable morbidity/mortality.

The objectives of this review are therefore: (1) to provide comprehensive insights regarding the current standards and issues in the diagnosis of both MS and NAFLD; (2) to clarify their respective impact on tumor progression as well as their influence on postoperative outcome; and (3) to discuss the measures which should be undertaken in upcoming years in order to improve the results of surgery.

DEFINITIONS AND ISSUES

Metabolic syndrome

The definition of MS has evolved during the past decade. Current consensual criteria for its diagnosis are summarized in Table 1. These include central (or android) obesity, hypertension, dyslipidemia, with either increased triglycerides level or decreased high density lipoprotein cholesterol level, and glucose intolerance[1]. Even although the presence of at least 3 out of 5 criteria of the consensual definition are required to define the MS[1], both liver histological manifestations and influence on surgical outcomes after liver surgery may occur in patients presenting with individual components of the MS. Indeed, fatty liver disease may also occur in patients with isolated diabetes mellitus (DM)[14], hypertriglyceridemia[15] and obesity[16,17]. Likewise, higher perioperative morbidity or mortality rates after liver resection are reported in patients with only DM[18,19] or overweight/obesity[20,21], whereas our groups found the association of just 2 disorders to be related to poor outcome of surgery[13,22].

Interestingly, most of the medical and surgical studies do not always gather all these consensual criteria but rather use substitutes for convenience. Such substitutes may lead to a certain degree of confusion. For example, it is frequently assumed that patients receiving statin or fenofibrate medication have dyslipidemia[8,11] and that patients receiving antihypertensive therapy have hypertension. However, some of these patients may receive such medications for primary cardiovascular prevention or renal protection. In the same way, central obesity, which reflects visceral adiposity, it is often measured using the BMI and various cut off values are proposed[8,12,13]. Yet, BMI does not allow distinguishing central obesity, which is a metabolic disorder included in the MS, from peripheral obesity. In that sense, circumferential waist appears to be more reliable and should be preferred[23,24]. Finally, the terms hyperglycemia and insulin-resistance are often used indiscriminately, whereas some authors suggest that they should not. Hence, the presence of insulin-resistance should be routinely assessed using the homeostasis model assessment of insulin resistance[25] whenever hyperglycemia is found.

NAFLD

NAFLD has emerged as one of the most frequent forms of chronic liver disease in Western countries[5,6] and should be considered in cases of fatty infiltration exceeding 5% of the liver parenchyma at histology in the absence of previous or ongoing significant alcohol consumption[26]. Although NAFLD is considered the hepatic manifestation of the MS, other conditions, including chronic hepatitis B and C infection[27,28], irinotecan based chemotherapy[29,30] and several other medications, including methotrexate, tamoxifen or amiodarone[31,32], may also lead to fatty liver disease and should be meticulously ruled out. NAFLD, which encompasses a wide spectrum of diseases ranging from simple steatosis to non-alcoholic steatohepatitis (NASH)[26], can progress to cirrhosis and may lead to end-stage liver disease[5,6]. Histological analysis remains the gold standard for the assessment of NAFLD and should be performed by a trained pathologist[33]. Several histological scores might be useful for diagnosis. The most frequently used score is the non-alcoholic liver disease activity score (NAS) proposed by Kleiner *et al*[26], which is a semiquantitative,

Table 1 Diagnostic criteria of the metabolic syndrome

Criteria	Consensual criteria definition[1]	Other non-consensual criteria
Central obesity	Abdominal waist[2] > 102 cm (United States) or 94 cm (Europe) in men > 88 cm (United States) or 80 cm (Europe) in women	Different cutoff values of BMI ⩾ 28 or ⩾ 28.8 or ⩾ 30 kg/m^2
Dyslipidemia	Triglycerides ⩾ 150 mg/dL (1.7 mmol/L) HDL cholesterol < 40 mg/dL (1.03 mmol/L) in men < 50 mg/dL (1.29 mmol/L) in women	Statin or fenofibrate medication[3]
Hypertension	Blood pressure > 135/85 mmHg	Any antihypertensive therapy[3]
Glucose intolerance	Hyperglycemia Fasting glucose ⩾ 110 mg/dL, or type Ⅱ diabetes	Any diabetes Any antidiabetic therapy (oral or insulin)

[1]Diagnosis of metabolic syndrome (MS) requires at least 3 out of 5 criteria; [2]Other cut off values have been established for Asians and Latin Americans; [3]These treatments can be taken in account for the diagnosis of MS unless if given in preemptive purpose.

histology-based score system including three parameters, namely steatosis (on a scale of 0-3), lobular inflammation and hepatocellular ballooning (on a scale of 0-2 each) and therefore ranges from 0 to 7. Likewise, Bedossa *et al*[34] recently published a histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients.

NASH

NASH is considered the result of long-lasting inflammation. It is characterized by several histological alterations, including steatosis, lobular inflammation and ballooning, and may also be associated with fibrosis. Even although the diagnosis of NASH was initially suggested for NAS values of 4 or 5[26], there is an ongoing debate regarding the accuracy of NAS in assessing NASH. Interestingly, Brunt *et al*[33] have emphasized that the diagnosis of NASH based on evaluation of patterns as well as individual lesions on liver biopsies did not always correlated with threshold values of the semi quantitative NAS. Moreover, NAS does not include other histological alterations often present in NAFLD, such as microcirculation modifications, which are not routinely reported by pathologists[35]. Thus, rather than being based on the NAS value alone, the differentiation between NASH and no-NASH should rather take into account the pathologist report[33].

Identification of NASH in patients with MS/NAFLD

Since the increasing incidence of both MS and NAFLD in Western populations de facto puts a great amount of patients at risk of developing NASH, any large scale screening policy aimed at obtaining histological diagnosis of NAFLD does not seem reasonable. Furthermore, the accuracy of histology in identifying NASH is suboptimal as both inter-observer variations[36] and discrepancies from one sample to the other within the same parenchyma may occur[37]. In order to increase cost/effectiveness and accuracy of diagnosis, and also to avoid the intrinsic invasiveness of biopsy, there has been significant interest in identifying non-invasive methods of predicting liver histology in patients with suspected NASH. Hence, numerous biological (alanine aminotransferase/aspartate aminotransferase ratio, FIB-4, analysis of organic compounds in breath)[38] and imaging techniques (magnetic resonance imaging (MRI) for quantification of liver steatosis[39] or magnetic resonance spectroscopy) have been proposed for the detection of underlying parenchymal changes among patients with MS, but none has become the "gold standard". In particular, although MRI has shown high accuracy in detecting steatosis, its effectiveness in evaluating (and possibly ruling out) fibrosis is questionable in the presence of fat[40].

