

REVIEW ARTICLE

Metabolic syndrome and hepatic resection: improving outcome

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Abstract

Objective: A review of the peri-operative risk associated with hepatic resection in patients with metabolic syndrome (MetS) and identification of measures for the improvement of cardiometabolic disturbances and liver-related mortality.

Background: MetS and its hepatic manifestation non-alcoholic fatty liver disease (NAFLD) are associated with an increased operative mortality in spite of a significant improvement in peri-operative outcome after hepatic resection.

Methods: A review of the English literature on MetS, liver resection and steatosis was performed from 1980 to 2011 using the MEDLINE and PubMed databases.

Results: MetS is a predictor of NAFLD and patients with multiple metabolic risk factors may harbour non-alcoholic steatohepatitis (NASH) predictive of operative and cardiovascular mortality. Pre-operative diagnosis of unsuspected NASH with the selective use of a liver biopsy can modify the operative strategy by limiting the extent of hepatic resection, avoiding or altering the pre-operative chemotherapy regimen and the utilization of portal vein embolization. Thiazolidinediones are therapeutic for MetS and NASH and Vitamin E for active NASH; however, their utility in improving the peri-operative outcome after hepatic resection is unknown. A short-term regimen for weight loss improves post-operative patient and liver-related outcomes in patients with >30% steatosis. Cardiovascular disease associated with MetS or NAFLD should be managed aggressively. Peri-operative measures to minimize thrombotic events and acute renal injury secondary to the pro-inflammatory, prothrombotic state of MetS may further improve the outcome.

Conclusion: Potential candidates for hepatic resection should be screened for MetS as the pre-operative identification of NASH, short-term treatment of significant steatosis, cardiovascular risk assessment and optimization of each component of MetS may improve the peri-operative outcome in this high-risk subset of patients.

Keywords

liver resection, steatohepatitis, cardiovascular risk, operative mortality

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Introduction

Metabolic syndrome (MetS) is a constellation of inter-related risk factors of metabolic origin including abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance and a pro-inflammatory prothrombotic state which has an adverse impact on the peri-operative outcome.¹⁻⁹ Patients with MetS have a two-fold risk of operative mortality and are at an increased risk for

cardiac events, acute kidney injury, stroke and infectious complications. MetS is prevalent in 23.7% of adults and 43.5% of adults aged >60 years in the United States and non-alcoholic fatty liver disease (NAFLD) is widely accepted as the hepatic manifestation of MetS.^{10,11} MetS is prevalent in 36% NAFLD, 67% obese NAFLD and 88% patients with NASH.^{12,13} It is important to identify the presence of MetS in NAFLD patients as they frequently have advanced histologic injury of the liver and an elevated risk of

mortality from cardiovascular disease (CVD) and liver-related causes.^{13–15} Over the past two decades, high-volume centres have reported a significant decline in operative mortality after hepatic resection; however, the presence of $\geq 30\%$ hepatic steatosis is associated with a three-fold risk of mortality and a two-fold risk of post-operative morbidity.^{16–23}

Optimization of peri-operative outcome in this high-risk subset of patients requires treatment of the individual components of MetS, NAFLD and CVD. Insulin sensitizers including thiazolidinediones (TZD) are beneficial in the treatment of MetS and NASH as insulin resistance is central to their development.^{24,25} Vitamin E has demonstrated therapeutic efficacy in the reduction of the histologic severity of steatosis and NASH.²⁶ A short-term regimen for pre-operative weight loss improves patient and liver-related outcome in patients with $>30\%$ steatosis.²⁷ Patients with multiple metabolic risk factors may harbour unsuspected NASH identifiable by a liver biopsy which will determine the extent of hepatectomy and the use of pre-operative chemotherapy or portal vein embolization (PVE). Peri-operative measures to minimize cardiovascular risk, thrombotic events and acute renal injury associated with MetS may further improve the outcome.^{5–9} The present study is a review of the peri-operative risk associated with hepatic resection in patients with MetS with the objective of identifying measures for the improvement of cardiometabolic risk and liver-related mortality.

Methods

A search of the English literature for articles published between 1980 and 2011 was performed using the MEDLINE database with PubMed and Ovid as search engines. The keywords included metabolic syndrome, liver resection and steatosis. All titles and abstracts of the publications were screened and relevant articles were retrieved excluding case reports. The reference lists of the retrieved articles were reviewed for potentially related studies and relevant articles were selected.

