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Article

Evaluation of Histological Liver Changes in Obese Patients Compared with Normal-Weight Individuals

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Abstract: Background: Obesity is one of the most important health risk factors globally and is known to be one of the most important risk factors for the occurrence of non-alcoholic fatty liver disease (NAFLD) and its histopathological complications. Hepatic lipid accumulation, chronic inflammation and hepatocellular damage and fibrosis, which result from excessive adiposity, represent the risk factors for cirrhosis and liver failure. Objective: To perform comparative and evaluative analysis of the histological changes in liver of obese patient vs. normal weight patient and the correlation between the severity of liver histological changes and obesity. Materials and methods: This was a comparative observational histopathological study that was carried out for two years (May 2024 – May 2026) in the histopathology department of Baghdad Teaching Hospital, Medical city, Baghdad, Iraq. Five hundred pieces of liver were obtained, 50 of which were obese, and 50 normal weight patients. Standard histological methods were used for processing tissue specimens and they were stained with Hematoxylin and Eosin (H&E) and Masson's Trichrome stains and then observed with light microscopy. Histopathological evaluation comprised of macrovesicular steatosis, microvesicular steatosis, hepatocellular ballooning, lobular inflammation, portal inflammation, hepatocyte necrosis, sinusoidal dilatation, glycogenated nuclei, fibrosis stage and Non-alcoholic Fatty Liver Disease Activity Score (NAS). Statistic analysis (SPSS version 27.0) and significance ($P < 0.05$) were used. The prevalence and severity of macrovesicular steatosis, microvesicular steatosis, hepatocellular ballooning, lobular inflammation, portal inflammation, hepatocyte necrosis, sinusoidal dilatation and glycogenated nuclei were significantly increased in obese compared with normal weight patients (all $P < 0.05$). Fibrosis and non-alcoholic steatohepatitis (NASH) were also significantly increased in obese patients compared with normal weight patients ($P < 0.05$). Furthermore, obese patients had significantly increased grades of steatosis, stage of fibrosis and NAS. The liver injury was progressive and all severity parameters of the liver was positively correlated with BMI on histopathology. Finally, the present study confirms the close association between obesity and liver damage, manifested as steatosis, inflammation, hepatocellular degeneration and fibrosis. These results further confirm previous reports indicating that liver biopsy continues to be the standard of care to assess severity of NAFLD and how it progresses to NASH. Early detection of the histo-pathological changes that occur with obesity may facilitate early therapeutic intervention and prevent end-stage liver disease, fibrosis and cirrhosis.

Keywords: Obesity; Histopathology; Non-Alcoholic Fatty Liver Disease (NAFLD); Hepatic Steatosis; Liver Fibrosis.

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1. Introduction

Obesity has emerged as one of the most acute public health problems in the 21st century, and is on the rise in both developed and developing countries. Obesity is considered to be excessive or abnormal fat accumulation that poses a risk to health, and is generally measured by body mass index (BMI), which is a BMI of 30 kg/m2 or above

[1]. The incidence of obesity and obesity-related metabolic diseases like type 2 diabetes mellitus, hypertension, dyslipidaemia, cardiovascular diseases and chronic liver disease has been on the rise [2,3]. Liver involvement has been a major focus of attention of all these complications because of its high incidence, progressive course and potential to progress to irreversible hepatic damage. Over the years, obesity-associated metabolic disturbances have made non-alcoholic fatty liver disease (NAFLD) a major cause of chronic liver disease around the world, impacting millions of people and putting a significant strain on health care systems [4, 5].

NAFLD is a continuum of liver disease, characterized by the presence of a higher concentration of lipid within the liver cell, but without the presence of secondary causes of liver accumulation of fat such as alcohol abuse or certain other diseases [5]. The disease can progress from a simple steatosis, which is usually reversible, to the more aggressive non-alcoholic steatohepatitis (NASH), which is often accompanied by hepatocellular ballooning, infiltration of cells of inflammation and progressive fibrosis. If left untreated, untreated NASH can progress to advanced fibrosis, cirrhosis, portal hypertension, hepatocellular carcinoma and liver failure [6]. Recently epidemiological studies have indicated that up to one third to one quarter of the adult population in the world is affected with NAFLD and even higher in patients with obesity and metabolic syndrome. Therefore, obesity is now known to be one of the strongest independent risk factors for fatty liver disease development and progression [7,8].

