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The Interplay between High Hemoglobin Concentration and Non-Alcoholic Fatty Liver Disease: A Rising Health Concern

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is increasing globally and represents a significant liver health challenge. Concurrently, elevated hemoglobin concentration (HBC) has emerged as a health concern due to its potential to increase hepatic workload and contribute to liver pathology.

Objective: This study aimed to examine the relationship between high hemoglobin levels and the development of NAFLD.

Patients and Methods: At Misr University for Science and Technology Teaching Hospital, 330 patients suspected of NAFLD were evaluated clinically. Diagnosis included abdominal ultrasound to assess hepatic steatosis and elastography to determine liver stiffness and fibrosis. Blood samples were analyzed for hemoglobin, hematocrit (HTC), and NAFLD-related laboratory parameters, with insulin resistance assessed using the HOMA-IR method. Patients were classified into high (H-HBC) and normal (N-HBC) hemoglobin groups.

Results: Of 330 patients, 223 had normal hemoglobin (N-HBC), while 107 had high hemoglobin (H-HBC). The H-HBC group demonstrated a significantly higher incidence of increased Hepatic Risk Index (HRI) and NAFLD Fibrosis Score (NFS). There was also a slight rise in patients with Hepatic Steatosis Index (HSI) above 36 in the H-HBC group. Statistical analysis revealed that higher HTC strongly predicted increased HRI, and high HBC was effective in identifying patients with HSI >36. A HOMA-IR threshold of 2.1 moderately identified patients with advanced (grades 3–4) fibrosis.

Conclusion: Elevated HBC and HTC—routine laboratory tests—can help predict hepatic steatosis and fibrosis. A high HOMA-IR score reliably identifies patients with high-grade liver fibrosis.

Keywords: High Hemoglobin, Non-Alcoholic Fatty Liver Disease, Health Concern.

INTRODUCTION

Non-alcoholic fatty liver (NALF) and the more severe non-alcoholic steatohepatitis (NASH) represent two variations of hepatic steatosis, a metabolic disorder marked by fat accumulation in the liver cells without alcohol involvement [(1)].

NAFLD, or non-alcoholic fatty liver disease, has the potential to advance into more serious conditions such as liver cirrhosis, fibrosis, end-stage liver disease[(2)], or even hepatocellular carcinoma[(3)]. It's estimated that around 25% of the population is affected by NAFLD[(4)], with its occurrence being five-fold more common among diabetic individuals compared to non-diabetics. The prevalence of NAFLD continues to increase[(5)].

Type 2 diabetes mellitus (T2DM) is a multifaceted metabolic disorder that involves numerous metabolic complications, including heightened insulin resistance, dysfunction of β-cells, and increased levels of triglycerides and tumor necrosis factor-α[(6,7)]. From a clinical perspective, insulin resistance is described as the failure of a given amount of insulin to promote the uptake and use of glucose in tissues, which is insulin's expected physiological function[(8)].

Hemoglobin serves as the primary storage for iron in the body, which is a vital element for sustaining life[(9)]. Overconsumption of iron, particularly through injections, can lead to iron overload, causing negative health effects such as the onset of type 2 diabetes, cardiovascular diseases, and cancer [(10)], as well as abnormal immune responses that tilt the immune system towards inflammation and cellular oxidative stress, elevating the production of reactive oxygen species[(11,12)].

The goal of the current study was to assess the association between the incidence and severity of NAFLD and high hemoglobin concentration (H-HBC).

PATIENTS AND METHODS

This Prospective observational double-blinded study was performed at Department of Internal Medicine, Faculty of Medicine, Misr University for Science and Technology

All patients presenting with symptoms suggestive of NAFLD to the internal medicine outpatient clinic from March 2020 to August 2022 were eligible for the evaluation of the existence of exclusion and inclusion criteria.

Inclusion criteria: The study included patients with NAFLD symptoms who did not meet any exclusion criteria.

Exclusion criteria: Anemia, maintenance on erythropoietin or bone marrow suppressing medications, chronic renal diseases, bone marrow problems, blood transfusions for whatever reason in the

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past one month, protein malnutrition, copper deficiency and unwillingness to participate in the study.