Metabolic syndrome

MetS has existed in various forms and definitions for over eight decades; however, it is only recently that its significance and the need for a unified definition have emerged. The National Cholesterol Education Program's Adult Treatment Panel III report (NCEP-ATP III) identified MetS as a multiplex risk factor which doubles the risk for atherosclerotic CVD.^{15,28} In a meta-analysis of MetS and the risk of CVD, MetS significantly increased all-cause and CVD-related mortality as well as the incidence of CVD and stroke.²⁹ In 1988, Reaven noted that several risk factors cluster together and called it *Syndrome X* or *insulin resistance syndrome* as insulin resistance is a key component conferring increased risk for type 2 diabetes and CVD.³⁰ ATP III prefers the term *metabolic syndrome* and has identified six components: abdominal obesity, atherogenic dyslipidemia, hypertension,

Table 1 Criteria for the clinical diagnosis of metabolic syndrome [Alberti KG *et al.* *Circulation* 2009; 120 (16):1640–1645]³¹

Measure	Categorical Cut Points
Increased waist circumference	Population-specific and country-specific definitions
Increased triglycerides (drug treatment for elevated TG is alternate indicator)	≥ 150 mg/dl
Reduced HDL cholesterol (drug treatment for reduced HDL is alternate indicator)	<40 mg/dl in males <50 mg/dl in females
Increased blood pressure (antihypertensive drug treatment in patient with history of hypertension is alternate indicator)	Systolic ≥ 130 and/or Diastolic ≥ 85 mm Hg
Increased fasting glucose (drug treatment of increased glucose is alternate indicator)	>100 mg/dl

The diagnosis of metabolic syndrome requires three out of five abnormal findings. HDL, high-density lipoprotein; TG, triglycerides.

insulin resistance, pro-inflammatory and prothrombotic state of which the last five components are termed *metabolic risk factors*.¹

Diagnostic criteria for MetS

Several diagnostic criteria have been proposed by different organizations and most recently they have come from the International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI). The main difference concerns waist measurement, the measure for central obesity, which is an obligatory component of the IDF criteria. In a consensus meeting of several major organizations attempting to unify the diagnostic criteria it was agreed upon that there should not be an obligatory component, however, waist measurement would continue to be a useful preliminary screening tool.³¹ Three out of five abnormal findings would qualify a person for the diagnosis of MetS as shown in Table 1. Measurement of waist circumference is ethnic-specific and the use of national or regional cutpoints was recommended. The recommended waist circumference threshold for abdominal obesity in United States is ≥ 102 cm and ≥ 88 cm in men and women, respectively.³²

Pathogenesis of MetS

The AHA/NHLBI identified three potential aetiologic categories: obesity and disorders of adipose tissue, insulin resistance and a constellation of independent factors of hepatic, vascular and immunologic origin.³³

Abdominal obesity

The NCEP-ATP III recommendation to measure waist circumference in the diagnosis of MetS rather than body mass index (BMI)

Figure 1 The channelling of surplus calories from excess dietary consumption and sedentary lifestyle into insulin-sensitive subcutaneous adipose tissue will protect against the development of metabolic syndrome. However, in the presence of dysfunctional adipose tissue, genetic predisposition and a neuroendocrine profile related to a maladaptive response to stress, the triacylglycerol surplus will be deposited at undesirable sites such as the liver, heart, skeletal muscle and visceral adipose tissue – a phenomenon known as ectopic fat deposition. Metabolic consequences of this defect in energy partitioning include visceral obesity, insulin resistance, atherogenic dyslipidemia and a prothrombotic proinflammatory profile the defining features of metabolic syndrome. Reprinted by permission from Macmillan Publishers Ltd: Després & Lemieux³⁴, copyright 2006.

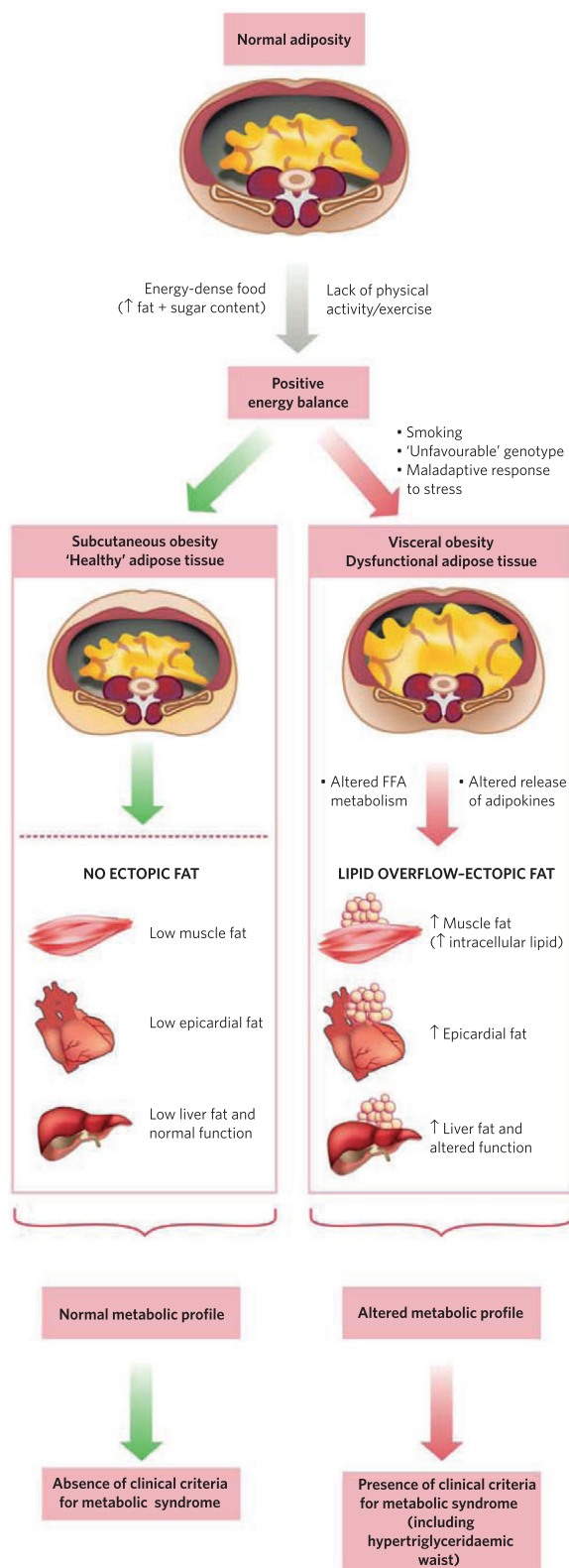
recognizes its greater accuracy in the assessment of cardiometabolic risk and the close correlation with visceral adiposity.³⁴ Impaired metabolism of non-esterified fatty acids (NEFA) contributes to the insulin-resistant state in visceral obesity and the excess energy instead of being channelled into the insulin-sensitive subcutaneous adipose tissue and protecting against the development of MetS is deposited at undesirable sites such as the liver, heart, skeletal muscle and visceral adipose tissue – a phenomenon described as *ectopic fat deposition* as shown in Fig. 1.³⁴ The dysfunctional visceral adipose tissue is characterized by a hyperlipolytic state resistant to the anti-lipolytic effect of insulin leading to NEFA flux to the liver promoting a fatty liver and atherogenic dyslipidemia.