There are multiple metabolic, inflammatory and molecular pathways that contribute to the underlying cause of obesity-associated liver damage. With chronic positive energy balance, excess triglyceride deposition in adipose tissue and later on in hepatocytes [9] will take place. The primary pathogenic mechanism is thought to be insulin resistance, which increases lipolysis in fat tissues and leads to a greater supply of fatty acids to the liver, and simultaneously increases de novo lipogenesis in the liver [10]. This lipid overloading results in oxidative stress, ER activation, ER stress, mitochondrial dysfunction and activation of inflammatory signaling pathways. Hepatocellular damages, recruitment of inflammatory cells, activation of hepatic stellate cells and excessive deposition of extracellular matrix contribute to the development of hepatic fibrosis, through the mediation of inflammatory mediators such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and transforming growth factor beta (TGF-β). Early diagnosis and treatment is crucial since chronic inflammation and fibrosis is a significant risk factor for progression to cirrhosis and HCC [11, 12].

The gold standard for the evaluation of severity and progression of liver disease due to obesity is the histopathology. While imaging and biochemical markers are not always sufficient to fully depict structural changes, liver biopsy is the only means of directly evaluating these changes [13]. Histological analysis can identify and grade macrovesicular and microvesicular steatosis, hepatocellular ballooning, lobular and portal inflammation, hepatocyte necrosis, sinusoidal dilatation, glycogenated nuclei and hepatic fibrosis [14]. Standardized scoring systems such as the Non-Alcoholic Fatty Disease Activity Score (NAS), fibrosis staging can provide objective assessment of the severity of the disease and useful prognostic information. These histological features are important for the distinction of simple steatosis from NASH and it is important to evaluate disease activity and treatment efficacy [15].

Although there have been many advances, there is still a lack of understanding regarding the association between obesity and chronic liver disease and the different histopathologic types in different populations are not well characterised. Liver injury and its severity and progression may be influenced by genetic variation, diet, environment and metabolism. Hence, extensive histopathological investigations of obese and normal weight populations are required to gain a better understanding of liver disease in the obese and the development of appropriate prevention and therapeutic interventions [16,17].

The present study, therefore, was planned to evaluate and compare liver alterations in obese and normal weight patients, and to find the correlation between obesity and degree of liver histopathology changes. Moreover, this research aimed to evaluate the

association between BMI with the level of liver damage of steatosis, inflammation, hepatocellular degeneration, fibrosis and Non-Alcoholic Fatty Liver Disease Activity Score (NAS).

2. Materials and Methods

The current study was an observational comparative histopathology study was conducted in the Histopathology Laboratory of the Baghdad Teaching Hospital (Medical City) a governmental tertiary healthcare center in Baghdad, Iraq during 2-year period from May 2024 till May 2026 in a specialized path lab.

A total of 100 liver tissue samples from 50 obese patients (BMI ≥30 kg/m2) and 50 normal-weight patients (BMI 18.5-24.9 kg/m2) undergoing liver biopsy or hepatic tissue sampling for diagnosis or therapy that were not specific of malignant liver disease were included. Demographic and clinical data, such as age, sex, BMI, medical history and biochemical parameters were retrieved from hospital medical records.

Liver was then immediately fixed in 10% neutral buffered formalin for 24–48 hours and then processed with an automated tissue processor, embedded in paraffin wax, cut into 4–5 μm sections using a rotary microtome and placed on glass slides. The tissue blocks were stained with Hematoxylin and Eosin (H&E) for routine microscopic examination and Masson's Trichrome stain for evaluation of hepatic fibrosis.

All slides were individually examined by two expert consultant histopathologists using an Olympus BX53 microscope and digital imaging system at ×100, ×200 and ×400. Histopathological evaluation consisted of the following parameters: macrovesicular and microvesicular steatosis, hepatocellular ballooning degeneration, lobular inflammation, portal inflammation, hepatocyte necrosis, sinusoidal dilatation, fibrosis stage, and features of non-alcoholic steatohepatitis (NASH).