MS/NAFLD INFLUENCE ON CARCINOGENESIS

The association between individual components of the MS, such as diabetes[41] and being overweight[42], and an increased risk of cancer has long been known. More recently, it has been suggested that the MS itself was implicated in carcinogenesis, especially in the liver[4]. Indeed, two recent series have shown that the MS itself was associated with an increased risk of developing of both HCC[3] and intrahepatic cholangiocarcinoma[43]. In particular, HCC incidence in patients with MS is reportedly 2-4 fold higher than in general population[7].

How the MS acts to promote carcinogenesis remains to be fully elucidated. Several genetic mechanisms are supposed to be involved in MS-related carcinogenesis. Firstly, direct oncological effects may play a role in the carcinogenesis by loss of tumor suppression genes, deregulation of IL-6 signal or inhibition of JNK1 phosphorylation[22]. This mechanism is supposed to be at the origin of malignant transformation of liver cell adenoma in men[44]. Secondly, the MS has been reported to be associated with low-grade, chronic systemic inflammation, implying a serum increase of inflammatory cytokines, such as TNF-α and IL-6[5], and a decrease in anti-inflammatory ones, including adipocytokines[45].

Interestingly, most studies focusing on HCC occurring in patients with MS (or arising in a context of NAFLD) have consistently reported that 30%-60% of the patients displayed no feature of severe underlying fibrosis[7,8,22,46]. More surprisingly, almost 20% of the

patients had a normal underlying liver parenchyma after conventional pathological examination. In this setting, HCCs furthermore tended to be isolated and of large size[8,22]. These findings seem to indicate that several different pathways may be implicated in liver carcinogenesis in patients with MS, as suggested by the inconstant presence of various histology alterations.

Although not always present, NASH related cirrhosis may possibly be considered a precancerous lesion as it is associated with a yearly incidence of HCC as high as 2.6%[5], leading to a cumulative 5-year incidence ranging from 7.6%[47] to 11%[48]. In the event of NASH related cirrhosis, both presence and pattern of hepatic iron deposition[49] have been incriminated to further accentuate parenchymal changes, thus promoting liver carcinogenesis.

Virus infection may also play an indirect role in tumor development in patients with MS. In particular, the specific subset of patients with chronic hepatitis C virus (HCV) infection developing an HCC is worth being mentioned. Several authors have emphasized that chronic HCV infection was associated with fatty infiltration of the liver parenchyma in 50%-70% of cases, including massive steatosis and NASH[27,28,50,51]. A non-negligible number of the latter display the so-called "viral steatosis" as a consequence of virus interference with fat metabolism (in the absence of pre-existing metabolic disorders). Thus, in this setting, steatosis itself could be responsible for the occurrence of secondary insulin-resistance and systemic inflammation. Even although the "viral steatosis" has been shown to regress after viral eradication[52], its existence has been incriminated in recurrence of HCV related HCC[53] after curative surgery. However, since steatosis and lobular inflammation may be found in HCV infection regardless of MS/NAFLD, the supposed association between HCC, HCV and NAFLD could be more a statistical artifact than a real oncogenic mechanism. Taken together, the supposed pathway from viral infection to viral steatosis and HCC, as well as the possible mechanisms finally leading to HCC development (fibrosis, inflammation or induced insulin-resistance), still remain to be assessed.

Finally, the association between MS, NAFLD and colorectal liver metastases (CLM) has to be considered. Indeed, whereas several studies on colorectal cancer patients analyzed the impact of 5FU + irinotecan based chemotherapy on the development of steatohepatitis[28,30], it is only recently that studies have focused on the specific oncological influence of both MS and NAFLD on CLM, with various results. On one hand, Hamady *et al*[54] found that liver steatosis was associated with a 1.3 fold risk of local recurrence following liver resection for CLM, regardless of the chemotherapy regimen used. On the other hand, Viganò *et al*[55], studying the impact of chemotherapy-related liver injuries, pathological tumor regression grade and micrometastases on long-term survival, found that higher grade (2-3) steatosis was significantly associated with improved 5 year overall survival compared to lesser steatosis (grade 0-1) after resection of CLM (52.5% *vs* 35.2%, $P = 0.002$). Even although these studies lacked specific histological assessment of NAFLD and precise identification of metabolic disorders, the observed results clearly reflect the growing enthusiasm of surgeons in exploring the impact of NAFLD on the long-term outcomes of patients with CLM.

MS/NAFLD IMPACT ON OUTCOME OF LIVER SURGERY

The impact of individual components of the MS and liver steatosis on the postoperative course following liver resection has been extensively investigated[18,56-60]. Accordingly, it has been established that liver surgery provided poorer results in patients affected by diabetes[18] or obesity[56,57] than in otherwise healthy patients. Similarly, several studies have highlighted that steatosis per se was a risk factor for postoperative complications after major hepatectomy[58-60]. In experimental models, liver fatty infiltration, such as mild or severe steatosis, has been found to be associated with lower regenerative ability following portal vein occlusion, elevated sensitivity to ischemia-reperfusion injury and higher hepatocellular injury after partial liver resection[61]. Nevertheless, it is only recently that surgeons have focused on the results of surgery, liver resection and transplantation in the specific subset of patients with MS or NASH.