Insulin resistance

Several investigators consider insulin resistance and its accomplice hyperinsulinemia as the key mechanism in the development and manifestations of MetS.³³ Homeostasis Model Assessment (HOMA) is used for the quantitative assessment of insulin resistance and deficient β -cell function utilizing the patient's fasting plasma insulin and glucose concentrations.³⁵ Insulin resistance rises with increasing body fat content and most people with a BMI ≥ 30 kg/m² have postprandial hyperinsulinemia with relatively low insulin sensitivity.³⁶ Insulin resistance in muscle predisposes to glucose intolerance which is worsened by increased hepatic gluconeogenesis in an insulin-resistant liver.¹

Pro-inflammatory state

Adipose tissue specializing in the storage of lipids is also an important endocrine organ releasing numerous hormones, adipocytokines and pro-inflammatory molecules such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) contributing to the inflammatory profile of the abdominally obese patients.^{37,38} A pro-inflammatory state recognized clinically by the elevation of C-reactive protein (CRP) is commonly present in MetS and CRP ≥ 3 mg/l is a risk factor for CVD.^{28,39,40} Low levels of adiponectin in blood is a salient feature of visceral obesity responsible for the



atherogenic, diabetogenic and proinflammatory profile of MetS and is associated with an increased risk of a myocardial infarction.^{41–43}

Prothrombotic state

A prothrombotic state characterized by increased plasma plasminogen activator inhibitor (PAI)-1 and fibrinogen is associated with MetS.^{44,45} Fibrinogen and acute-phase reactants such as CRP rise in response to a high-cytokine state suggesting that the prothrombotic and proinflammatory states may be metabolically interconnected.^{46–48}

Non-alcoholic fatty liver disease

NAFLD is a spectrum of fatty liver infiltration from simple steatosis (NAFL) to necroinflammation and fibrosis (NASH). The prevalence of NAFLD in asymptomatic US adults estimated on the basis of unexplained elevation of aminotransferases on the third National Health and Nutrition Examination Survey (NHANES-III) was 7.9% and strongly correlated with the presence of MetS.^{49,50} Unlike simple steatosis, NASH is a progressive liver disorder and it is estimated that 10–25% of those with NAFLD will develop NASH and 5% will progress to cirrhosis and liver failure.^{51–54} NAFLD is an important cause of liver-related morbidity and mortality and increases CVD-related mortality independent of MetS.^{55–57} Analysis of the NHANES-III participants including 980 with NAFLD and 6594 without NAFLD demonstrated that the former had a significantly higher all-cause [hazard ratio (HR) 4.10, 95% confidence interval (CI) 1.27–13.23] and cardiovascular mortality (HR 8.15, 95% CI 2.00–33.2) in the 45–54 years age group after adjusting for conventional cardiovascular risk factors.⁵⁵ The authors concluded that NAFLD is a strong independent risk factor for cardiovascular death and warrants modification of CVD risk management guidelines.

