Prevalence, patterns and predictive factors of non-alcoholic fatty liver disease among morbidly obese patients undergoing sleeve gastrectomy

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RESEARCH

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ABSTRACT

Background
Obesity related non-alcoholic fatty liver disease (NAFLD) is increasingly recognized worldwide.

Aims
We aim to describe prevalence, histologic patterns, and risk factors of NAFLD in morbidly obese patients undergoing sleeve gastrectomy.

Methods
A prospective study included 49 obese patients undergoing sleeve gastrectomy, with concomitant true cut liver biopsy. Exclusion criteria included history of alcohol intake, liver disease, or hepatotoxic agents' intake. Clinical, biochemical, and histological features were evaluated. Histological patterns were classified based on the NIH-sponsored NASH Clinical Research Network NAFLD Activity Score (NAS).

Results
Seventy-three per cent were females, mean age 34 (range 17–58). Mean BMI was 43 (35–52). 45 patients (91.8 per cent) showed NAFLD. Nineteen (39 per cent) showed non-alcoholic steatohepatitis (NASH) and 5 (10 per cent) showed fibrosis. 4 biopsies (8 per cent) were normal. About 31 per cent of NAFLD patients had metabolic syndrome as defined by the international diabetes federation consensus. While nineteen patients (38.5 per cent) had abnormality in one or both transaminase levels, 71 per cent of patients with elevated AST had NASH. The prevalence of dyslipidaemia (abnormal lipid profile) in all study patients was found to be 47 per cent. 24 per cent of NAFLD patients and 16 per cent of NASH patients had DM.

Conclusion
NAFLD has a very high prevalence among our morbidly obese patients. Multiple biochemical abnormalities were evident in association with the histological changes detected in NAFLD categories. Intraoperative liver biopsy is safe during sleeve gastrectomy for the diagnosis of NAFLD.

Key Words
NASH, NAFLD, steatosis, sleeve, fatty liver, bariatric

What this study adds:

1. What is known about this subject?
NAFLD, especially non-alcoholic steatohepatitis (NASH), is increasingly recognized as the predominant cause of liver disease affecting all age groups in many parts of the world.

2. What new information is offered in this study?
NAFLD has a very high prevalence among our morbidly obese patients. A significant correlation is evident between

multiple biochemical markers and histological components of liver assessment. Intraoperative liver biopsy is safe during sleeve gastrectomy for the diagnosis of NAFLD.

3. What are the implications for research, policy, or practice?

This research should contribute to the increasing awareness toward obesity in Jordan and the possible catastrophic consequences of untreated obesity on the liver.

Background

It is essential for the diagnosis of non-alcoholic fatty liver disease (NAFLD) to obtain evidence of hepatic steatosis utilizing either radiologic or histopathologic tests. This category of disorders requires also exclusion of secondary causes of fat accumulation in the liver parenchyma, such as: excessive alcohol consumption, hepatotoxic medications, viral hepatitis or hereditary liver diseases.[1]

According to the National Health and Nutrition Survey from 1988–2008, the number of patients diagnosed with NAFLD has increased markedly over the last two decades, while reported cases of other chronic liver diseases has remained stable or even decreased.[2] The prevalence of NAFLD varies widely depending on the population studied and the screening method used,[1] with a reported prevalence of 9.6 per cent among adolescents and preadolescents,[3] and 34 per cent among patients aged 30 to 65 years.[4]

NAFLD, especially nonalcoholic steatohepatitis (NASH), is increasingly recognized as the predominant cause of liver disease affecting all age groups in many parts of the world. NAFLD is a multi-factorial disease resulting from a complex interaction of environmental "hits" and a genetic background. This "multi-hit theory", described progression into NASH as a consequence of events originating within liver and distal organs, with metabolic syndrome playing a major role, due to insulin resistance and pro-inflammatory mediators.[5]

The importance of investigating NAFLD arises from the fact that patients with NAFLD have increased overall mortality compared to match control populations.[6] Although the most common cause of death in patients with NAFLD, nonalcoholic fatty liver (NAFL) and NASH is still cardiovascular disease, patients with NASH (but not NAFL) have an increased liver-related mortality rate[1]. In addition, bridging fibrosis is seen in 25–33 per cent of NASH patients at diagnosis, including cirrhosis in 10–15 per cent.[7]

This is the first study of NAFLD from Jordan; we aimed to determine the prevalence, patterns and predictors of NAFLD in a cohort of morbidly obese Jordanian patients undergoing sleeve gastrectomy.

