NONALCOHOLIC FATTY LIVER DISEASE AND ITS COMPLICATIONS - ASSESSING THE POPULATION AT RISK. A SMALL SERIES REPORT AND LITERATURE REVIEW

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(Abstract): The aim of the study was to highlight correlations between serum biochemical markers and different degrees of liver inflammation or fibrosis revealed by liver biopsy in morbidly obese patients. We also wanted to emphasize that the occurrence of hepatocellular carcinoma (HCC) is increasingly associated with obesity, metabolic syndrome and nonalcoholic fatty liver disease. Material and methods: A clinical retrospective study was carried out on a series of 13 patients operated for morbid obesity in our surgical unit. Included in this study were only the obese patients referred for bariatric surgery without other risk factors for liver disease and in whom a liver biopsy was taken during metabolic surgery. Results: The pathology report revealed different stages of nonalcoholic fatty liver disease in all 13 patients: pathological features of steatohepatitis (7 patients), hepatic steatosis (5 patients) and lesions specific for evolving cirrhosis (1 patient). Regardless of the pathological changes of the liver, except the patient with evolving cirrhosis, none of these patients showed changes in classical liver function blood tests. Discussions: Hepatic alteration in obese patients, ranging from simple steatosis to steatohepatitis or even cirrhosis, is not always correlated with the values of classical biological liver function tests. Literature data suggest the involvement of adipokines in the development and progression of steatosis as the hepatic expression of metabolic and chronic inflammation syndrome occurring in obese patients. Furthermore, these proteins secreted by adipose tissue seem to be related to the HCC occurrence. However, none of these studies show the exact pathway followed by the hepatic cell from simple fatty liver to hepatocellular carcinoma. Conclusions: finding and selecting the population at risk for fatty liver disease progression and for HCC development among obese patients is mandatory. Keywords: OBESITY, NAFLD, HCC, BARIATRIC SURGERY.

Obesity is defined by the World Health Organization (WHO) as an abnormal or excessive fat accumulation that may impair health, with body mass index (BMI) greater than or equal to 30 kg/m² (1). WHO and International Obesity Task Force reported that 312 million adults worldwide are obese. Overall, more than one in 10 of the
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According to International Agency for Research on Cancer (IARC), hepatocellular carcinoma (HCC) is the fifth most common cancer in men and the seventh most common cancer in women, with more than 500,000 new cases per year (3, 4). It is already established that chronic conditions such as viral hepatitis B and C, alcoholic liver disease and hemochromatosis are the main risk factors for developing HCC. Nowadays, due to the growing number of cryptogenic HCC (with no readily identifiable risk factor) along with a dramatic increase in the number of patients with nonalcoholic fatty liver disease (NAFLD) related to obesity and metabolic syndrome, the association of these pathological conditions is becoming a topic increasingly discussed.

NAFLD comprises a spectrum of liver diseases defined by excessive fat accumulation in the form of triglycerides (steatosis) in the liver which cannot be explained by alcohol consumption. It ranges from simple steatosis to non-alcoholic steatohepatitis (NASH) that can have different degrees of fibrosis and can progress to liver cirrhosis and end-stage liver disease. Among patients with NAFLD, one to two in each ten patients will have NASH (5). A recent survey showed that NAFLD-associated cirrhosis is the third indication for liver transplantation in the United States, and it is expected to be the number one indication in 2020 (6).

NAFLD is strongly associated with obesity, insulin resistance (IR) / type 2 diabetes mellitus (T2DM) and the metabolic syndrome. In overweight subjects, the prevalence of steatosis is at least two times more frequent than in lean subjects (7), being directly proportional to the increase of body mass index.

Although cirrhosis precedes the diagnosis of HCC in most individuals, the number of cases in which HCC develops in the absence of cirrhosis is not negligible. A clinical-histopathological review of 804 American patients with HCC confirmed the lack of cirrhosis in as many as 42.6% of all cases (8). A recent review of a United States healthcare claims database covering 18 million lives per year identified 4406 cases of HCC associated with NAFLD as the most common underlying risk factor (59%) followed by diabetes (36%) and chronic HCV infection (22%) (9). Only 46% of all NAFLD-associated HCC cases were reported to have cirrhosis in this study, while 78% of HCC cases associated with chronic hepatitis C occurred in cirrhotic liver (9).

MATERIAL AND METHODS

With the increasing number of bariatric surgeries in our service, we started to take liver biopsy during bariatric surgical intervention as a diagnostic method of liver damage. We retrospectively reviewed the medical records of 13 obese patients receiving sleeve gastrectomy and hepatic biopsy during the past three months in our surgical unit. Inclusion criteria: patients aged over 18 years meeting the NIH criteria for bariatric surgery, irrespective of age, sex or geographical origin. The NIH criteria for bariatric surgery are BMI ≥40 kg/m² or BMI ≥35 kg/m² and at least one significant weight-related morbidity (10). Exclusion criteria: patients diagnosed with viral hepatitis B and C, history of any liver disease, chronic treatment with hepatotoxic drugs or alcohol consumption over 20g per day. Also excluded were the patients in whom liver biopsy was not taken due to
patient refusal or any technical reasons. In all study patients age, clinical parameters (BMI), medical history, pathology reports and biological parameters (AST, ALT, GGT, ALP, PLT, HOMA-IR, Ferritin) were reviewed.