The precise pathogenesis of NASH is unclear; however, the two 'hit' theory is most widely accepted wherein the first hit is hepatic steatosis secondary to obesity or MetS and the second hit includes insulin resistance, oxidative stress and abnormal cytokine production which plays a key role in hepatocellular injury, inflammation and fibrosis.^{58–60} Insulin resistance is nearly universal in NASH and plays an important role in its pathogenesis by promoting peripheral lipolysis and *de novo* lipogenesis.^{61,62} Circulating levels of IL-6 a proinflammatory cytokine elevated in MetS demonstrated a positive correlation with hepatic IL-6 expression, degree of inflammation, fibrosis and systemic insulin resistance in patients with NASH.⁶³

Radiologic assessment of NAFLD

The adverse impact of steatosis and chemotherapy-associated liver injury on peri-operative outcome after liver resection is well recognized emphasizing the importance of its pre-operative recognition.^{17–23} Liver biopsy the reference for diagnosis and

quantification of steatosis provides an accurate diagnosis in 90% patients; however, it is limited by its invasive nature, mortality rate of 1 in 10 000 and sampling variability.^{64–70} Radiologic investigations, the non-invasive alternative to liver biopsy, have demonstrated wide variability in their sensitivity and specificity for the detection and quantification of steatosis.⁷¹

More recently, *in vivo* proton magnetic resonance spectroscopy (MRS) [hydrogen 1 (¹H) MR spectroscopy] has emerged as the reference standard in several clinical studies.^{72–74} However, ¹H MR spectroscopy is time-consuming and has limited availability. Several modifications of the MR technique have been used with results similar to MRS.^{75–80} In a comparative study of the diagnostic performance of ultrasonography (US), computed tomography (CT), T1-weighted MR imaging and ¹H MR spectroscopy in the preoperative assessment of steatosis in patients undergoing liver resection, MR imaging and MR spectroscopic measurements of hepatic fat had a significantly stronger correlation with histologic assessment and were able to differentiate between the 3 grades of steatosis: none, mild, moderate and severe unlike US and CT.⁸¹ The sensitivities of US, CT, T1-weighted MR imaging and MR spectroscopy were 65%, 74%, 90% and 91% and specificities were 77%, 70%, 91% and 87%, respectively. This led the authors to conclude that T1-weighted MR imaging and ¹H MR spectroscopy had the best diagnostic accuracy and strongly correlate with the histologic assessment and grade of steatosis. MR elastography measuring liver stiffness demonstrated high accuracy in distinguishing simple steatosis from NASH even before the onset of fibrosis with a sensitivity of 94% and specificity of 73% using a threshold of 2.74 kPa.⁸² NAFLD patients with inflammation and no fibrosis had greater liver stiffness than those with simple steatosis and lower mean stiffness than those with fibrosis.

Pre-operative planning for a hepatectomy is usually based on CT findings and MR imaging is not performed routinely. In a prospective determination of the diagnostic performance of unenhanced CT in the assessment of $\geq 30\%$ macrovesicular steatosis in potential donors for living donor liver transplantation using same-day biopsy as a reference standard, Park *et al.* reported that a liver-to-spleen (L/S ratio) attenuation ratio of 0.8 and a difference between liver and splenic attenuation of -9 yielded a 100% specificity and 82% sensitivity for both indices.^{83–85} The authors concluded that unenhanced CT is not clinically acceptable for quantitative assessment, however, provides high performance in the qualitative diagnosis of macrovesicular steatosis $\geq 30\%$. In a randomized placebo-controlled study of healthy individuals diagnosed with radiographically defined NAFLD based on a L/S ratio < 1 on CT scan indicative of $> 30\%$ hepatic steatosis, antioxidant and statin therapy significantly reduced the odds of having NAFLD at the end of follow-up.⁵⁴ While these results will require validation in a trial with a liver biopsy as an end point, they demonstrate the utility of a CT scan in the radiographic diagnosis of NAFLD.

Table 2 NAFLD activity score (NAS) [Kleiner DE *et al. Hepatology* 2005; 41 (6): 1313–1321]⁸⁶

Pathologic feature	Definition	Score (0–8)
Steatosis	Extent of parenchymal involvement	
	<5%	0
	5–33%	1
	>33%–66%	2
	>66%	3
Lobular inflammation	Assessment of inflammatory foci	
	No foci	0
	<2 foci per 200× field	1
	2–4 foci per 200× field	2
	>4 foci per 200× field	3
Ballooning	Liver cell injury	
	None	0
	Few balloon cells	1
	Many cells/ prominent ballooning	2

NAS ≥ 5 , definite NASH; NAS 3–4, borderline NASH; NAS < 3 , not NASH; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

Pathologic assessment of NAFLD

The Pathology Committee of the NASH Clinical Research Network designed and validated a histologic scoring system based on the grading proposal of Brunt *et al.* that addresses the full spectrum of lesions of NAFLD and proposed a NAFLD activity score (NAS) for use in clinical trials.^{86,87} NAS specifically includes only features of active injury that are potentially reversible in the short term. The score is defined as the unweighted sum of the scores for steatosis (0–3), lobular inflammation (0–3) and ballooning (0–2) thus ranging from 0–8 as shown in Table 2. Fibrosis is not included in the scoring system as it is less reversible and considered a consequence of disease activity which is an accepted paradigm for staging and grading of NASH.⁸⁷ NAS ≥ 5 correlated with a diagnosis of NASH and biopsies with scores < 3 were diagnosed as ‘not NASH.’ The inter-observer agreement was 0.84 for fibrosis, 0.79 for steatosis, 0.56 for injury and 0.45 for lobular inflammation. The authors concluded that NAS was a strong scoring system with reasonable inter-observer variability that should be useful for clinical studies in both adults and children with any degree of NAFLD.