Preliminary evaluation:

Subsequently, after taking a detailed history and demographics including age, sex, height, and weight, the patient was subjected to a thorough clinical examination, with emphasis on the liver examination.

Evaluation tools:

Body mass index (BMI) was calculated as weight (kg) divided by height (m^2) [(13)], and was graded according to WHO guidelines as average or overweight and obesity I-III grades[(14)].

The computerised Hepatorenal Index (HRI) was used to sonographically grade liver steatosis. It may predict >5-25%, >25-<60%, and ≥60% steatosis at cutoff values of 1.49, 1.86, and 2.23, respectively [(15)]. The HSI was calculated by the formula ([ALT/AST ratio]*[8] + BMI + 2 in cases of diabetes of the patient + 2 in the case of the female patient), and an HIS ≥ 36 indicates NASH [(16)].

Diagnosis of NASH-induced fibrosis using the NAFLD fibrosis score (NFS) depends on 6 parameters; age, BMI, impaired fasting glucose, serum albumin level, platelet count, and AST/ALT ratio. NFS value of <-1.455 was graded as F0-2; i.e., no significant fibrosis and a value of >0.675 could predict significant fibrosis (F3-4 fibrosis grade) [(17)].

For patients with intermediate NFS that ranged between -1.455 and 0.675, the BRAD score was calculated as a 4-point score: a point for BMI>28 kg/m^2, two points for AST/ALT ratio > 0.8, and a point for the presence of diabetes [(18)].

BRAD score value of <2 excludes advanced fibrosis with a negative predictive value of 95-97%, while a score value of >2 is associated with advanced liver fibrosis (F3-4) with sensitivity and specificity of 88% and 89% respectively [(19)].

For patients between the ages of 20 and 60, hematological parameters were interpreted as follows: an HTC value at cutoff points of 35.5-44.9% and 38.3-48.6% for females and men, respectively, and an HBC level of 12.2-15 and 13.5-16.5 g/dl for females and males, respectively, were deemed normal. Conversely, individuals with HBC <12.2 and 13.7 g/dl for females and males, respectively, were classified as anemic patients, while those with HBC >15 and 16.5 g/dl for females and males, respectively, were classified as having high HBC [(20)].

Insulin resistance was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR) score that could be calculated as fasting serum insulin (FSI) multiplied by fasting blood glucose (FBG) that was divided by 18 and the resultant was divided by 22.5 to yield HOMA-IR score, which if >2 was suggestive of the presence of IR [(21)].

Grouping:

Patients were categorized according to their baseline HBC, which was estimated at the time of enrollment into high (H-HBC) and normal HBC (N-HBC) groups.

Laboratory investigations:

All patients were then requested to come back to the outpatient lab in a fasting state for at least eight hours to provide blood samples. Blood samples were drawn from the antecubital vein under strict aseptic conditions for estimating HBC, HTC, platelet count, FBG, postprandial blood glucose, serum levels of insulin, creatinine, aspartate and alanine transaminases (AST and ALT), albumin, and plasma lipid profile.

Radiology investigations:

Radiology plays a pivotal role in the non-invasive evaluation of hepatic steatosis and fibrosis. Advanced imaging techniques provide quantitative and qualitative insights, enabling early detection and monitoring of liver disease.

Ultrasound Imaging:

Hepatorenal Index (HRI): A quantitative tool for grading liver steatosis based on echogenicity, useful in stratifying levels of fat deposition (Fig. 1).