Method

This is a prospective study included obese patients undergoing sleeve gastrectomy with concomitant true cut liver biopsy, at King Abdullah university hospital (KAUH), Jordan, between July 2016 and January 2017. Patients' confidentiality was protected in accordance with declaration of Helsinki provisions. The study was approved by KAUH Ethics Committee and registered with a research grant number of (20160209). A study-specific informed consent forms were obtained from the patients.

Patients' demographics (age, sex) and anthropometric measurements (height, weight, body mass index (BMI)) were reported. Data regarding comorbidities (diabetes, hypertension, hyperlipidaemia, or obesity related illnesses), alcohol intake and hepatotoxic drugs were collected. All patients underwent laboratory testing for total bilirubin (TB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), hepatitis C antibodies (anti-HCV) and hepatitis B surface antigen (HBsAg) and lipid profile including total cholesterol, high density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TGs).

Sleeve gastrectomy was performed for a body mass index (BMI) greater than 40 or a BMI of 35–40 with presence of one or more significant comorbidities attributable to obesity.[8] Patients were excluded if they have history of alcohol intake, hepatotoxic drugs intake (i.e., corticosteroids, diltiazem, nifedipine, amiodarone, high dose estrogen, or any other hepatotoxic medicine), tested seropositive for viral hepatitis or with history of chronic liver disease. Sleeve gastrectomy operations were carried out by the laparoscopic approach in all patients by one surgeon. All subjects provided specific written informed consent to undergo a liver biopsy as part of their bariatric operation.

Using an 18-gauge Tru-Core™ II biopsy Instrument (Argon medical devices, TX, USA), liver biopsy of the left hepatic lobe was performed under laparoscopic guidance. Area of biopsy was cauterized and haemostasis was confirmed. Wedge biopsies were not used for procurement of the liver biopsies.

Two experienced pathologists studied all biopsies. Each case had haematoxylin and eosin (H&E) and Masson trichrome stains submitted. A sample of 1.5cm in length that is 1–2

mm in diameter and contains at least ten portal triads was considered adequate. Along with histologic assessment for fatty liver disease, other liver disorders, similar to primary biliary cirrhosis, autoimmune hepatitis, hepatitis C, hepatitis B, and iron overload, were excluded.

Three main histological features of NAFLD (steatosis, lobular inflammation, and ballooning) in each biopsy were grouped and scored using the NIH-sponsored NASH Clinical Research Network NAFLD Activity Score (NAS).[9] 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 to 8. Fibrosis is not included as a component of the activity score. Fibrosis was staged as 0 (no fibrosis), 1 (perisinusoidal or periportal fibrosis), 2 (perisinusoidal and portal/periportal fibrosis), 3 (bridging fibrosis), and 4 (cirrhosis). The term NAFLD Encompasses the entire spectrum of fatty liver disease in individuals without significant alcohol consumption, ranging from simple steatosis (≥5 per cent) to steatohepatitis (NASH) and cirrhosis. NAFL is defined as the presence of hepatic steatosis (NAS score≥1) with no evidence of hepatocellular injury in the form of ballooning. NAS of ≥5 correlated with a diagnosis of NASH, in which the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) (with or without fibrosis) is essential. Cases with activity scores of 3 and 4 with steatosis grade 1 and ballooning were included in the NASH category. A biopsy was reported as normal if steatosis was <5 per cent with no inflammation, ballooning, or fibrosis, corresponding to a NAS of 0.

The International Diabetes Federation consensus worldwide definition[10] of the metabolic syndrome (2006) requires the presence of central obesity (increased ethnicity specific waist circumferences or if BMI was >30kg/m^2, central obesity can be assumed without measuring waist circumference) and at least two of the following: Raised TGs (≥1.7mmol/L). Reduced HDL cholesterol (<1.03mmol/L in males or <1.29mmol/L in females), or specific treatment for lipid abnormality, raised blood pressure (BP) (≥130/85mm Hg or treatment for previously diagnosed hypertension), elevated fasting plasma glucose (≥100mg/dl (5.6mmol/l)), or previously diagnosed type 2 diabetes. In all our patients, BMI was >30kg/m^2, so, central obesity was assumed and waist circumference was not measured.