Impact of MetS on surgical outcome

MetS adversely impacts peri-operative outcome in patients undergoing cardiac and non-cardiac operations.^{2–7} In a retrospective review of 5304 consecutive patients who underwent coronary artery bypass graft (CABG) surgery, 46% patients met the diagnostic criteria for MetS and it was a strong independent predictor of operative mortality (2.4% vs. 0.9%).⁴ Patients with MetS had a significantly higher incidence of post-operative stroke, renal

failure and infectious complications attributable to an exacerbation of the low-grade inflammatory and prothrombotic state of MetS by the systemic inflammatory response to cardiopulmonary bypass and operative stress.⁸⁸ Moreover, patients with MetS have systemic oxidative stress secondary to the increased oxidative transformation of low-density lipoprotein.⁸⁹ The authors recommend modification of the components of MetS with pre-operative dietary changes, an increase in physical activity and peri-operative glucose homeostasis for an improvement in outcome. CRP and albumin levels are considered as parameters of systemic inflammation and a combination of CRP ≥ 10 mg/l and albumin level ≤ 35 g/l in the Glasgow Prognostic Score for cancer is an independent predictor of peri-operative morbidity and mortality in patients with oesophageal and colorectal cancer.^{90,91} Other authors have identified MetS as a risk factor for post-operative atrial fibrillation, acute kidney injury, myocardial infarction and stroke.^{5–7}

In a review of 310 208 patients with modified MetS based on obesity as the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database does not include information on abdominal circumference, presence of MetS was associated with a two-fold risk of death, 2.5-fold risk of cardiac adverse events and a three- to seven-fold higher risk of acute kidney injury leading the authors to conclude that ‘metabolically obese’ patients have a dramatically higher risk of complications after non-cardiac surgery.² Other authors have also reported a higher rate of complications and longer hospital stay in patients with MetS undergoing elective surgery for colorectal cancer.³

Several authors have reported a significantly higher prevalence of MetS in patients with idiopathic venous thromboembolism (VTE).^{92–94} In a case-control study to investigate the presence of MetS in patients with confirmed VTE, 116 patients were compared with 129 healthy controls and the prevalence of MetS was significantly higher in patients with VTE, 35% vs. 20%.⁹² Individuals with MetS had significantly higher levels of high-sensitivity CRP, fibrinogen and factor VIII activity compared with those without MetS. The authors concluded that MetS is associated with a two-fold increased risk of VTE and may contribute to its development.

Impact of MetS on outcome after hepatic resection

There are several studies which evaluate the impact of steatosis on peri-operative outcome after hepatic resection, however, none specifically evaluate the outcome in patients with MetS.^{17–22} Furthermore, most of these studies have classified the degree of steatosis into mild, moderate and severe based on the presence of fat vacuoles in the cytoplasm of $< 30\%$, 30–60% and $> 60\%$ hepatocytes without application of the NAS system for distinguishing the presence of steatohepatitis associated with a higher risk of liver failure and death after a major hepatectomy.^{23,86,95} An important element of the NAS system is that NAFLD can manifest with steatohepatitis in the presence of minimal steatosis.⁹⁶

Table 3 Impact of hepatic steatosis on peri-operative outcome after hepatic resection

Author	Year	N	Steatosis	N	Mortality (%)	Morbidity (%)
Behrns ²²	1998	135	None	72	3	4
			Mild	56	7	9
			Moderate-severe	7	14	14
Belghiti ¹⁷	2000	478	Absent	441	1	8
			Present	37	0	22
Little ¹⁰¹	2002	727	Absent	505	2.0	37
			Present	222	4.9	45
Kooby ²¹	2003	485	None	160	5	35
			Mild	223	5	48
			Moderate-severe	102	9.4	62
Gomez ²⁰	2007	386	None	192	1	22
			Mild	122	2.5	43
			Moderate	60	3	62
			Severe	12	0	58
McCormack ¹⁹	2007	116	Absent	58	1.7	25
			Present	58	8.6	50

Mild steatosis, <30% hepatocytes involved; moderate steatosis, 30–60% hepatocytes involved; severe steatosis, >60% hepatocytes involved.