Liver injury was evaluated as severity based on Non-Alcoholic Fatty Liver Disease Activity Score (NAS) and fibrosis was classified by the Brunt classification system. These quantitative parameters were the percentage of hepatic steatosis, the score for inflammatory cell infiltration, the score for ballooning, stage of fibrosis, and the overall NAS score.

All the microscopic data were documented using digital photomicrography and the results were statistically analysed using IBM SPSS Statistics 27.0. The mean ± SD was used to summarise data for continuous variables, and the frequency and percentage for categorical variables. Differences between the groups of obese and normal weight based on their type were analyzed by Independent-samples t-test, Mann–Whitney U test or Chi-square test. A P value of <0.05 was deemed statistically significant, throughout the study.

3. Results and Discussion

Results

Histopathological Findings

Histopathological changes were significant in liver specimens from obese patients when compared with normal weight patients as seen through the microscope. Obese patients had significantly higher frequencies of macrovesicular steatosis, microvesicular steatosis, hepatocellular ballooning, lobular inflammation, portal inflammation, hepatocyte necrosis, sinusoidal dilatation, and glycogenated nuclei and histological features suggestive of non-alcoholic steatohepatitis (NASH) (Table 1).

Table 1. Comparison of Histopathological Findings Between Obese Patients and Normal-Weight Individuals

Histological finding	Obese (n=50)	Normal weight (n=50)	P value
Macrovesicular steatosis	42 (84%)	8 (16%)	<0.001
Microvesicular steatosis	26 (52%)	5 (10%)	<0.001
Hepatocellular ballooning	35 (70%)	4 (8%)	<0.001
Lobular inflammation	31 (62%)	6 (12%)	<0.001
Portal inflammation	24 (48%)	5 (10%)	<0.001

Hepatocyte necrosis	16 (32%)	3 (6%)	0.001
Sinusoidal dilatation	22 (44%)	6 (12%)	0.002
Glycogenated nuclei	28 (56%)	7 (14%)	<0.001
Histological NASH	20 (40%)	2 (4%)	<0.001

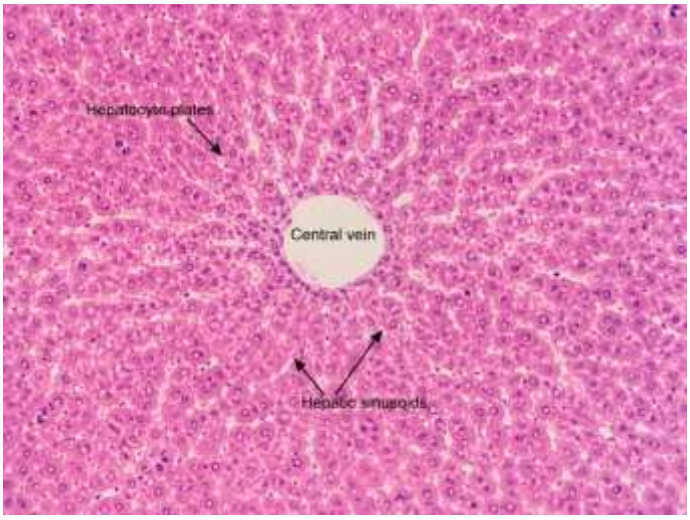

Figure 1. Normal hepatic architecture in a normal-weight individual showing intact hepatocyte plates, central vein, and hepatic sinusoids (Hematoxylin and Eosin stain, original magnification ×200).

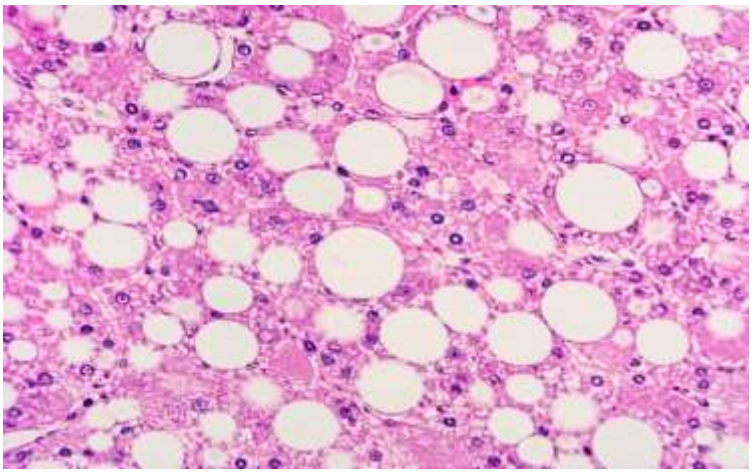

Figure 2. Extensive macrovesicular steatosis in an obese patient with large intracellular lipid vacuoles displacing hepatocyte nuclei (Hematoxylin and Eosin stain, ×400).