Liver resection

Table 2 summarizes the results of recent series analyzing the early outcome of patients undergoing liver resection in a setting of MS/NASH[8-13]. Of these six series, three aimed at assessing the influence of the MS on outcome[8,12,13], whereas the remaining three aimed at evaluating the impact of histological modifications, including NAFLD and NASH[9-11]. The fact that data concerning metabolic disorders (and MS) and liver histology were gathered together in only half of the series[8,11,13] emphasizes the absence of clear understanding of the relationship between MS and MS-related liver disease. In these studies, mortality after liver resection varied from 3% up to 30% and was related to the primarily studied parameter, *i.e.,* MS, NAFLD or NASH. In this setting, it has been recently suggested that MS patients with a NAS > 2[8] or those with an histological diagnosis of NASH[11] had a 2.7-fold higher risk of experiencing liver related but also cardio-respiratory complications than those with normal underlying parenchyma. Hence, it seems that steatohepatitis rather than simple steatosis was a risk factor for postoperative complications[11]. Even if these recent findings may appear to be in opposition with previously published results maintaining a negative impact of steatosis on outcome[58-60], it is likely that the poor assessment of inflammatory changes in the underlying steatosic parenchyma may have biased older series. On the opposite hand, the progressively increasing degree of parenchymal change, damage and inflammation from steatosis to steatohepatitis is nowadays considered as a continuum, which progressively and proportionally increases overall

Table 2 Studies focusing on liver resection in a context of metabolic syndrome, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis

Ref.	Endpoint	Underlying parenchyma	Assessment of metabolic factors	Morbidity			Mortality
				Overall	Liver related	CV and respiratory	
Wakai *et al*[9]	Influence of the underlying liver on liver resection	NAFLD (n = 17)	BMI	59%	47%	6%	12%
Neal *et al*[10]	Influence of the underlying liver on right trisectionectomy	NASH (n = 9)	All factors	NA	NA	NA	22%
Reddy *et al*[11]	Influence of the underlying liver on liver resection	Simple steatosis (n = 72)	All factors	35%	19%	28%	4%
		NASH (n = 102)		57%	28%	13%	4%
Bhayani *et al*[12]	Influence of the MS on liver resection	NA	MS (n = 256)	29%	NA	22%	6%
			No MS (n = 3.717)	23%		15%	2%
Zarzavadjian Le Bian *et al*[13]	Influence of the MS on right trisectionectomy	NAFLD (n = 27)	> 2 MS factors (n = 30)	60%	53%	NA	30%
			≥ 3 MS factors (n = 13)	NA	NA	NA	54%
Cauchy *et al*[8]	Influence of the MS on liver resection	NASH (n = 16)	MS (n = 62)	58%	21%[1]	17%[1]	11%

[1]Major complications: Clavien Ⅲ-Ⅴ. MS: Metabolic syndrome; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; CV: Cardiovascular; NA: Not applicable.

postoperative morbidity/mortality.

Intuitively, not only the "quality" but also the "quantity" of liver remnant should be considered. In fact, it has been recently suggested that NASH was independently associated with both higher postoperative liver insufficiency and mortality following right hepatectomy (including extended right hepatectomy)[13], and trisectionectomy[10], although a (usually) "safe" amount of liver parenchyma was left in place. This result clearly emphasizes the worse tolerance to extended resection of fatty and inflammatory livers. This feature may be of particular importance in the case of HCC developing in a MS/NAFLD context, where large lesions often require major resections[8,22].

Considering cardiovascular morbidity/mortality, it has been shown that NASH was an independent risk-factor for the development of coronary artery disease and calcifications regardless of the degree of visceral adiposity[62,63], thus leading to a higher incidence of cardio-respiratory events following liver resection. Possibly, the recently described hemorheological alterations occurring in MS patients, including increased erythrocyte aggregation[64,65], may play a role in ischemic cardiac events.

Liver transplantation

NASH can progress to cirrhosis[2,4] and may lead to end-stage liver disease requiring liver transplantation (LT). During the last decade, the rate of LT performed for NASH related end-stage liver disease has dramatically increased from about 3% in the early 2000s up to 19% in 2011[2]. Currently, non-alcoholic steatohepatitis is the third most common cause of LT in the US and is on pace to become the most common within the next two decades in Western countries[66].

LT in NASH patients has peculiar aspects. Compared with other patients undergoing LT, recipients with NASH tend to be older[67] and obviously have a higher frequency of metabolic disorders[62]. In this setting, procedures significantly last longer and are associated with higher blood loss and longer post-transplantation hospital stay[62]. Accordingly, 30 d mortality after LT in patients with NASH tends to be higher than that for other indications[68]. Several studies have reported increased liver related morbidity rates in NASH patients, such as acute rejection rates[67], but also extra-hepatic complications, including sepsis and renal dysfunction[69]. Similarly to patients undergoing liver resectional surgery, NASH patients also have a higher likelihood of developing cardio-vascular complications after LT[62,67,69]. These events, which mainly occur within the first year after LT, have been reported to be responsible for as high as 50% of the total mortality following LT[62]. The relationship between MS/NASH and cardiovascular morbidity seems more complex than a generic multi-organ vascular disorder due to MS, as suggested by the significantly higher occurrence of cardiovascular events associated with MS whenever NASH is present[70]. In fact, similarly to what has been observed after LR, NASH is nowadays thought to put patients at an even higher risk of cardio-vascular complications, regardless of comorbidities and patient-specific cardiac risk[62]. Here again, it is likely that the degree of inflammation in the underlying liver represents a key factor in the occurrence of increased cardiovascular sensitivity.

Long-term results of LT following transplantation for NASH are encouraging. One, three and five year survivals after LT for NASH range from 84%-87.6%, 75%-82.2% and 70%-76.7%, respectively, and are at least similar to that observed for LT for other traditional indications[2,62,67,68,71]. Even more remarkable, LT for HCC developed in patients with NASH seems to provide excellent long-term outcomes with higher survivals compared with patients transplanted for HCV related HCC[72]. These observations could be the result of less aggressive tumors in NASH patients with lower micro vascular invasion and decreased rates of poorly differentiated lesions[8,72].

LT in patients with NASH related cirrhosis presents peculiar issues, including cirrhosis recurrence, to be discussed separately. Recurrent disease after LT for NASH

related cirrhosis has been reported to occur in as high as 34% of recipients[68,73]. There is little information detailing the occurrence and histological evolution of NAFLD recurrence after LT and the long-term natural history of NAFLD recurrence itself is unclear[74]. Nevertheless, in these patients, recurrence is often associated with the presence of the MS or its individual components[73]. Accordingly, recurrence should be further evaluated in larger studies, with special emphasis on management of MS and secondary prevention strategies[73].

WHICH IMPROVEMENTS SHOULD BE UNDERTAKEN IN UPCOMING YEARS?