Clinical factors (age, gender, BMI, diabetes mellitus, hypertension) and biochemical factors (ALT, AST, glucose, TGs, LDL, HDL and cholesterol levels) were analysed for association with NAS, NAFLD and its histological categories

NAFL, NASH and fibrosis. Data was expressed as mean and range for continuous data. Analysis was performed with the IBM SPSS v.20.0 (Chicago, IL, USA) software. A *p* value <0.05 was considered as statistically significant.

Results

In a high volume bariatric surgery centre, consecutive 50 morbidly obese patients were enrolled in this study. One patient was excluded from the study due to missing data. Table 1 demonstrates demographic and clinical characteristics of study participants. No morbidity or mortality was reported with liver biopsy in this study. All biopsies were deemed adequate for scoring.

The prevalence of NAFLD among our patients was 91.8 per cent. Only four biopsies (8 per cent) were reported as normal. Nineteen patients (39 per cent) had NASH and 26 (53 per cent) had NAFL. Fibrosis was present in 5 biopsies (10 per cent).

Obesity related comorbidities encountered in study patients are illustrated in Table 1. Interestingly, 31 per cent of NAFLD patients had metabolic syndrome as defined by the International Diabetes Federation criteria.

There was no significant difference in age and BMI between those with and without NAFLD. However, the incidence of NAFLD was higher among female patients. Normal histopathology was more probable in male subjects.

Nineteen patients (38.5 per cent) had abnormality in one or both transaminase levels. A total of 7 (14.0 per cent) patients exhibited high serum AST levels (AST >34IU/L), and 12 (24.5 per cent) showed high serum ALT levels (ALT>31IU/L). About 71 per cent of patients with elevated AST had NASH.

The prevalence of dyslipidaemia (abnormal lipid profile) in all study patients was found to be 47 per cent. About one third of patients (30.6 per cent) had elevated TGs, 10 (20.4 per cent) had low HDL, 7 (14.3 per cent) had elevated LDL (>4.4mmol/l), and 13(26.5 per cent) had elevated cholesterol (≥6.2mmol/l). Table 2 summarizes biochemical abnormalities in patients with NAFL, NAFLD and NASH diagnoses.

While 22 per cent of study patients were diabetic, 24 per cent (11/45) of NAFLD patients and 16 per cent (3/19) of NASH patients had DM.

Discussion

Over the last two decades, the increased awareness of obesity and its' related morbidities contributed to the perception of NAFLD in bariatric patients as well as in general population. Since obese patients are more likely to experience fat deposition in their livers,[11] they have been investigated by multiple studies screening for NAFLD. Liver biopsy, the gold standard diagnostic test, is best attempted during bariatric surgery.

The NAFLD-Obesity association has been elucidated in multiple studies. Morita and colleagues[12] study involved 184 morbidly obese adults who underwent Roux-en-Y gastric bypass surgery. The prevalence of NAFLD was 84 per cent (steatosis 22.0 per cent; mild steatohepatitis 30.8 per cent; moderate-severe steatohepatitis 32.0 per cent). In another prospective trial that included 134 bariatric surgery patients, 65.7 per cent showed NAFLD, 33.6 per cent showed NASH and 31.3 per cent showed fibrosis.[13] Similarly, a study of 60 obese patients from Brazil detected NAFLD in 95 per cent and NASH in 66.7 per cent of the patients.[14] The prevalence rates of NAFLD and NASH among our obese patients are as high as reported in the literature.