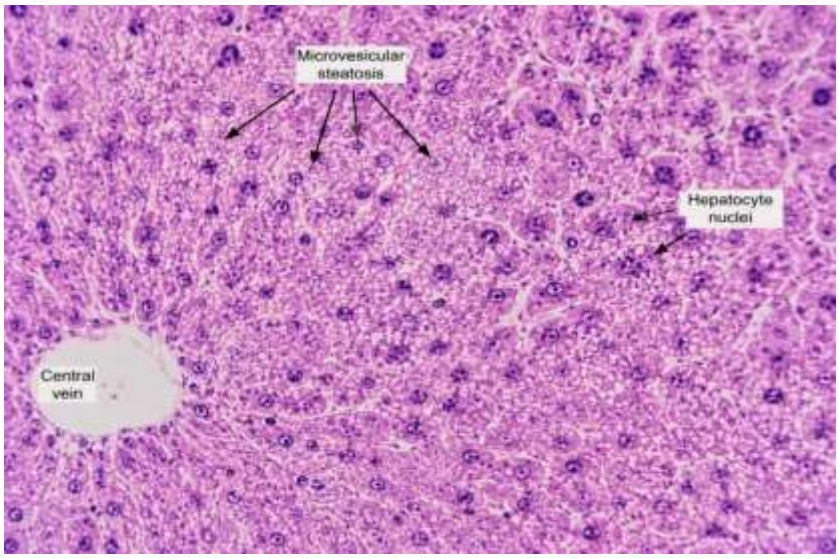

Figure 3. Microvesicular steatosis involving multiple hepatocytes in an obese patient (H&E stain, ×400).

Histological Severity Scores

Patients that were obese showed the greater severity of hepatic injury. Table 2 showed that the steatosis grades, ballooning scores, lobular inflammation scores and fibrosis stages were significantly higher in obese compared to normal-weight controls.

Table 2. Histological Severity Scores

Parameter	Obese	Normal	P value
Steatosis grade	2.36±0.69	0.42±0.51	<0.001
Ballooning score	1.28±0.61	0.14±0.35	<0.001
Lobular inflammation score	1.61±0.74	0.41±0.56	<0.001
Fibrosis stage	1.42±0.88	0.22±0.46	<0.001

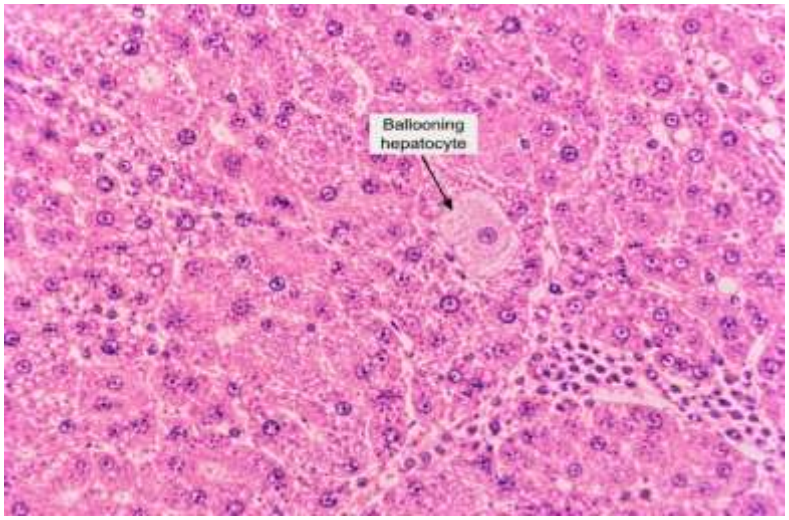

Figure 4. Ballooning degeneration characterized by enlarged swollen hepatocytes with pale cytoplasm (H&E stain, ×400).