Both MS and NAFLD/NASH adversely affect short and long-term results of liver surgery. Considering that the rate of patients presenting with such conditions will keep on increasing in upcoming years, it appears crucial that specific measures should be undertaken in order to improve those unsatisfactory results. Above all, the worse tolerance to extended resection of fatty and inflammatory livers (as a consequence of lower regenerative ability) requires that this issue should be attentively pondered in the preoperative planning of surgical strategy whenever a major resection is needed. Unfortunately, the culture of considering just MS or steatosis (even without liver biopsy confirmation) a potential risk factor for major surgery has not already entered clinical practice, even in specialized environments. Addressing this issue, our group has recently shown that MS patients operated on for HCC less frequently underwent preoperative PVE when they displayed a NAS > 2 without severe fibrosis compared to those with severe underlying fibrosis, suggesting that these latter patients would probably benefit from a better anticipation of their operative risk, especially in cases of planned major LR[8].

In general, preventative measures to reduce MS/NAFLD related morbidity/mortality should include: (1) better characterization of the underlying parenchyma using invasive or non-invasive means knowing that patients with inflammatory fatty liver even without severe fibrosis are at similar operative risk as those with severe underlying fibrosis; (2) targeted perioperative management, including complete preoperative cardio-vascular work-up and intraoperative cardio-vascular and pulmonary monitoring; and, finally (3) specific "NAFLD-tailored" perioperative surgical care, such as parenchymal sparing resections, wide use of liver volume modulation techniques, including portal vein embolization and portal vein ligation, but also targeted medical therapies developed in order to improve the tolerance of LR. Concerning this latter issue, a recent experimental study has highlighted the benefits of omega-3 acids in reducing severe steatosis in a preoperative setting leading to improved liver regeneration and functional recovery following partial hepatectomy[75]. These encouraging preliminary results still require confirmation in a clinical setting but may already be considered a promising future field of research.

Concerning the relationship between MS/NAFLD and neoplastic disease, several strategies should be developed in order to prevent both occurrence and recurrence of primary liver cancer in MS/NASH patients. Even although it is generally recommended that overweight and obese patients with NAFLD lose 7%-10% of their body weight by dietary modification and exercise over the course of 6-12 mo, the paucity of data makes it difficult to make evidence-based recommendations about dietary modification and exercise to treat NAFLD and NASH[76]. In fact, medical research has mainly focused on reducing NASH in MS patients using medical therapies. Several randomized controlled trials have shown significant downstaging of NASH following the administration of specific medications, including vitamin E and pioglitazone[77-79]. Retrospective studies have shown that the use of biguanides, such as metformin, was associated with HCC risk reduction among diabetic patients[80,81]. Experimentally, metformin has been shown to provide antineoplastic effects through deregulation of the m-TOR pathway[82,83]. Hence, in a context of MS/NAFLD related HCC, metformin would theoretically represent an ideal preventative therapy reducing both incidence of HCC following parenchymal alterations or systemic inflammation and also providing inherent antitumoral properties. Nevertheless, despite the encouraging results of all these medications and the possible future development of others that are even more effective, it should be kept in mind that none have currently been tested in a surgical context. In fact, the prolonged time interval required by medications to obtain relevant effects on liver parenchyma possibly reducing morbidity definitely questions its applicability in a surgical environment prior to (or after) surgery. This consideration gains interest if one considers that the great majority of patients undergoing major liver surgery (LR and LT) presents with cancer or end stage liver disease, needing prompt management. Obviously, any medical/preventative strategy should ideally require a large-scale evaluation in a surgical setting.

CONCLUSION

Both the pro-oncogenic effect on the underlying liver and the rising incidence of MS/NASH imply that an increased number of patients with such conditions referred to HPB units has to be expected. The higher operative risk observed in these patients can be partially explained by both underestimated liver related risk and also high perioperative cardio-vascular and respiratory susceptibility. These unsatisfactory postoperative results will require targeted perioperative management. Such actions are justified by the observed favorable long-term outcomes.

ACKNOWLEDGMENTS

The authors would like to thank Clemence Sebag for her precious help in reviewing the manuscript.