Transplantation of liver with severe steatosis is associated with a high risk of primary non-function in contrast to mildly steatotic grafts which yield results similar to non-steatotic livers.^{97,98} Fatty hepatocytes have a reduced tolerance to ischemia/reperfusion injury demonstrating a predominantly necrotic form of cell death owing to microcirculatory failure as opposed to apoptosis a key feature of ischaemic injury in the normal liver.⁹⁹ Hepatocellular necrosis leads to the release of cytoplasmic contents which further increase the inflammatory response and liver injury. In addition, the ability of hepatocytes to regenerate after major tissue loss is impaired in the steatotic liver further contributing to the morbidity and mortality of hepatic resection.¹⁰⁰

A meta-analysis of 1000 patients demonstrated a significantly increased risk of post-operative morbidity and mortality with moderate or greater steatosis after major hepatic resection.¹⁸ Several authors have confirmed steatosis as an independent predictor of complications after hepatic resection with a positive correlation between the degree of steatosis and post-operative hepatic insufficiency and an insignificant trend towards increased mortality with lobe or greater resections as shown in Table 3. Data on the influence of alcohol-related liver injury on peri-operative outcome after hepatic resection are limited with Kooby *et al.* reporting a similar incidence of heavy alcohol use in the steatotic and control groups.²¹ Little *et al.* reported a significantly greater operative mortality in diabetic patients undergoing hepatic resection compared with non-diabetic patients (8% vs. 2%) and the long-term survival was identical highlighting the increased peri-operative risk in these patients.¹⁰¹ Four of the five deaths were as a result of liver failure of which three patients had steatosis. McCormack *et al.* in a matched case-control study reported a mortality

of 8.5% with steatotic livers compared with 1.7% in patients with lean livers [$P =$ non-significant (NS)]. Mortality was not liver related and attributed to mesenteric infarction ($n = 1$), sepsis and multi-organ failure ($n = 3$) and cardiac failure ($n = 1$).¹⁹ They also reported a significantly higher incidence of major complications in the steatotic group (27% vs. 5%) and all four patients with renal failure and VTE were in the steatotic group. These data suggest that patients undergoing liver resection in the presence of steatosis are at an increased peri-operative risk not only from liver-related causes but also the systemic manifestations of MetS.

Impact of pre-operative chemotherapy on NAFLD

Chemotherapy-associated steatohepatitis (CASH) based on NAS ≥ 4 criteria is associated with a significant increase in 90-day mortality after hepatic resection (14.7% vs. 1.6%).²³ Use of irinotecan was associated with an increased risk of steatohepatitis and the effect was more pronounced in patients with a higher BMI (12.1% in BMI <25 kg/m² and 24.6% in BMI ≥ 25 kg/m²) suggesting that obesity and pre-existing steatosis are risk factors for the development of CASH.^{23,102,103} The authors also reported a direct correlation between increasing BMI and the severity of chemotherapy-associated liver injury.¹⁰² In contrast, the use of 5-fluorouracil (5-FU) was associated with the development of steatosis without steatohepatitis in 47% of patients.¹⁰⁴

The key molecular event underlying the development of CASH is the production of reactive oxygen species (ROS) resulting in oxidative stress in the hepatocytes.^{105,106} A two-hit theory for the development of CASH proposes that obesity rendering the liver susceptible to oxidative stress is the first hit and chemotherapy results in the second toxic hit.¹⁰⁷ The generally higher BMI in the

Table 4 Prospective studies on the effects of diet and exercise in NAFLD

Author	Year	N	Indication	Additional therapy	Duration (months)	Histologic Improvement		
						NAS	Steatosis	Fibrosis
Promrat ¹¹⁷ RCT	2010	31	NASH		12	+	+	-
Hickman ¹¹⁸	2004	14	NAFLD		6		+	+
Nakamuta ²⁷	2005	11	Pre-transplant	Bezafibrate	½-2		+	
Chen ¹²²	2008	23	Pre-transplant		1-3		+	

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NAS, NAFLD activity score; RCT, randomized controlled trial.

North American population compared with the European population may explain why the US study reported steatohepatitis and European studies reported vascular changes as the dominant pattern of chemotherapy-associated liver injury.^{102,103,108-110} These data suggest that irinotecan and oxaliplatin probably affect progression but not the development of steatosis.

Therapeutic strategies to improve outcome after hepatic resection in MetS

MetS increases the risk for advanced NAFLD and CVD suggesting that potential candidates for hepatic resection should be screened for the presence of MetS and the optimization of surgical outcome in this particularly high-risk subset of patients will require a multidisciplinary effort to treat individual components of MetS and NAFLD in consultation with a cardiologist and hepatologist.¹¹¹⁻¹¹³

Management of MetS

The primary goal in the management of MetS is the reduction in the risk of clinical atherosclerotic disease.¹¹⁴ First line therapy is directed towards the major risk factors of elevated LDL cholesterol, hypertension and diabetes with the emphasis on lifestyle interventions including weight reduction, dietary modification, increased physical activity and drug therapy should be considered based on the individual cardiovascular risk.¹¹⁵ TZDs a peroxisome proliferator-activated receptor- γ (PPAR γ) agonist class of drugs ameliorate insulin resistance and the pro-inflammatory state of MetS by modifying the secretion of free fatty acids and adipocytokines.²⁴ Weight reduction and drug treatment of the metabolic risk factors will reduce CRP levels and the underlying inflammatory stimulus in MetS.^{40,115} Aspirin prophylaxis maybe considered to counter the prothrombotic state of MetS predisposing to vascular events.¹¹⁴

Treatment of NAFLD

NAFLD is the most common cause of chronic liver disease in the Western world and the primary goal of treatment is to prevent associated cardiac and liver-related morbidity and mortality.¹¹⁶