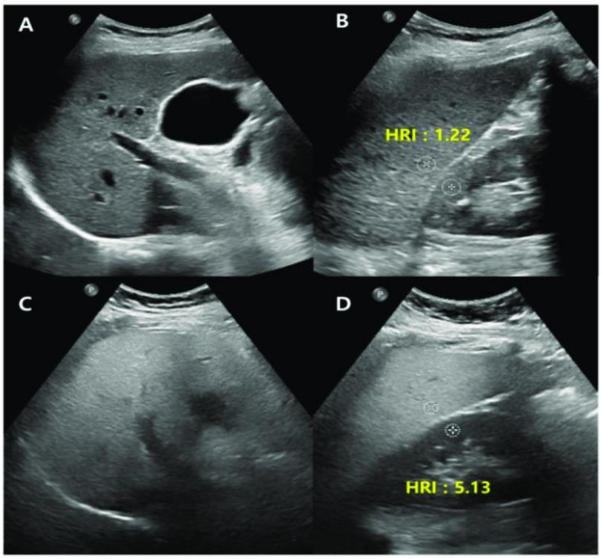

Figure (1): Hepatorenal index (HRI) (B, D) and conventional ultrasound of a healthy liver (A) and severe hepatic steatosis (C). The portal vein, hepatic vein, and liver parenchyma are among the intrahepatic structures that are clearly seen when the hepatic parenchyma echogenicity is normal (A). In a healthy liver, the HRI is 1.22 (35.1/28.8, normal < 1.5) (B). The hepatic vein and portal vein wall echo are not clearly seen in cases of severe hepatic steatosis (C), and the HRI is 5.13 (66.8/13.0) (D).

Elastography: (Figs. 2 and 3)

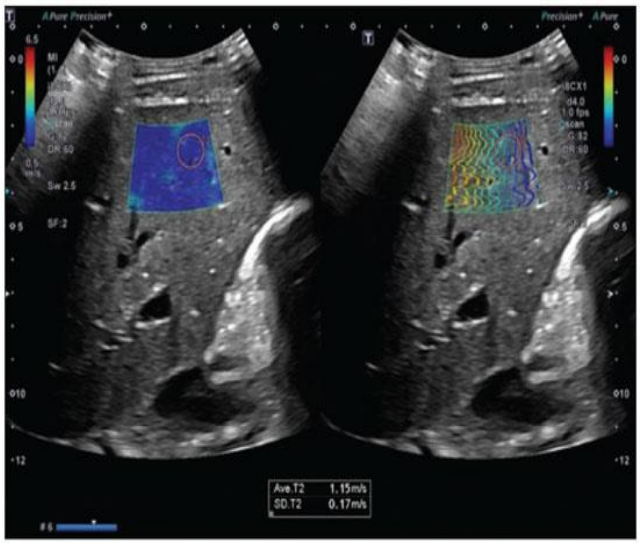

Figure (2): A 2D-SWE examination reveals normal liver parenchyma elasticity (1.15 m/s), corresponding to a stage of F0. The elastography map is uniform and mostly blue, indicating lower stiffness, while the propagation mode (on the right) suggests normal findings.

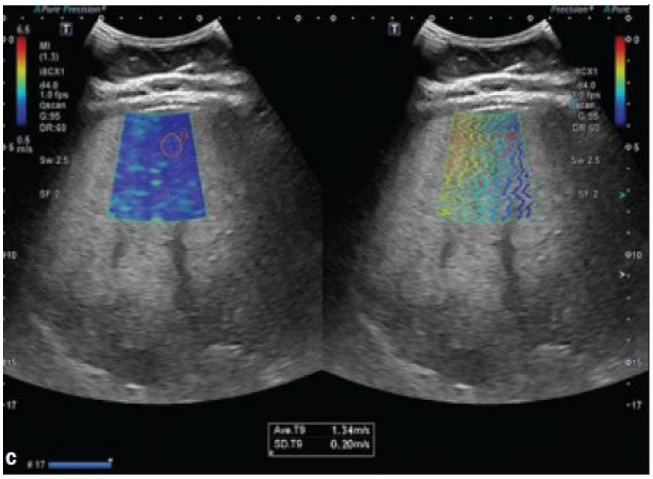

Figure (3): A 2D-SWE examination shows increased parenchymal stiffness, though still within normal ranges (1.34 m/s), corresponding to a stage of F0/F1. While the elastography map is slightly less uniform, it remains mostly blue, indicating lower stiffness, despite the presence of more green areas.

Study outcome:

The study outcome is the relation and predictability of at-enrolment HBC, HTC, and HOMA-IR for the NAFLD scorings; HRI, HIS, and NFS.