REFERENCES

1 **Eckel RH**, Alberti KG, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2010; **375**: 181-183 [PMID: 20109902 DOI: 10.1016/S0140-6736(09)61794-3]
2 **Agopian VG**, Kaldas FM, Hong JC, Whittaker M, Holt C, Rana A, Zarrinpar A, Petrowsky H, Farmer D, Yersiz H, Xia V, Hiatt JR, Busuttil RW. Liver transplantation for nonalcoholic steatohepatitis: the new epidemic. *Ann Surg* 2012; **256**: 624-633 [PMID: 22964732 DOI: 10.1097/SLA.0b013e31826b4b7e]
3 **Fierbinteanu-Braticevici C**, Negreanu L, Tarantino G. Is fatty liver always benign and should not consequently be treated? *J Physiol Pharmacol* 2013; **64**: 3-9 [PMID: 23568965]
4 **Welzel TM**, Graubard BI, Zeuzem S, El-Serag HB, Davila JA, McGlynn KA. Metabolic syndrome increases the risk of primary liver cancer in the United States: a study in the SEER-Medicare database. *Hepatology* 2011; **54**: 463-471 [PMID: 21538440 DOI: 10.1002/hep.24397]
5 **Starley BQ**, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. *Hepatology* 2010; **51**: 1820-1832 [PMID: 20432259 DOI: 10.1002/hep.23594]
6 **Ascha MS**, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *Hepatology* 2010; **51**: 1972-1978 [PMID: 20209604 DOI: 10.1002/hep.23527]
7 **Turati F**, Talamini R, Pelucchi C, Polesel J, Franceschi S, Crispo A, Izzo F, La Vecchia C, Boffetta P, Montella M. Metabolic syndrome and hepatocellular carcinoma risk. *Br J Cancer* 2013; **108**: 222-228 [PMID: 23169288 DOI: 10.1038/bjc.2012.492]
8 **Cauchy F**, Zalinski S, Dokmak S, Fuks D, Farges O, Castera L, Paradis V, Belghiti J. Surgical treatment of hepatocellular carcinoma associated with the metabolic syndrome. *Br J Surg* 2013; **100**: 113-121 [PMID: 23147992 DOI: 10.1002/bjs.8963]
9 **Wakai T**, Shirai Y, Sakata J, Korita PV, Ajioka Y, Hatakeyama K. Surgical outcomes for hepatocellular carcinoma in nonalcoholic fatty liver disease. *J Gastrointest Surg* 2011; **15**: 1450-1458 [PMID: 21512848 DOI: 10.1007/s11605-011-1540-8]
10 **Neal CP**, Mann CD, Pointen E, McGregor A, Garcea G, Metcalfe MS, Berry DP, Dennison AR. Influence of hepatic parenchymal histology on outcome following right hepatic trisectionectomy. *J Gastrointest Surg* 2012; **16**: 2064-2073 [PMID: 22923210 DOI: 10.1007/s11605-012-2008-1]
11 **Reddy SK**, Marsh JW, Varley PR, Mock BK, Chopra KB, Geller DA, Tsung A. Underlying steatohepatitis, but not simple hepatic steatosis, increases morbidity after liver resection: a case-control study. *Hepatology* 2012; **56**: 2221-2230 [PMID: 22767263 DOI: 10.1002/hep.25935]
12 **Bhayani NH**, Hyder O, Frederick W, Schulick RD, Wolgang CL, Hirose K, Edil B, Herman JM, Choti MA, Pawlik TM. Effect of metabolic syndrome on perioperative outcomes after liver surgery: A National Surgical Quality Improvement Program (NSQIP) analysis. *Surgery* 2012; **152**: 218-226 [PMID: 22828143 DOI: 10.1016/j.surg.2012.05.037]
13 **Zarzavadjian Le Bian A**, Costi R, Constantinides V, Smadja C. Metabolic disorders, non-alcoholic fatty liver disease and major liver resection: an underestimated perioperative risk. *J Gastrointest Surg* 2012; **16**: 2247-2255 [PMID: 23054903 DOI: 10.1007/s11605-012-2044-x]
14 **El-Serag HB**, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 2004; **126**: 460-468 [PMID: 14762783 DOI: 10.1053/j.gastro.2003.10.065]
15 **Fiatarone JR**, Coverdale SA, Batey RG, Farrell GC. Non-alcoholic steatohepatitis: impaired antipyrine metabolism and hypertriglyceridaemia may be clues to its pathogenesis. *J Gastroenterol Hepatol* 1991; **6**: 585-590 [PMID: 1782374]
16 **Ratziu V**, Giral P, Charlotte F, Bruckert E, Thibault V, Theodorou I, Khalil L, Turpin G, Opolon P, Poynard T. Liver fibrosis in overweight patients. *Gastroenterology* 2000; **118**: 1117-1123 [PMID: 10833486]
17 **Gholam PM**, Flancbaum L, Machan JT, Charney DA, Kotler DP. Nonalcoholic fatty liver disease in severely obese subjects. *Am J Gastroenterol* 2007; **102**: 399-408 [PMID: 17311652 DOI: 10.1111/j.1572-0241.2006.01041.x]
18 **Huo TI**, Lui WY, Huang YH, Chau GY, Wu JC, Lee PC, Chang FY, Lee SD. Diabetes mellitus is a risk factor for hepatic decompensation in patients with hepatocellular carcinoma undergoing resection: a longitudinal study. *Am J Gastroenterol* 2003; **98**: 2293-2298 [PMID: 14572582 DOI: 10.1111/j.1572-0241.2003.07688.x]
19 **Slankamenac K**, Breitenstein S, Held U, Beck-Schimmer B, Puhan MA, Clavien PA. Development and validation of a prediction score for postoperative acute renal failure following liver resection. *Ann Surg* 2009; **250**: 720-728 [PMID: 19809295 DOI: 10.1097/SLA.0b013e3181bdd840]
20 **Pathak S**, Tang JM, Terlizzo M, Poston GJ, Malik HZ. Hepatic steatosis, body mass index and long term outcome in patients undergoing hepatectomy for colorectal liver metastases. *Eur J Surg Oncol* 2010; **36**: 52-57 [PMID: 19879103 DOI: 10.1016/j.ejso.2009.09.004]
21 **Mathur AK**, Ghaferi AA, Sell K, Sonnenday CJ, Englesbe MJ, Welling TH. Influence of body mass index on complications and oncologic outcomes following hepatectomy for malignancy. *J Gastrointest Surg* 2010; **14**: 849-857 [PMID: 20140536 DOI: 10.1007/s11605-010-1163-5]v]
22 **Paradis V**, Zalinski S, Chelbi E, Guedj N, Degos F, Vilgrain V, Bedossa P, Belghiti J. Hepatocellular carcinomas in patients with metabolic syndrome often develop without significant liver fibrosis: a pathological analysis. *Hepatology* 2009; **49**: 851-859 [PMID: 19115377 DOI: 10.1002/hep.22734]
23 **Janssen I**, Katzmarzyk PT, Ross R. Body mass index, waist circumference, and health risk: evidence in support of current National Institutes of Health guidelines. *Arch Intern Med* 2002; **162**: 2074-2079 [PMID: 12374515 DOI: 10.1001/jamainternmed.2013.339]
24 **Janssen I**, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. *Am J Clin Nutr* 2004; **79**: 379-384 [PMID: 14985210]
25 **Bonora E**, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauni T, Muggeo M. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 2000; **23**: 57-63 [PMID: 10857969 DOI: 10.2337/diacare.23.1.57]
26 **Kleiner DE**, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, Ferrell LD, Liu YC, Torbenson MS, Unalp-Arida A, Yeh M, McCullough AJ, Sanyal AJ. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005; **41**: 1313-1321 [PMID: 15915461 DOI: 10.1002/hep.20701]
27 **Bedossa P**, Moucari R, Chelbi E, Asselah T, Paradis V, Vidaud M, Cazals-Hatem D, Boyer N, Valla D, Marcellin P. Evidence for a role of nonalcoholic steatohepatitis in hepatitis C: a prospective study. *Hepatology* 2007; **46**: 380-387 [PMID: 17659580 DOI: 10.1002/hep.21711]
28 **Moucari R**, Asselah T, Cazals-Hatem D, Voitot H, Boyer N, Ripault MP, Sobesky R, Martinot-Peignoux M, Maylin S, Nicolas-Chanoine MH, Paradis V, Vidaud M, Valla D, Bedossa P, Marcellin P. Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. *Gastroenterology* 2008; **134**: 416-423 [PMID: 18164296 DOI: 10.1053/j.gastro.2007.11.010]
29 **Fernandez FG**, Ritter J, Goodwin JW, Linehan DC, Hawkins WG, Strasberg SM. Effect of steatohepatitis associated with irinotecan or oxaliplatin pretreatment on resectability of hepatic colorectal metastases. *J Am Coll Surg* 2005; **200**: 845-853