In general population, a recent global meta-analysis assessed NAFLD prevalence worldwide.[15] The pooled overall prevalence of NAFLD, diagnosed by imaging, was estimated to be 25 per cent. The highest prevalence rate was reported from South America (30.5 per cent) and the Middle East (31.8 per cent), while the lowest rate was from Africa (13. 5 per cent). In this meta-analysis, NASH prevalence estimate among biopsied NAFLD patients was 59 per cent. The worldwide prevalence of obesity has nearly doubled between 1980 and 2008,[16] In 2008, 35 per cent of adults aged 20+ were overweight (body mass index (BMI) ≥25kg/m²). According to the Jordan demographic health survey (2009),[17] the overall prevalence of overweight was 30 per cent. As the incidence rate of NAFLD is expected to increase with the increasing obesity rates,[18] more attention should be paid to control the predisposing factors.

It is well established that NAFLD and NASH carry systemic risks beyond liver damage. Glycaemic control is worsened secondary to increased insulin resistance and reduction of insulin clearance in patients with type 2 diabetes. Cardiovascular risk is increased independently of the classic cardiovascular risk factors and, in some cases, of the metabolic syndrome.[19] Significant atherosclerosis is proved to take place many years earlier in subjects with NAFLD than normal individuals.[20] Moreover, NAFLD patients are at an increased cancer risk, especially liver cancer.[21,22] Only 14.3

per cent of our patients had hypertension, 22 per cent had DM, none of them complained of other cardiovascular events or malignancy. The incidence maybe low because young adults constituted most of our study subjects. For research and patient follow up purposes, we suggest using a new term; the Obesity-age, which can be defined as: the estimated period between reaching BMI of 30 and undergoing bariatric surgery. This concept, once registered, and tracked by investigators, may help to explain the variation in occurrence/absence of many obesity-related morbidities, including fatty liver changes. In a single large, multivariable analysis of two cohorts of patients, the association between duration of adiposity and risk of type 2 DM in US women was assessed; Both overweight and obesity duration carried a significantly higher risk of Type 2 DM.[23]

NASH is recognized as one of the leading causes of cirrhosis in adults.[24] A comparison study suggested that NASH has a fibrotic potential similar to that of chronic hepatitis C after adjustment for fibrotic confounders.[25] Argo and colleagues observed bridging fibrosis in 25–33 per cent of NASH patients at diagnosis, including cirrhosis in 10–15 per cent.[26] Our study showed that fibrosis was present in association with NASH in 29 per cent of cases.

Since 2004, the number of adults with NASH awaiting liver transplants has almost tripled in the United States. In 2013, NASH became the second-leading disease among liver transplant waitlist registrants, preceded only by hepatitis C.[27]

Many clinical, imaging and laboratory factors were linked to NAFLD and its categories.[28-30] Some studies showed that NAFLD correlated with male gender and others showed no correlation with any gender.[31] This difference may be caused by ethnic disparities between populations. The absence of correlation between BMI and NAFLD/NASH could be attributed to difference between people in fat distribution. Two individuals with the same BMI may have different subcutaneous /visceral fat ratio and different fat deposition ratio in the liver.[32,33]

It is obvious from published data that normal liver enzymes do not exclude the presence of NAFLD or its categories, therefore, the sensitivity of these enzymes as a screening test for NAFLD is low.[34] In our study, about 26 per cent of patients with NAFLD and similar number of NASH patients, had abnormality in one or both transaminases. Our numbers support the fact that normal AST and ALT levels don't exclude NAFLD or its categories because most of

biopsy-proved NAFLD patients will have normal liver enzymes. Other biopsy-based surveys that studied the association between liver enzymes and NAFLD, reported similar results to ours.[13,35] Further analysis showed that 71 per cent of patients with elevated AST had NASH, which consorts with the association between AST and both NAS and steatosis grade. We suggest that obese patients with elevated AST or ALT should be further investigated for asymptomatic NAFLD.

NAFLD that refers to the existence of hepatic steatosis, in the absence of the competing aetiologies and coexisting liver disease (listed above), is currently acknowledged as the liver pathologic arm of metabolic syndrome.[1] The link between NAFLD and metabolic syndrome is sustained in studies that demonstrated significant clinical and histological improvement of hepatic steatosis in obese patients with metabolic syndrome after weight reduction surgery.[18] Several studies reported the presence of metabolic syndrome in 21-68 per cent of NAFLD patients.[36,37] Others showed that metabolic syndrome affected 60 per cent of females and 30 per cent of males diagnosed with NAFLD.[38] We encountered metabolic syndrome in 31 per cent of our NAFLD patients. The presence of metabolic syndrome elements, as predictors of fatty liver changes in patients with NAFLD, is associated with a higher risk to progress to NASH and liver fibrosis.[39]