RESULTS
The patients had a median age of 36.25 years and a BMI ranging from 44.19Kg/m² to 60 Kg/m², with a median BMI of 48.04 Kg/m².

Fig. 1. Age histogram

![Age histogram](image)

Fig. 2. Hepatic features in obese patients

![Hepatic features](image)

The pathology reports of all these 13 patients who underwent sleeve gastrectomy and hepatic biopsy showed different stages of nonalcoholic fatty liver disease. The histological changes in the liver ranged from simple steatosis (5 patients) to steatohepatitis (7 patients) expressed by ballooning degeneration of hepatocytes and vacuolation of the nuclei with additional porto-biliary fibrosis- in 2 cases; one patient presented obvious features of evolving liver cirrhosis.

Noteworthy, except for the patient diagnosed with liver cirrhosis who presented a slight increase in AST value (AST=49U/L), none of the patients diagnosed with any stage of fatty liver disease had pathologic changes of ALT, AST, GGT or ALP. They also had normal thrombocyte levels and normal coagulation. As to biological markers, we noticed elevated ferritin in 2 of the patients with hepatic steatosis, 3 of the patients with steatohepatitis and 1 patient with evolving cirrhosis; moderately increased cholesterol levels were found in 6 cases of steatohepatitis (range 203mg/dl-271mg/dl). Concerning obesity-related comorbidities, only 2 patients had history of type II diabetes and 1 patient was on antihypertensive therapy. According to HOMA-IR test, moderate insulin resistance was detected in 4 nondiabetic patients (2 of them having steatohepatitis and 2 hepatic steatosis); we considered that in the two study patients with type 2 diabetes abnormal HOMA-IR was a common situation.

DISCUSSION
Although the number of cases included in the study is small, our study shows that, except for the patient with evolving cirrhosis who presented a slight increased AST level, liver disease demonstrated by pathological examination had no impact on liver transaminases, blood count, alkaline phosphatase or coagulation tests. The results are in accordance with recent literature data showing that patients with normal versus elevated ALT had similar severity of
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NASH and suggesting that plasma aminotransferase levels are misleading parameters for guiding clinical management (11).

Calculation of APRI (aspartate aminotransferase to platelet ratio index) showed values ranging from 0.135 to 0.297 with a median of 0.232; values higher than 0.5 were found in patient diagnosed with liver cirrhosis (0.572) and in one of the two patients presenting steatohepatitis and liver fibrosis (0.508). These data are partly in concordance with literature data showing that APRI values ≤ 0.3 and ≤ 0.5 rules out significant fibrosis and cirrhosis (12).

In recent years, adipose tissue has been considered an endocrine organ because of its capacity to secrete a variety of proteins named adipokines, with broad biological activities. The adipose tissue expansion may occur in inert subcutaneous tissue but the metabolically active adipose tissue is the visceral fat. The incrimination of the activity of adipokines in the development of associated morbidities makes them among the most studied proteins today. Even so, the exact causal link between obesity, secretion of adipokines and the hepatic manifestation of metabolic syndrome - nonalcoholic liver disease with its possible complications, steatohepatitis, liver cirrhosis and even hepatocellular carcinoma has not been found.

Speaking of the least common but most dangerous morbidity associated to NAFLD, the incriminated mechanisms in hepatic carcinogenesis related to NAFLD are insulin resistance, oxidative stress and lipotoxicity, on a background of low-grade inflammatory status associated with obesity and metabolic syndrome. Another important factor that contributes to the pathogenesis of HCC is hyperinsulinemia, resulting in increased insulin growth factor-1 (IGF-1) which has important proliferative and antiapoptotic effects. IGF-1 promotes angiogenesis through increased vascular endothelial growth factor production, which in turn leads to cancer cell proliferation (13). In our study group, excepting the two diabetic patients, we detected 4 more cases with elevated insulin, 2 patients presenting steatohepatitis and 2 steatosis.

Normally, insulin suppresses lipolysis, hydrolysis of triglycerides to free fatty acids (FFA). In conditions involving insulin resistance, such as fatty liver disease, lipolysis is active, resulting in the release of FFA from the adipose tissue. Insulin resistance (IR) has a major role in the occurrence of hepatic steatosis and in the progressive development of steatohepatitis, liver cirrhosis and even hepatocellular carcinoma. Steatosis itself also promotes IR, endorsing a self-perpetuating vicious cycle (14). The excessive accumulation of fat in adipocytes promotes an increase in oxidative stress, which deregulates adipocytokines production and promotes low grade inflammatory state in the adipose tissue, through the release of interleukin (IL)-6 among others (15). Subsequently, macrophages and lymphocytes are activated, promoting further release of pro inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interferon-γ. The spillover of FFA from the adipose tissue leads to ectopic accumulation of fat in muscles and liver. Noteworthy, in the liver, not all insulin actions are impaired; it preserves its lipogenic actions further inducing steatosis, and its pro-mitogenic actions, which may enhance hepato-carcinogenesis (16). Excepting the two patients with type 2 diabetes in whom abnormal HOMA-IR was a common situation, moderate IR was present in 4 nondiabetic patients (2 with
steatohepatitis and 2 with hepatic steatosis).