[PMID: 15922194 DOI: 10.1016/j.jamcollsurg.2005.01.024]
30 **Vauthey JN**, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, Xiong HQ, Eng C, Lauwers GY, Mino-Kenudson M, Risio M, Muratore A, Capussotti L, Curley SA, Abdalla EK. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol* 2006; **24**: 2065-2072 [PMID: 16648507 DOI: 10.1200/JCO.2005.05.3074]
31 **Angulo P**. Nonalcoholic fatty liver disease. *N Engl J Med* 2002; **346**: 1221-1231 [PMID: 11961152 DOI: 10.1056/NEJMra011775]
32 **Vuppalanchi R**, Chalasani N. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: Selected practical issues in their evaluation and management. *Hepatology* 2009; **49**: 306-317 [PMID: 19065650 DOI: 10.1002/hep.22603]
33 **Brunt EM**, Kleiner DE, Wilson LA, Belt P, Neuschwander-Tetri BA. Nonalcoholic fatty liver disease (NAFLD) activity score and the histopathologic diagnosis in NAFLD: distinct clinicopathologic meanings. *Hepatology* 2011; **53**: 810-820 [PMID: 21319198 DOI: 10.1002/hep.24127]
34 **Bedossa P**, Poitou C, Veyrie N, Bouillot JL, Basdevant A, Paradis V, Tordjman J, Clement K. Histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients. *Hepatology* 2012; **56**: 1751-1759 [PMID: 22707395 DOI: 10.1002/hep.25889]
35 **Farrell GC**, Teoh NC, McCuskey RS. Hepatic microcirculation in fatty liver disease. *Anat Rec* (Hoboken) 2008; **291**: 684-692 [PMID: 18484615 DOI: 10.1002/ar.20715]
36 **Merriman RB**, Ferrell LD, Patti MG, Weston SR, Pabst MS, Aouizerat BE, Bass NM. Correlation of paired liver biopsies in morbidly obese patients with suspected nonalcoholic fatty liver disease. *Hepatology* 2006; **44**: 874-880 [PMID: 17006934 DOI: 10.1002/hep.21346]
37 **Ratziu V**, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, Grimaldi A, Capron F, Poynard T. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology* 2005; **128**: 1898-1906 [PMID: 15940625 DOI: 10.1053/j.gastro.2005.03.084]
38 **McPherson S**, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. *Gut* 2010; **59**: 1265-1269 [PMID: 20801772 DOI: 10.1136/gut.2010.216077]
39 **Raptis DA**, Fischer MA, Graf R, Nanz D, Weber A, Moritz W, Tian Y, Oberkofler CE, Clavien PA. MRI: the new reference standard in quantifying hepatic steatosis? *Gut* 2012; **61**: 117-127 [PMID: 21997548 DOI: 10.1136/gutjnl-2011-300155]
40 **Bülow R**, Mensel B, Meffert P, Hernando D, Evert M, Kühn JP. Diffusion-weighted magnetic resonance imaging for staging liver fibrosis is less reliable in the presence of fat and iron. *Eur Radiol* 2013; **23**: 1281-1287 [PMID: 23138385 DOI: 10.1007/s00330-012-2700-2]
41 **Arase Y**, Kobayashi M, Suzuki F, Suzuki Y, Kawamura Y, Akuta N, Kobayashi M, Sezaki H, Saito S, Hosaka T, Ikeda K, Kumada H, Kobayashi T. Effect of type 2 diabetes on risk for malignancies includes hepatocellular carcinoma in chronic hepatitis C. *Hepatology* 2013; **57**: 964-973 [PMID: 22991257 DOI: 10.1002/hep.26087]
42 **Calle EE**, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003; **348**: 1625-1638 [PMID: 12711737 DOI: 10.1056/NEJMoa021423]
43 **Reddy SK**, Hyder O, Marsh JW, Sotiropoulos GC, Paul A, Alexandrescu S, Marques H, Pulitano C, Barroso E, Aldrighetti L, Geller DA, Sempoux C, Herlea V, Popescu I, Anders R, Rubbia-Brandt L, Gigot JF, Mentha G, Pawlik TM. Prevalence of nonalcoholic steatohepatitis among patients with resectable intrahepatic cholangiocarcinoma. *J Gastrointest Surg* 2013; **17**: 748-755 [PMID: 23355033 DOI: 10.1007/s11605-013-2149-x]
44 **Farges O**, Dokmak S. Malignant transformation of liver adenoma: an analysis of the literature. *Dig Surg* 2010; **27**: 32-38 [PMID: 20357449 DOI: 10.1136/gut.2010.222109]
45 **Saxena NK**, Fu PP, Nagalingam A, Wang J, Handy J, Cohen C, Tighiouart M, Sharma D, Anania FA. Adiponectin modulates C-jun N-terminal kinase and mammalian target of rapamycin and inhibits hepatocellular carcinoma. *Gastroenterology* 2010; **139**: 1762-1773, 1773.e1-5 [PMID: 20637208 DOI: 10.1053/j.gastro.2010.07.001]
46 **Ertle J**, Dechêne A, Sowa JP, Penndorf V, Herzer K, Kaiser G, Schlaak JF, Gerken G, Syn WK, Canbay A. Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis. *Int J Cancer* 2011; **128**: 2436-2443 [PMID: 21128245 DOI: 10.1002/ijc.25797]
47 **Hashimoto E**, Yatsuji S, Tobari M, Taniai M, Torii N, Tokushige K, Shiratori K. Hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *J Gastroenterol* 2009; **44** Suppl 19: 89-95 [PMID: 19148800 DOI: 10.1007/s00535-008-2262-x]
48 **Yatsuji S**, Hashimoto E, Tobari M, Taniai M, Tokushige K, Shiratori K. Clinical features and outcomes of cirrhosis due to non-alcoholic steatohepatitis compared with cirrhosis caused by chronic hepatitis C. *J Gastroenterol Hepatol* 2009; **24**: 248-254 [PMID: 19032450 DOI: 10.1111/j.1440-1746.2008.05640.x]
49 **Valenti L**, Fracanzani AL, Bugianesi E, Dongiovanni P, Galmozzi E, Vanni E, Canavesi E, Lattuada E, Roviaro G, Marchesini G, Fargion S. HFE genotype, parenchymal iron accumulation, and liver fibrosis in patients with nonalcoholic fatty liver disease. *Gastroenterology* 2010; **138**: 905-912 [PMID: 19931264 DOI: 10.1053/j.gastro.2009.11.013]
50 **Asselah T**, Rubbia-Brandt L, Marcellin P, Negro F. Steatosis in chronic hepatitis C: why does it really matter? *Gut* 2006; **55**: 123-130 [PMID: 16344578 DOI: 10.1136/gut.2005.069757]
51 **Serfaty L**, Andreani T, Giral P, Carbonell N, Chazouillères O, Poupon R. Hepatitis C virus induced hypobetalipoproteinemia: a possible mechanism for steatosis in chronic hepatitis C. *J Hepatol* 2001; **34**: 428-434 [PMID: 11322205 DOI: 10.1111/j.1572-0241.2002.05793.x]
52 **Serfaty L**, Poujol-Robert A, Carbonell N, Chazouillères O, Poupon RE, Poupon R. Effect of the interaction between steatosis and alcohol intake on liver fibrosis progression in chronic hepatitis C. *Am J Gastroenterol* 2002; **97**: 1807-1812 [PMID: 12135040]
53 **Takuma Y**, Nouso K, Makino Y, Saito S, Takayama H, Takahara M, Takahashi H, Murakami I, Takeuchi H. Hepatic steatosis correlates with the postoperative recurrence of hepatitis C virus-associated hepatocellular carcinoma. *Liver Int* 2007; **27**: 620-626 [PMID: 17498246 DOI: 10.1111/j.1478-3231.2007.01462.x]
54 **Hamady ZZ**, Rees M, Welsh FK, Toogood GJ, Prasad KR, John TK, Lodge JP. Fatty liver disease as a predictor of local recurrence following resection of colorectal liver metastases. *Br J Surg* 2013; **100**: 820-826 [PMID: 23354994 DOI: 10.1002/bjs.9057]
55 **Viganò L**, Capussotti L, De Rosa G, De Saussure WO, Mentha G, Rubbia-Brandt L. Liver resection for colorectal metastases after chemotherapy: impact of chemotherapy-related liver injuries, pathological tumor response, and micrometastases on long-term survival. *Ann Surg* 2013; **258**: 731-740; discussion 741-742 [PMID: 24045448 DOI: 10.1097/SLA.0b013e3182a6183e]
56 **Balzan S**, Nagarajan G, Farges O, Galleano CZ, Dokmak S, Paugam C, Belghiti J. Safety of liver resections in obese and overweight patients. *World J Surg* 2010; **34**: 2960-2968 [PMID: 20711580 DOI: 10.1007/s00268-010-0756-1]
57 **Cucchetti A**, Cescon M, Ercolani G, Di Gioia P, Peri E, Pinna AD. Safety of hepatic resection in overweight and obese patients with cirrhosis. *Br J Surg* 2011; **98**: 1147-1154 [PMID: 21509752 DOI: 10.1002/bjs.7516]