Weight loss

The current standard of care for NAFLD is weight loss which improves liver histology, inflammatory markers and insulin resistance a key aetiologic factor in NASH.^{115,117-122} A randomized con-

trolled trial to examine the effects of diet and exercise with a goal of 7-10% weight reduction demonstrated a significant improvement in serum aminotransferases and a reduction in NAS ≥ 3 points compared with the control group (72% vs. 30%).¹¹⁷ Long-term efficacy of lifestyle interventions is generally disappointing because of poor compliance; however, biochemical and histologic improvements have been reported with short-term interventions of 2-4 weeks.¹²⁰⁻¹²² Significant histologic improvements reported in prospective studies evaluating the effects of lifestyle intervention in patients with NAFLD are shown in Table 4. In an effort to improve utilization of steatotic livers in living-donor liver transplantation, Nakamuta *et al.* treated 11 moderately steatotic donors with a short intensive treatment of a protein-rich diet (1000 kcal/day), exercise (600 kcal/day) and bezafibrate (400 mg/day) for 2-8 weeks.²⁷ There was a significant reduction in body weight, BMI, normalization of liver function tests, lipid profile, biopsy-proven macrovesicular steatosis ($30 \pm 4\%$ vs. $12 \pm 2\%$) in the donors and the post-operative graft function was similar to donor livers without steatosis. The treated donors showed good liver function post-operatively and there was no difference in functional parameters between the treated and control groups. The best responders in the study in terms of improvement of steatosis were patients with a higher BMI. The authors concluded that the short-term intensive treatment effectively reduced steatosis and contributed to safer living-donor liver transplantation suggesting that even severely steatotic livers can be used after their intensive regimen. In a similar study of 23 potential living donors with fatty livers using a diet and exercise regimen for weight loss over 1-3 months, the authors reported a reduction in the hepatic fat content of 16.9% to 6.6% on biopsy.¹²² These data suggest that a pre-operative weight reduction before hepatic resection in the presence of clinically significant steatosis is feasible and useful in optimizing the peri-operative outcome.

Pharmacological treatment

A liver biopsy is required for histologic confirmation of NASH before pharmacologic therapy. As the entire histological spectrum of NAFLD including NASH and bridging fibrosis can be seen in individuals with normal alanine aminotransferase (ALT) levels and low normal ALT does not guarantee freedom from underlying steatohepatitis, serum transaminase levels cannot be used for screening patients for NASH to enhance the yield of a

Table 5 Randomized controlled trials evaluating the therapeutic efficacy of thiazolidinediones (insulin sensitizers) in NASH

Author	Year	N	Intervention	Comparator	Duration (months)	Histologic improvement			
						Steatosis	Inflammation	Fibrosis	Hepatocyte injury
Sanyal ²⁶	2010	247	Pioglitazone or Vitamin E	Placebo	24	+	+	-	
						+	+	-	
Aithal ¹²⁷	2008	74	Pioglitazone	Placebo	12	-	-	+	+
Ratziu ¹²⁸	2008	63	Rosiglitazone	Placebo	12	+	-	-	
Belfort ²⁵	2006	55	Pioglitazone	Placebo	6	+	+	-	+
Sanyal ¹²⁹	2004	20	Pioglitazone + Vitamin E	Vitamin E	6	+		+	+

NASH, non-alcoholic steatohepatitis.

Table 6 Randomized controlled trials evaluating the therapeutic efficacy of Vitamin E in NASH

Author	Year	N	Intervention	Comparator	Duration (months)	Histologic improvement		
						Steatosis	Inflammation	Fibrosis
Sanyal ²⁶	2010	247	Vitamin E or Pioglitazone	Placebo	24	+	+	-
						+	+	-
Dufour ¹³⁶	2006	48	Vitamin E + UDCA	UDCA + Placebo or Placebo only	24	+	-	-
Sanyal ¹²⁹	2004	20	Vitamin E + Pioglitazone	Vitamin E	6	+		+
Harrison ¹³⁴	2003	49	Vitamin E + Vitamin C	Placebo	6		-	+

UDCA, ursodeoxycholic acid; NASH, non-alcoholic steatohepatitis.

liver biopsy.¹²³ In contrast, the risk of developing NASH and advanced fibrosis is related to increasing age, obesity and type 2 diabetes mellitus and the yield of a liver biopsy can be increased by targeting patients with these risk factors.¹²⁴ Pharmacologic therapy should be considered in patients with active NASH to reverse fibrosis and prevent cirrhosis; however, its role in improving surgical outcome after hepatic resection is unknown.¹²⁵

Insulin sensitizers Insulin sensitizers improve insulin resistance and promote fat redistribution from ectopic tissues, liver and muscle to adipose tissue.¹²⁶ Of the five randomized clinical trials evaluating the efficacy of TZDs in NASH other than PIVENS (Pioglitazone or Vitamin E for NASH Study) none were adequately powered; however, they demonstrated some consistent findings including an improvement in steatosis and liver enzymes as shown in Table 5.¹²⁵ Pioglitazone is preferred because of the increased cardiovascular risk with rosiglitazone and it is reserved for the second line treatment of NASH except in select patients with diabetes and NASH where it is therapeutic for both conditions.^{125,128,130}