The association between DM and NAFLD is strong, yet vague; In their analysis of 15 studies, Hazlehurst et al. found that the individual's risk of developing DM is increased approximately 5 folds if they have NAFLD. However, whether DM increases the risk of developing NAFLD was not clear.[40] In a large series of 432 patients, the coexistence of DM with NAFLD was found to be an independent risk factor for fibrosis.[41] The prevalence of NAFLD among DM patients varies with the method of diagnosis and the population studied; some studies have shown that NAFLD may be present in up to 70 per cent of patients with DM.[42] In an ultrasound-based study that involved 100 DM subjects from India, 65 per cent had fatty liver.[43] In our study, DM coexisted with NAFLD and NASH in 24 per cent(11/45), and 16 per cent (3/19) of patients, respectively. As part of this survey, we aimed to identify the incidence of DM in obese patients with NAFLD, rather than to report the rate of NAFLD in DM patients, which was attempted by many studies. Therefore, comparing our results to these studies was not amenable.

It is documented that disturbances of fat metabolism consequently lead to fat accumulation in the liver.[44] The most common form of dyslipidaemia in NAFLD patients is atherogenic dyslipidaemia, which is characterized by hypertriglyceridemia, low HDL levels, and high LDL levels.[45] The prevalence of dyslipidaemia, as a component of metabolic syndrome, among NAFLD patients varies from 20 per cent to 80 per cent.[46] In our study, more than half of NAFLD patients (55.5 per cent) and about two thirds of NASH patients (63 per cent) had deranged serum lipids, primarily elevated total cholesterol and TGs.

Conclusion

In conclusion; NAFLD has a very high prevalence among our morbidly obese patients. Multiple biochemical abnormalities were evident in association with the histological changes detected in NAFLD categories. Intraoperative liver biopsy is safe during sleeve gastrectomy for the diagnosis of NAFLD.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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ETHICS COMMITTEE APPROVAL

This study was approved by the Jordan University of science and technology ethics committee, study reference number: 193-2016.

Table 1: Patients' demographic and clinical characteristics

Variable	n	%
Age (years), mean (range)	34 (17–58)	
Body mass index (Kg/m^2), mean (range)	43 (35–52)	
Gender		
Male	13	26.5
Female	36	73.5
Comorbidities		
Diabetes mellitus		
Known Diabetes (on treatment)	4	8.2
Newly diagnosed Diabetes (while assessing for surgery)	7	14.2
Hypertension	7	14.3
Metabolic syndrome	14	25.6
Obesity-related Comorbidities		
Hypothyroidism	6	12.2
Sleep apnoea	1	2.0
Polycystic ovary syndrome	1	2.0

Table 2: Biochemical abnormalities in patients with nonalcoholic steatohepatitis, nonalcoholic fatty liver disease and nonalcoholic fatty liver

	Nonalcoholic steatohepatitis (N=19)	Nonalcoholic fatty liver disease (N=45)	Nonalcoholic fatty liver (N=26)
	Total patients with abnormal values (%)	Total patients with abnormal values (%)	Total patients with abnormal values (%)
Raised Triglycerides	7(37%)	14(31%)	7(28%)
Raised Cholesterol	8(42%)	12(27%)	5(20%)
Reduced High Density Lipoprotein level	3(16%)	10(22%)	7(28%)
Raised Low Density Lipoprotein level	6(32%)	7(16%)	1(4%)
Raised Glucose	5(26%)	11(24%)	5(20%)
Raised Aspartate aminotransferase	5(26%)	7(16%)	2(85)
Raised Alanine aminotransferase	7(37%)	12(27%)	5(205)
Reference normal values: Triglycerides (0–1.7mmol/l), Cholesterol (≥6.2mmol/l), High Density Lipoprotein (M:0.9–1.45, F:1.15–1.68), Low Density Lipoprotein (≥0–4.4mmol/l), Glucose (3.9–5.5mmol/l), Aspartate aminotransferase(0–34u/l) , Alanine aminotransferase (0–31u/l).			