58 **McCormack L**, Petrowsky H, Jochum W, Furrer K, Clavien PA. Hepatic steatosis is a risk factor for postoperative complications after major hepatectomy: a matched case-control study. *Ann Surg* 2007; **245**: 923-930 [PMID: 17522518 DOI: 10.1097/01.sla.0000251747.80025.b7]

59 **Veteläinen R**, van Vliet A, Gouma DJ, van Gulik TM. Steatosis as a risk factor in liver surgery. *Ann Surg* 2007; **245**: 20-30 [PMID: 17197961]

60 **de Meijer VE**, Kalish BT, Puder M, Ijzermans JN. Systematic review and meta-analysis of steatosis as a risk factor in major hepatic resection. *Br J Surg* 2010; **97**: 1331-1339 [PMID: 20641066 DOI: 10.1002/bjs.7194]

61 **Veteläinen R**, van Vliet AK, van Gulik TM. Severe steatosis increases hepatocellular injury and impairs liver regeneration in a rat model of partial hepatectomy. *Ann Surg* 2007; **245**: 44-50 [PMID: 17197964]

62 **Vanwagner LB**, Bhave M, Te HS, Feinglass J, Alvarez L, Rinella ME. Patients transplanted for nonalcoholic steatohepatitis are at increased risk for postoperative cardiovascular events. *Hepatology* 2012; **56**: 1741-1750 [PMID: 22611040 DOI: 10.1002/hep.25855]

63 **Wong VW**, Wong GL, Yip GW, Lo AO, Limquiaco J, Chu WC, Chim AM, Yu CM, Yu J, Chan FK, Sung JJ, Chan HL. Coronary artery disease and cardiovascular outcomes in patients with non-alcoholic fatty liver disease. *Gut* 2011; **60**: 1721-1727 [PMID: 21602530 DOI: 10.1136/gut.2011.242016]

64 **Vayá A**, Hernández-Mijares A, Bonet E, Sendra R, Solá E, Pérez R, Corella D, Laiz B. Association between hemorheological alterations and metabolic syndrome. *Clin Hemorheol Microcirc* 2011; **49**: 493-503 [PMID: 22214720 DOI: 10.3233/CH-2011-1499]

65 **Gyawali P**, Richards RS, Hughes DL, Tinley P. Erythrocyte aggregation and metabolic syndrome. *Clin Hemorheol Microcirc* 2013; Epub ahead of print [PMID: 24192695]

66 **Charlton MR**, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. *Gastroenterology* 2011; **141**: 1249-1253 [PMID: 21726509 DOI: 10.1053/j.gastro.2011.06.061]

67 **Bhagat V**, Mindikoglu AL, Nudo CG, Schiff ER, Tzakis A, Regev A. Outcomes of liver transplantation in patients with cirrhosis due to nonalcoholic steatohepatitis versus patients with cirrhosis due to alcoholic liver disease. *Liver Transpl* 2009; **15**: 1814-1820 [PMID: 19938128 DOI: 10.1002/lt.21927]