Ethical consideration:

The study protocol was approved by the Institutional Review Board at Misr University for Science and Technology (MUST-IRB) with its number 2022/0019. MUST-IRB is registered under the US Department of Health and Human Services' Office for Human Research Protections and operates under Federal Wide Assurance No. FWA00025577. Following receipt of all information, signed consent was provided by each participant. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

In this context, IBM® SPSS® Statistics Version 22 from the year 2015 was utilized in this analysis. For analyzing nonnumeric data, Chi-square test has been implied, whereas numeric data were compared using independent t-test. The steatosis score was implied as its association with HBC, HTC, and HOMA-IR using Pearson's correlation analysis. Regression analysis and the receiver characteristic curve, measured by the area under the curve, which was compared with the area under the reference line (AUC=0.5), were used to determine the predictors for liver fibrosis, defined as F3-4 on NFS. A P value of less than 0.05 was considered statistically significant.

RESULTS

368 patients were assessed for exclusion criteria during the case collecting period; 326 patients were reviewed, and 42 patients were excluded. In 223 individuals (N-HBC group), the baseline HBC was within the normal range; in 103 patients (H-HBC group), it was above the normal range (Fig. 4).

A threshold value of 2.1 for the HOMA-IR score could moderately distinguish patients with grades 3-4 fibrosis (Table 4), further supported by elastography and ultrasound findings.

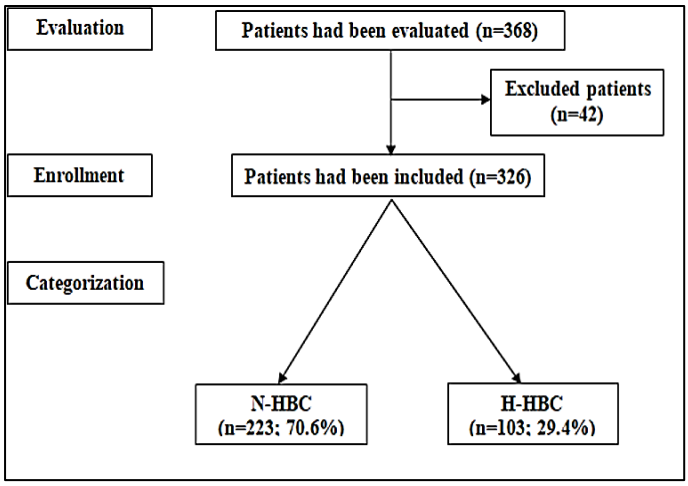

Figure (4): Flow Chart.

Table 1 indicates that patients with H-HBC were more obese than those with N-HBC, with significantly higher BMIs, HBC, and HTC.

Statistical analysis revealed that a high hematocrit value was a strong indicator of increased HRI scores. Additionally, high hemoglobin levels were effective in identifying patients with HSI scores over 36. Elastography-based measures of liver stiffness (using HRI) were also instrumental in detecting a significant number of patients with advanced fibrosis (F3-4), suggesting that these imaging modalities, when combined with hemoglobin and hematocrit values, provide reliable diagnostic data for the severity of liver disease (Tables 1 and 2).

Table (1): Patients' demographic and clinical data and baseline laboratory findings

Data			N-HBC (n=223)	H-HBC (n=103)	P-value
Age (years)			34.9±8.9	34.4±8.8	**0.462**
Gender; M:F			107:116	51:52	**0.797**
Body mass index (kg/m^2)			31.4±3.4	32.7±4.2	**0.004**
Lab findings					
	Fasting blood glucose		90.6±15.2	94.3±20.8	**0.064**
	Postprandial blood glucose		147.6±41.5	156.8±53.2	**0.093**
	Frequency of DM		31 (13.9%)	21 (20.4%)	**0.137**
	Serum insulin		7.9±2.5	8.11±2.8	**0.528**
	HOMA-IR	Score	1.77±0.66	1.95±0.95	**0.866**
		Frequency of IR	42 (18.8%)	25 (24.3%)	**0.259**
	Serum creatinine		0.89±0.14	0.9±0.15	**0.709**
	Serum Aspartate transaminase		15.3±3.6	15.7±3.4	**0.377**
	Serum Alanine transaminase		39.7±8.8	38.9±7.1	**0.458**
	AST/ALT ratio		0.4±0.11	0.43±0.12	**0.079**
	Serum albumin		4.2±0.12	4.19±0.15	**0.077**
	Plasma total cholesterol		198.1±22.6	203.6±25.7	**0.052**
	Plasma high-density lipoprotein		42.8±4.2	42.9±4.8	**0.808**
	Plasma triglycerides		151.4±23.6	149.8±31	**0.628**
	Plasma low-density lipoprotein		185.6±26.6	190.7±29.7	**0.125**
	HBC		14.37±1.28	16.85±1.79	**<0.001**
	HTC		40.3±3.2	44.6±4.3	**<0.001**
	Platelet count		282.6±13.8	282.9±12.3	**0.844**