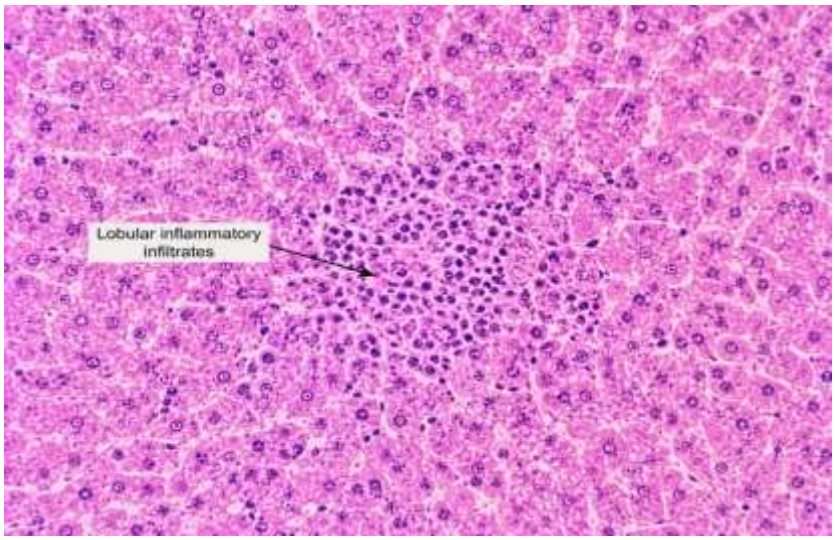

Figure 5. Lobular inflammatory infiltrates surrounding injured hepatocytes (H&E stain, ×400).

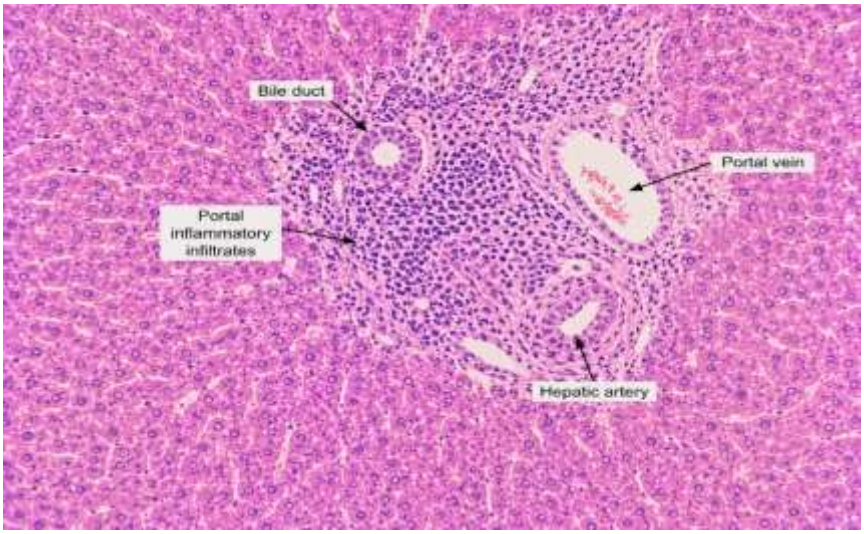

Figure 6. Portal inflammatory infiltrates within the portal tract (H&E stain, ×200).

NAFLD Activity Score

Obese subjects had significantly higher mean NAFLD Activity Score (NAS) than normal subjects, indicating higher disease activity (Table 3).

Table 3. Comparison of NAFLD Activity Score

Group	NAS score	P value
Obese	5.14±1.23	<0.001
Normal weight	1.18±0.81	

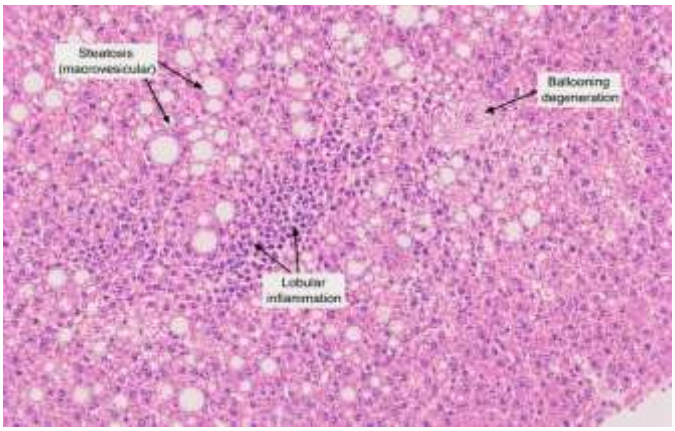

Figure 7. Representative liver biopsy demonstrating non-alcoholic steatohepatitis (NASH) characterized by steatosis, ballooning degeneration, and lobular inflammation (H&E stain, ×200).