Increased serum ferritin levels are present in more than 30% of patients with NAFLD and it has been reported to correlate with IR and the other metabolic abnormalities defining the metabolic syndrome (17, 18). Our data are consistent with the literature data, showing increased ferritin levels in 46.15% of our NAFLD patients, changes not related to a specific degree of liver damage. Other mechanisms involved in hepatic disorders up to HHC development, such as hepatic iron overload, seem to be linked to IR and metabolic syndrome (19). Iron overload has been hypothesized to induce IR by catalyzing oxidative stress in the liver (20). The iron may fuel oxidative stress-driven cell toxicity or activate signaling pathways involved in fibro genesis or carcinogenesis occurring in the metabolic syndrome (18). Metabolic derangement and progression of liver disease are more severe with NASH than with NAFLD and hepatic iron deposition has been shown to increase the risk of malignant transformation in NASH-derived cirrhosis (17, 21). Considering these data, we believe that the assessment of liver iron overload should be part of the diagnosis of NASH.

All these mechanisms have in common the involvement of adipokines in their occurrence and development. Leptin, a protein mainly produced by adipose tissues is best known as a regulator of food intake and energy expenditure via hypothalamic-mediated effects. This adipokine has many additional effects, including angiogenesis - by induction of VEGF activation with an important impact on liver fibrosis, as formation of new blood vessels is a key component of the wound-healing, with important implications in the development of liver fibrosis, cirrhosis and HCC (22). Considering that obesity induces a chronic inflammatory status, it has been demonstrated that leptin also has a regulatory immune function. Leptin levels are acutely increased by, and also may affect the secretion of many acute phase factors such as tumor necrosis factor (TNF), interleukin (IL)-1 and IL-6 (23, 24). Both dietary and genetic obesity promote liver inflammation and tumor genesis by enhancing IL-6 and TNF expression (25). As we can see, hepatic impairment in obese patients, ranging from simple steatosis to steatohepatitis or even cirrhosis, does not always have an impact on classical biological liver function test values. Liver biopsy remains the gold standard for differentiating nonalcoholic steatosis from other stages of fatty liver disease; still, it is an invasive procedure, associated with morbidity, mortality and several limitations (26). The clinical experience shows that most patients refuse invasive methods for assessing the progression of liver pathology associated with obesity. Therefore we believe that finding a noninvasive algorithm for assessing the degree of liver damage and especially the evolution of liver lesions after bariatric surgery is required.

CONCLUSIONS

As our study shows, the number of cases of nonalcoholic steatohepatitis with different degrees of liver fibrosis that do not present any pathological changes in liver function blood tests is not to be neglected. There is increasing evidence that obesity, associated metabolic disorders and mainly NAFLD - the hepatic expression of metabolic syndrome - are involved in the development of HCC. The incidence of
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HCC occurrence in patients with NAFLD is low, but the number of obese patients is increasing constantly worldwide. A worrying fact is that cirrhosis is not indispensable for HCC development in patients with NAFLD. For an efficient follow-up, noninvasive algorithms to assess liver damage in patients with morbid obesity as well as selection criteria of patients at risk to develop HCC among patients with obesity and metabolic syndrome are needed.

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REFERENCES

**NEWS**

**SURGICAL TREATMENT OF AORTIC VALVE ENDOCARDITIS:**
**A 26-YEAR EXPERIENCE**

Microbial infection of the endothelial lining of any part of the heart, infective endocarditis (IE), is an uncommon but life threatening condition. Despite advances in diagnosis, antimicrobial therapy, surgical techniques, and management of complications, the incidence has not decreased in the past 30 years and patients with IE still have high morbidity and mortality rates related to this condition. Its management aims to eradicate the infecting organism as soon as possible mainly with antibioticotherapy but clinical complications and treatment failure suggest surgery up to 60% of the cases. IE effecting aortic valve accounts about 40-67% of all cases and about 60-70% of these cases undergo surgery in the acute phase. In spite of the high mortality and morbidity it carries, surgical therapy is still the mainstay in the treatment of aortic valve IE. Numerous studies have assessed different risk factors for mortality and morbidities in the treatment of IE but risk factors for surgical treatment of aortic valve IE patients need to be clarified. In this study, authors retrospective-ly assessed the results of the surgical treatment of patients with aortic valve endocarditis over a period of 26 years in an attempt to address these issues (Adademir T, Tuncer EY, Tas S et al. Surgical treatment of aortic valve endocarditis: a 26-year experience. *Rev Bras Cir Cardiovasc* 2014; 29 (1): 16-24).