In 24 and 35 patients, sonographic assessment using the HRI score indicated hepatic steatosis of ≥60 and ≥25, respectively, whereas in 267 individuals, the HRI indicated steatosis of >5%. Patients in the H-HBC group had a substantially higher number of patients with higher HRI values. But there was a non-significant difference between the two groups according to the computed HIS. While 267 patients had intermediate NFS scores and a significantly greater incidence of F3-4 fibrosis grade among H-HBC patients, 59 patients had suspected F3-4 fibrosis grade based on NAFLD fibrosis scoring. Only five patients in the N-HBC group had a score of >2, which is suggestive of F3-4 fibrosis grade, according to the BRAD grading of patients, which revealed an intermediate NFS score (Table 2).

Table (2): Evaluation data of hepatic steatosis status of patients of both groups

Data			N-HBC (n=223)	H-HBC (n=103)	P-value
Hepatorenal index (HRI)					
	>5% steatosis		191 (85.7%)	76 (73.8%)	**0.035**
	>25% steatosis		19 (8.5%)	16 (15.5%)	
	≥60 steatosis		13 (5.8%)	11 (10.7%)	
Hepatic steatosis index (HSI)					
	<36		131 (58.7%)	52 (50.5%)	**0.162**
	≥ 36		92 (41.3%)	51 (49.5%)	
NAFLD fibrosis score (NFS)					
	F0-2 fibrosis grade (NFS <-1.455)		0	0	**0.0228**
	F3-4 fibrosis grade (NFS>0.675)		33 (14.8%)	26 (25.2%)	
	Intermediate score (NFS=-1.455 to 0.675)		190 (85.2%)	77 (74.8%)	
	BRAD score of patients with Intermediate NFS score	≤2	185 (97.4%)	77 (100%)	**0.151**
		>2	5 (2.6%)	0	

HTC had a positive significant relationship with HRI and NFS, while the estimated HBC demonstrated a positive significant association with the three hepatic steatosis indices. Remarkably, there was a substantial positive connection between HOMA-IR and HTC (r=0.132) and HBC (r=0.161). Additionally, there was a strong correlation between NFS and the HOMA-IR score, but not between HRI and HSI scores. High HTC was identified as the important predictor for high-grade steatosis as determined by ultrasonography using the HRI score in both univariate and multivariate regression analysis. Multivariate analysis revealed that high HBC may significantly differentiate patients with an HSI score of >36, even though the univariate analysis found that high HBC, HTC, and HOMA-IR scores might predict high HSI scores. High HOMA-IR score was identified as a significant predictor of high NFS score in both univariate and multivariate regression analysis with regard to the prediction of NFS of grades 3–4 (Table 3).

Table (3): Correlation and Regression analyses for HBC, HTC, and HOMA-IR and hepatic steatosis indices

	HBC		HTC		HOMA-IR score	
Pearson's correlation analysis						
	"r"	**P**	**"r"**	**P**	**"r"**	**P**
Hepatorenal index (HRI)	0.149	0.007	0.179	0.001	0.019	**0.738**
Hepatic steatosis index (HSI)	0.179	0.001	0.106	0.056	0.104	**0.062**
NAFLD fibrosis score (NFS)	0.169	0.002	0.185	0.001	0.479	**<0.001**
Univariate Regression analysis						
	β	**P**	**β**	**P**	**β**	**P**
Hepatorenal index (HRI)	0.047	0.007	0.026	0.001	0.014	**0.738**
Hepatic steatosis index (HSI)	0.411	<0.001	0.112	0.046	0.577	**0.042**
NAFLD fibrosis score (NFS)	0.025	0.738	0.018	0.047	0.031	**0.018**
Multivariate Regression analysis						
	β	**P**	**β**	**P**	**β**	**P**
Hepatorenal index (HRI)	0.022	0.303	0.020	0.038	-	-
Hepatic steatosis index (HSI)	0.400	0.001	0.003	0.965	0.501	**0.053**
NAFLD fibrosis score (NFS)	-	-	0.015	0.249	0.012	0.021

As per table 4 and figure 5, the ROC curve analysis for HBC, HTC, and HOMA-IR as predictors of the presence of high fibrosis grade revealed that the score of HOMA-IR at a cutoff point of 2.1 can discriminate patients with fibrosis grade 3-4 with moderate accuracy (74.8%), high negative predictive value (92.3%), and AUC was 0.769.