Hepatic Steatosis Distribution

There was a significant difference in the distribution of steatosis grades between both the study groups. None of the lean patients had grade 3 steatosis (Table 4).

Table 4. Distribution of Hepatic Steatosis Grades

Grade	Obese	Normal
0	6	42
1	11	6
2	18	2
3	15	0

P<0.001

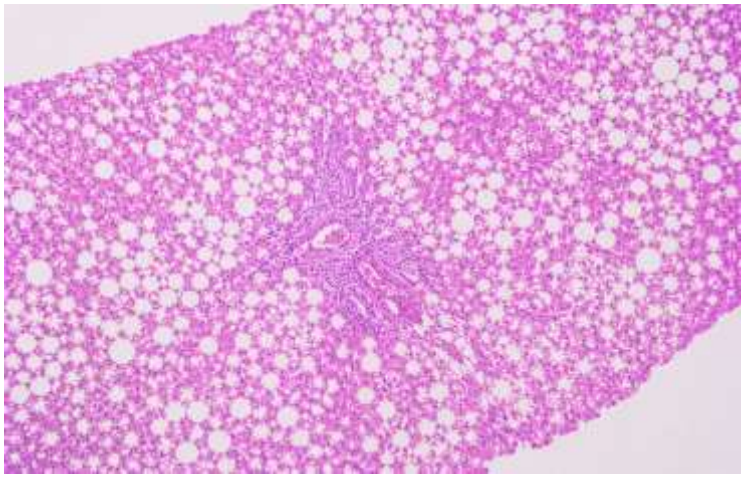

Figure 8. Severe Grade 3 macrovesicular steatosis involving more than two-thirds of hepatocytes (H&E stain, ×100).

Hepatic Fibrosis

There was significantly more liver fibrosis in obese patients as revealed by Masson's Trichrome staining. Fibrosis (stage 2 and stage 3) was seen only in those who were obese (Table 5).

Table 5. Distribution of Fibrosis Stages

Stage	Obese	Normal
0	17	46
1	15	3
2	11	1
3	7	0

P<0.001

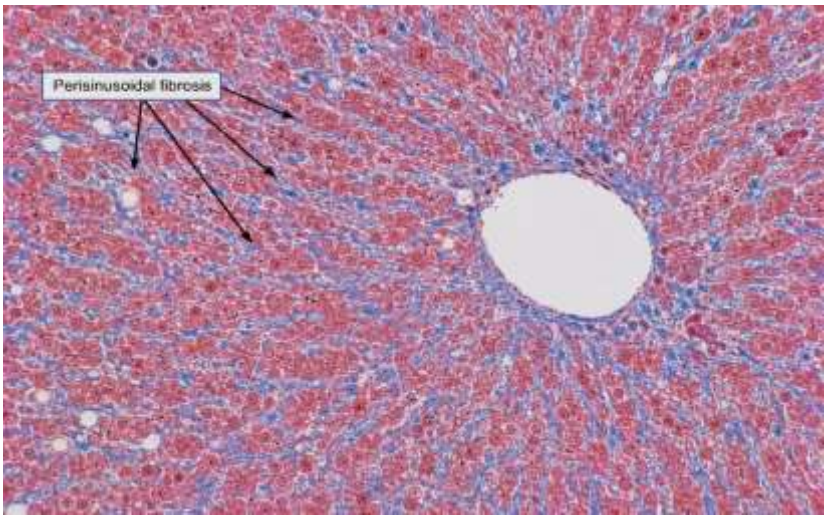

Figure 9. Perisinusoidal fibrosis highlighted by Masson's Trichrome stain (original magnification ×200).