68 **Malik SM**, deVera ME, Fontes P, Shaikh O, Ahmad J. Outcome after liver transplantation for NASH cirrhosis. *Am J Transplant* 2009; **9**: 782-793 [PMID: 19344467 DOI: 10.1111/j.1600-6143.2009.02590.x]

69 **Houlihan DD**, Armstrong MJ, Davidov Y, Hodson J, Nightingale P, Rowe IA, Paris S, Gunson BK, Bramhall SB, Mutimer DJ, Neuberger JM, Newsome PN. Renal function in patients undergoing transplantation for nonalcoholic steatohepatitis cirrhosis: time to reconsider immunosuppression regimens? *Liver Transpl* 2011; **17**: 1292-1298 [PMID: 21761549 DOI: 10.1002/lt.22382]

70 **Madhwal S**, Atreja A, Albeldawi M, Lopez R, Post A, Costa MA. Is liver transplantation a risk factor for cardiovascular disease? A meta-analysis of observational studies. *Liver Transpl* 2012; **18**: 1140-1146 [PMID: 22821899 DOI: 10.1002/lt.23508]

71 **Kennedy C**, Redden D, Gray S, Eckhoff D, Massoud O, McGuire B, Alkurdi B, Bloomer J, DuBay DA. Equivalent survival following liver transplantation in patients with non-alcoholic steatohepatitis compared with patients with other liver diseases. *HPB* (Oxford) 2012; **14**: 625-634 [PMID: 22882200 DOI: 10.1111/j.1477-2574.2012.00497.x]

72 **Reddy SK**, Steel JL, Chen HW, DeMateo DJ, Cardinal J, Behari J, Humar A, Marsh JW, Geller DA, Tsung A. Outcomes of curative treatment for hepatocellular cancer in nonalcoholic steatohepatitis versus hepatitis C and alcoholic liver disease. *Hepatology* 2012; **55**: 1809-1819 [PMID: 22183968 DOI: 10.1002/hep.25536]

73 **El Atrache MM**, Abouljoud MS, Divine G, Yoshida A, Kim DY, Kazimi MM, Moonka D, Huang MA, Brown K. Recurrence of non-alcoholic steatohepatitis and cryptogenic cirrhosis following orthotopic liver transplantation in the context of the metabolic syndrome. *Clin Transplant* 2012; **26**: E505-E512 [PMID: 23061759 DOI: 10.1111/ctr.12014]

74 **Patil DT**, Yerian LM. Evolution of nonalcoholic fatty liver disease recurrence after liver transplantation. *Liver Transpl* 2012; **18**: 1147-1153 [PMID: 22740341 DOI: 10.1002/lt.23499]

75 **Marsman HA**, de Graaf W, Heger M, van Golen RF, Ten Kate FJ, Bennink R, van Gulik TM. Hepatic regeneration and functional recovery following partial liver resection in an experimental model of hepatic steatosis treated with omega-3 fatty acids. *Br J Surg* 2013; **100**: 674-683 [PMID: 23456631 DOI: 10.1002/bjs.9059]

76 **Torres DM**, Harrison SA. Diagnosis and therapy of nonalcoholic steatohepatitis. *Gastroenterology* 2008; **134**: 1682-1698 [PMID: 18471547 DOI: 10.1053/j.gastro.2008.02.077]

77 **Belfort R**, Harrison SA, Brown K, Darland C, Finch J, Hardies J, Balas B, Gastaldelli A, Tio F, Pulcini J, Berria R, Ma JZ, Dwivedi S, Havranek R, Fincke C, DeFronzo R, Bannayan GA, Schenker S, Cusi K. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 2006; **355**: 2297-2307 [PMID: 17135584 DOI: 10.1056/NEJMoa060326]

78 **Lavine JE**, Schwimmer JB, Van Natta ML, Molleston JP, Murray KF, Rosenthal P, Abrams SH, Scheimann AO, Sanyal AJ, Chalasani N, Tonascia J, Ünalp A, Clark JM, Brunt EM, Kleiner DE, Hoofnagle JH, Robuck PR. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. *JAMA* 2011; **305**: 1659-1668 [PMID: 21521847 DOI: 10.1001/jama.2011.520]

79 **Sanyal AJ**, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, Neuschwander-Tetri BA, Lavine JE, Tonascia J, Unalp A, Van Natta M, Clark J, Brunt EM, Kleiner DE, Hoofnagle JH, Robuck PR. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010; **362**: 1675-1685 [PMID: 20427778 DOI: 10.1056/NEJMoa0907929]

80 **Hassan MM**, Curley SA, Li D, Kaseb A, Davila M, Abdalla EK, Javle M, Moghazy DM, Lozano RD, Abbruzzese JL, Vauthey JN. Association of diabetes duration and diabetes treatment with the risk of hepatocellular carcinoma. *Cancer* 2010; **116**: 1938-1946 [PMID: 20166205 DOI: 10.1002/cncr.24982]

81 **Donadon V**, Balbi M, Mas MD, Casarin P, Zanette G. Metformin and reduced risk of hepatocellular carcinoma in diabetic patients with chronic liver disease. *Liver Int* 2010; **30**: 750-758 [PMID: 20331505 DOI: 10.1111/j.1478-3231.2010.02223.x]

82 **Rocha GZ**, Dias MM, Ropelle ER, Osório-Costa F, Rossato FA, Vercesi AE, Saad MJ, Carvalheira JB. Metformin amplifies chemotherapy-induced AMPK activation and antitumoral growth. *Clin Cancer Res* 2011; **17**: 3993-4005 [PMID: 21543517 DOI: 10.1158/1078-0432.CCR-10-2243]

83 **Chen HP**, Shieh JJ, Chang CC, Chen TT, Lin JT, Wu MS, Lin JH, Wu CY. Metformin decreases hepatocellular carcinoma risk in a dose-dependent manner: population-based and in vitro studies. *Gut* 2013; **62**: 606-615 [PMID: 22773548 DOI: 10.1136/gutjnl-2011-301708]

P- Reviewers: Anty R, Bellentani S, Fierbinteanu-Braticevici C, Trovato GM **S- Editor**: Zhai HH **L- Editor**: Roemmele A **E- Editor**: Wang CH

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com