Table (4): ROC curve analysis of HBC, HTC, and HOMA-IR as predictors for high-grade hepatic fibrosis (NFS grade 3-4)

	AUC	95% CI	Cut off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
HBC	0.591	0.508-0.675	15.65	50	64.3	27.0	83.0	61.3
HTC	0.614	0.541-0.688	41.5	57.4	55.4	25.3	83.1	55.8
HOMA-IR	0.769	0.691-0.846	2.1	76.5	74.4	44.1	92.3	74.8

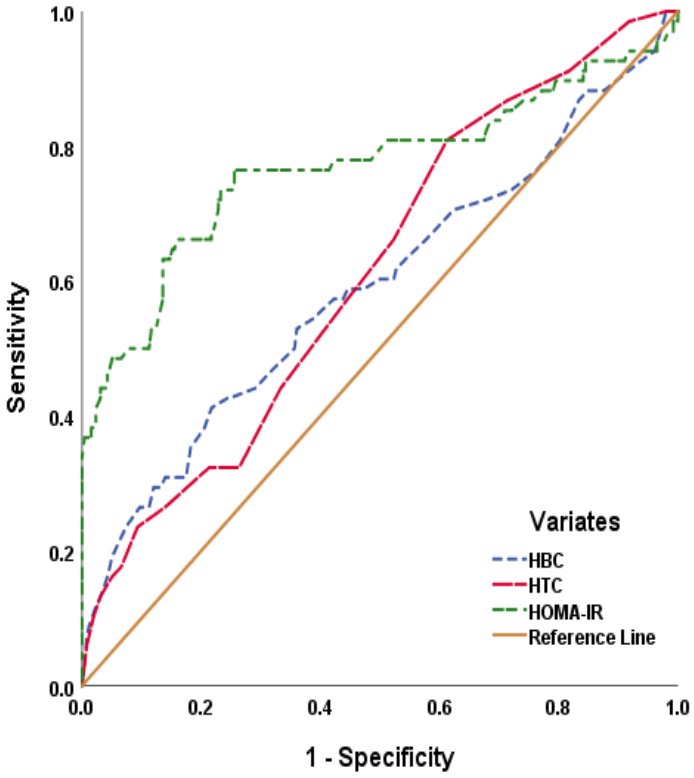

Figure (5): ROC curve analysis of at-admission HBC, HTC, and HOMA-IR as a predictor for F3-4 grade.

Imaging Modality	Findings
Ultrasound	Hepatic steatosis was assessed based on liver texture and size. Steatosis was observed in the H-HBC group with significantly higher incidence compared to the N-HBC group.
Elastography (HRI)	HRI scores were significantly higher in the H-HBC group, suggesting more severe hepatic steatosis and potential fibrosis. Higher HRI values correlated with increased liver stiffness.

DISCUSSION

The prevalence of H-HBC and hepatic steatosis, as measured by HRI and HIS, was approximately 31.6% in this single-institution study. Among the patients studied, high HRI (>25 steatosis) and elevated HIS (>36) were estimated at an approximate prevalence of 18.1% and 43.9%, respectively. High HRI and HIS values coexisted with high HBC in 27 and 51 cases, respectively.

The regression analysis showed that H-HBC was a significant positive predictor of high HSI score whereas correlation analysis showed that there was a strong positive relation between hepatic steatosis and HBC. Increased HTC, caused by increased hemoglobin in the

red blood cells, was a positive predictor of high values of both HRI and NFS scores.