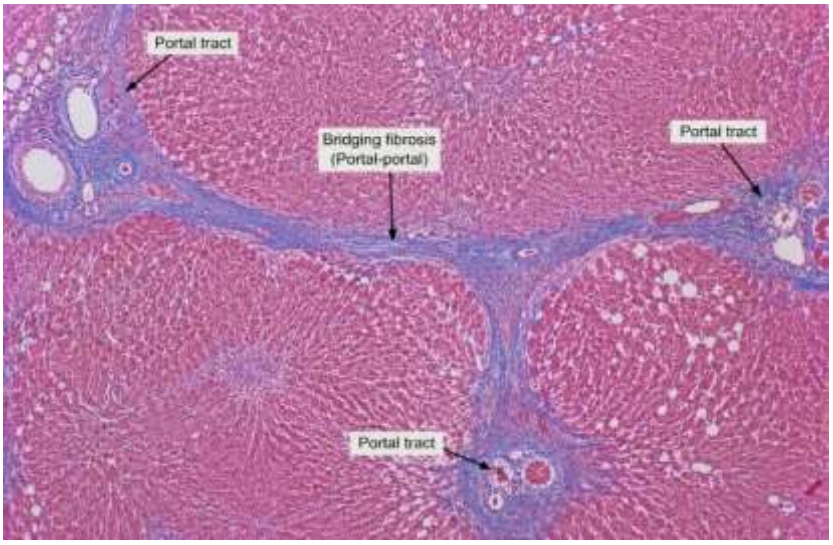

Figure 10. Bridging fibrosis connecting adjacent portal tracts (Masson's Trichrome stain, ×100).

Correlation Analysis

Significant positive correlations were identified between BMI with all histological severity scores using correlation analysis. BMI had the highest correlation with NAS score (Table 6).

Table 6. Correlation Between BMI and Histopathological Parameters

Variable	r	P value
Steatosis grade	0.71	<0.001
Ballooning score	0.66	<0.001
Lobular inflammation	0.63	<0.001
Fibrosis stage	0.58	<0.001
NAS score	0.74	<0.001

Discussion

Of all the findings of the current study, the significantly greater incidence of macrovesicular steatosis in the obese patients was of special interest. Macrovesicular steatosis is believed to be the earliest and most common histopathological changes in

NAFLD and this is a secondary phenomenon caused by excessive deposition of TG in the hepatocyte caused by insulin resistance and lipid metabolic abnormalities. Our findings are consistent with those of Brown and Kleiner [18] which have demonstrated that one of the most common pathological changes of liver disease in the obese is hepatic steatosis, which is usually the first step in the process of inflammatory damage and the development of fibrosis. Likewise, Brunt and Tiniakos pointed out that the primary histological finding in obese patients is macrovesicular steatosis, which is closely related to obesity and metabolic dysfunction [19].

Also, there was a significant difference in the frequency of microvesicular steatosis in obese subjects. Microvesicular steatosis is less common than macrovesicular steatosis and it is linked to defects in mitochondrial function and defects in the β-oxidation of fatty acids. Previous studies have revealed that the presence of macrovesicular and microvesicular steatosis can be a sign of more extensive metabolic injury and progression of disease [20]. These observations are similar to the current observations and support the idea that obesity results in multiple types of lipid accumulation in hepatocytes.

Another major finding was the significant increase of HCC in patients with ballooning degeneration, who were obese. Ballooning degeneration is one of the most useful and sensitive microscopic features that help distinguish simple steatosis from steatohepatitis. An increase in the severity of the disease from uncomplicated fatty liver to NASH resulted in disruption of the cytoskeleton, oxidative stress and cellular injury, known as "ballooning degeneration" by Kleiner and Makhlouf [21]. Brunt et al. also considered ballooning degeneration to be a key feature of NAFLD histological classification systems as it is a harbinger of irreversible hepatocellular damage and progression of the disease [22]. These current findings also support the notion that obesity is not just a factor that allows fat to accumulate, but it also leads to hepatocyte damage.

Lobular and portal inflammation were also significantly increased in obese patients in the present study. Chronic inflammation is a key pathway involved in the pathogenesis of NAFLD as the accumulation of lipids activates the Kupffer cells and promotes release of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and transforming growth factor-beta (TGF-β). Inflammatory cells are activated, up-regulated, in the hepatic lobules and portal tracts, thus causing injury to the hepatocytes and fibrosis. Brunt et al. (2009) found the same with portal inflammation showing strong association with advanced NAFLD and increasing severity of the disease [23]. Brown and Kleiner also reported that the severity of the inflammatory infiltrates correlates with disease severity and that as the severity of the infiltrates gets worse, the disease becomes worse [18].