Antioxidants Oxidative stress and abnormal cytokine production are 'second hits' in the development of NASH providing the basis for antioxidant therapy with Vitamin E.¹³¹⁻¹³⁶ Several randomized controlled trials including PIVENS have demonstrated the therapeutic efficacy of vitamin E in NASH as shown in Table 6. Vitamin E therapy should not be considered without pathologic

confirmation of the nature of the liver disease and α -tocopherol (800 IU/day) is recommended in patients with active NASH (NAS ≥ 4) without diabetes.¹²⁵ Weight loss, TZDs and antioxidants are the most extensively evaluated therapeutic strategies in the treatment of NAFL; however, the clinical utility of these drugs in the treatment of chemotherapy-associated steatohepatitis (CASH) is unknown.¹³⁷

Peri-operative strategies

MetS is a predictor of underlying steatosis or steatohepatitis suggesting that patients who are potential candidates for a hepatic resection should be screened for MetS. The selective use of a liver biopsy in patients with multiple metabolic risk factors can identify unsuspected NASH, a predictor of post-operative mortality.¹²⁴ This will permit modification of the operative strategy by limiting the extent of hepatic resection, avoiding or altering pre-operative chemotherapy regimens and the use of PVE to optimize the post-operative outcome. A standardized future liver remnant (sFLR) > 20% is adequate for the safe resection of a normal liver; however, PVE should be considered in patients with sFLR $\leq 30\%$ in the presence of liver injury identified on the basis of clinical, laboratory, imaging or histologic data ($\geq 30\%$ steatosis or severe fibrosis).¹³⁸⁻¹⁴⁰ PVE is also recommended in patients who have received ≥ 6 cycles of chemotherapy as they are at an increased risk for post-operative complications.¹⁴¹ Further clarification is required on the issues of routine versus selective PVE in the presence of significant steatosis and the optimal sFLR based on the severity of steatosis.¹⁴²

Irinotecan should be used with caution in patients with a BMI ≥ 25 kg/m² and in patients with multiple metabolic risk factors. As a result of the risk of pre-existing steatosis or steatohepatitis, consideration should be given to the avoidance of pre-operative chemotherapy in favour of initial surgery for resectable colorectal liver metastases and chemotherapy should be limited with short-interval evaluations to proceed with surgery when resectability is confirmed in borderline or unresectable tumours.¹¹⁰ A pre-operative liver biopsy should be considered in patients at risk for CASH and major hepatic resection should be avoided in those with confirmed CASH. As imaging cannot accurately identify steatohepatitis or sinusoidal injury and liver injury is not uniform, laparoscopy with direct inspection and core biopsy before a laparotomy is preferred over image-guided percutaneous biopsy.¹⁰⁶ Sinusoidal injury results in blue liver syndrome, steatosis in a yellow liver and non-specific findings of steatohepatitis include hepatomegaly, fatty accumulation in the round ligament and white or yellow markings or depressions on the surface of the liver.

Earlier studies have demonstrated that ischaemic preconditioning before continuous hepatic pedicle clamping reduces reperfusion injury particularly in steatotic livers.^{143,144} Subsequent randomized clinical trials have not confirmed a protective effect of ischaemic preconditioning with no significant difference in the mortality, liver failure, morbidity, blood loss, haemodynamic stability or hospital stay.^{145–147} Patients with MetS are at an increased peri-operative risk of acute kidney injury which may be aggravated by the low central venous pressure used for hepatic resection to minimize blood loss. Higher peri-operative glucose levels and glucose variability have been shown to be associated with increased complications after various types of surgical procedures including general, vascular, hepatobiliary and pancreatic surgery.^{148–150} These patients may benefit from a tight glucose control; however, MetS is characterized by insulin resistance and glucose homeostasis will have to be balanced against the risk of hypoglycaemia.^{151–153} MetS is associated with a prothrombotic state and an increased risk for VTE; however, currently there are no recommendations to modify standard prophylaxis for deep vein thrombosis.¹⁵⁴

In conclusion, patients who are potential candidates for liver resection should be screened for the presence of MetS as they are at a high risk for an adverse peri-operative outcome. CVD should be managed aggressively in patients with MetS and NAFLD. Pre-operative identification of NASH with the selective use of a liver biopsy should prompt consideration of pharmacological therapy. The extent of the hepatic resection, the use of chemotherapy and PVE are influenced by the extent of parenchymal injury. Short-term regimens for pre-operative weight loss may be considered in patients with significant steatosis. Peri-operative measures to minimize acute renal injury, thrombotic events and glucose homeostasis may further improve the outcome. Prospective data evaluating the peri-operative outcome after hepatic resection in patients systematically screened for MetS will provide further insight into the peri-operative management of these patients.

Additional research is required to identify the mechanisms responsible for the increased operative mortality associated with MetS and establish strategies to acutely modify the operative risk.

Conflicts of interest

None declared.

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