The hepatocyte necrosis and sinusoid dilatation that occurred in the present study were significantly more common in the obese patients. The pathogenesis of these changes is probably due to chronic oxidative stress, mitochondrial dysfunction and microvascular changes caused by the chronic lipid overload. In the past, too high a level of free fatty acids has also been found to induce ROS production, which results in membrane damage, apoptosis and focal hepatocyte necrosis [24]. After the microcirculatory dysfunction and endothelial dysfunction in the liver, sinusoidal dilatation is observed and is a typical feature in patients with more severe metabolic liver disease. Such mechanisms have been discussed in detail in review articles of the histopathology of NAFLD [25].

The greater number of glycogenated nuclei in obese patients is also a sign of metabolic dysregulation. Glycogenated nuclei is a microscopic characteristic known to be associated with insulin resistance as well as metabolic syndrome [26]. They were more prevalent in the obese group, which may be because of the chronic hyperinsulinemia and glucose metabolism problems associated with obesity. Glycogenated nuclei have also been reported as a common pathological feature in obesity-related NAFLD in previous studies [27].

One of the important results of this study was the significant difference in fibrosis stage among the cases and controls that were obese. Histologically, cirrhosis and hepatic failure are caused by progressive collagen deposition and is the most clinically relevant indicator of long-term liver-related morbidity and mortality [28]. The present results agree

with Kleiner's observation that bridging fibrosis is the initial manifestation of fibrosis in obesity-related NAFLD, which is followed by portal and perisinusoidal fibrosis [29]. Likewise, Brunt et al. found that the severity of fibrosis could be related to the inflammatory activity and hepatocyte ballooning, highlighting that fibrosis is a marker of cumulative chronic liver damage and not a marker of fat accumulation alone [23].

The obese cases had significantly higher scores on NAFD Activity Score (NAS) than normal weight controls. This finding reveals that there is much greater NAFLD activity in the obese population, which further emphasizes the value of NAS for the diagnosis of the severity of NAFLD. To standardize the evaluation of steatosis, inflammation, and ballooning degeneration, Kleiner et al. developed the NAS which proved to be useful for clinical research in validation studies [21]. Thus, the high NAS reached in the present study strongly indicate that obesity is linked not only with the accumulation of hepatic fat but is also with active inflammatory liver damage.

BMI was also positively correlated well with all the HPS scores including steatosis grade, ballooning score, lobular inflammation score, fibrosis stage and NAS score. These findings suggest that there is a progressive deterioration of liver histopathology with greater obesity. Such correlations have been repeatedly reported in previous studies that showed an independent correlation between BMI and the severity of NAFLD and the progression of histological changes. The biological explanation is increased insulin resistance, chronic low grade inflammation, imbalance in adipokines, oxidative stress and lipotoxicity as a result of excess adiposity [30, 31].

4. Conclusion

In the present study the liver tissues of obese and non-obese children were compared and significant histopathological changes were observed in the liver tissues of obese children. Hepatocellular steatosis, both macrovesicular and microvesicular, hepatocellular ballooning, lobular inflammation, portal inflammation, hepatocyte necrosis, sinusoidal dilatation and glycogenated nucleus were all significantly higher in the obese group while fibrosis and non-alcoholic steatohepatitis (NASH) were not. Furthermore, the higher NAFLD Activity Score (NAS) and the fibrosis stage in the obese patients indicate more liver damage and progression of liver disease. The high correlation between BMI and all severity parameters of liver histopathology further emphasizes the role of obesity in liver structure damage. The findings here support the importance of early screening and histological assessment of obese patients who are at risk of developing metabolic syndrome to ensure early diagnosis and intervention and prevent irreversible liver fibrosis. Control of weight and metabolism would likely greatly reduce the incidence of obesity-related liver disease, and improve long term liver outcomes. Large-scale, multicenter studies and molecular studies are needed in the future to better define mechanism of liver injury and therapeutic targets in obesity.

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