The established association between high HBC and HTC with liver steatosis, as reported by studies [22,23], confirmed previous studies that people with high levels of HBC and HTC are susceptible to liver dysfunction and may be an indicator of NAFLD. Moreover, the results are consistent with previous studies on children with NASH, who had already been found to be associated with increased hematocrit, HBC, and RBC[24]. Recently, in a study among youth with type-2 diabetes and NAFLD, an association between H-HBC and NAFLD was established. The odds ratio for NAFLD increased substantially with increased HBC when adjusted for BMI and sex[25].

According to the literature, obesity and diabetes were linked to higher levels of insulin resistance, as measured by the HOMA-IR index[26,27]. Of the patients in the study, 52 had insulin-resistant (IR) diabetes, 67 were IR non-diabetic, and all were overweight or obese. This study found a substantial positive association between the HOMA-IR score and HBC and HTC. In a similar vein, a recent study that followed a large number of middle-aged and older participants for three years found that high HBC was positively connected with HOMA-IR and associated with higher incidence and odds ratios for the development of NAFLD and the metabolic syndrome[28]. After that, a different investigation found that in young, healthy volunteers, HOMA-IR significantly correlated with BMI, lipid parameters, HCT, and HBC[29].

This study illustrates the utility of combining traditional lab tests, such as hemoglobin concentration and hematocrit value, with imaging modalities like ultrasound and elastography to assess liver health in patients with NAFLD. The ultrasound technique was essential for evaluating hepatic steatosis through liver texture analysis and echogenicity patterns, while elastography provided a quantitative measure of liver stiffness, which correlates with the degree of fibrosis. The significant relationship between high hemoglobin levels and increased HRI and NFS scores demonstrates the potential of using elastography as a diagnostic tool for NAFLD and fibrosis in patients with high hemoglobin concentrations.

According to statistical analyses, higher fibrosis grades were positively connected with higher HTC and HOMA-IR scores. HCT may be a potential predictor of fibrosis in pediatric and adult NASH [30]. This finding confirmed the previously reported HTC value was strongly and independently associated with hepatic fibrosis and correlates with its severity[31]. An RBC count of one unit was linked to a 53% higher risk of NAFLD progression, according to a recent study that found a favourable correlation between RBC count and incident NAFLD risk[32].

Patients with fibrosis grade 3–4 may be distinguished with moderate accuracy and high negative predictive value using the test validity of the specified HOMA-IR score at cutoff point 2.1. In keeping with this, earlier research discovered that elevated fasting insulin levels could forecast the degree of hepatic fibrosis prior to the onset of type 2 diabetes[33]. Another study concluded that IR might be regarded as a predictor of the histological severity of liver disease after finding that HOMA-IR and high insulin levels were significantly correlated with the grade of hepatic steatosis and fibrosis[34].

This trio of factors—obesity, IR, and hepatic steatosis—may explain the observed outcomes by contributing to the development of diabetes, steatosis, and IR, as well as obesity-related fat cell enlargement and low-grade inflammatory status of adipose tissue and the release of inflammatory mediators[35]. However, the reported incidence of NAFLD in lean patients and its increase in two cohorts in 2020, suggest that obesity may not be the main cause for the development of hepatic steatosis. Furthermore, as demonstrated by the previously found significant increases in HBC, HTC, and mean corpuscular hemoglobin concentration in NAFLD patients with BMI <25 compared to non-NAFLD subjects with BMI >25, obesity was unable to explain the relationship between steatosis and these parameters[35].

The previously reported relationship between elevated hepatocyte hemoglobin and iron's subsequent altering effect on hepatocyte insulin receptor expression, as well as the resulting increased oxidative stress from elevated iron, may prevent insulin internalisation and function, resulting in hyperinsulinemia and IR[35].

However, because sphingosine-1-phosphate (S1P) is released more readily from red blood cells (RBCs), which are already elevated and one of the primary sources of S1P, the association between H-HBC and steatosis may be secondary. In a Ca^{2+}-dependent mechanism that caused hepatic inflammation and steatosis, S1P was shown to activate the NLRP3 inflammasome and increase the expression levels of S1P-receptor 4 in hepatic macrophages[33].

According to a different experimental study, inflammation causes the hepatic bile acid transporters to be downregulated, which slows the enterohepatic circulation and raises the levels of conjugated bile acids in the liver. This activates the pro-inflammatory and fibrosis pathways, as well as S1P-receptor 2, which accelerates the progression of NASH[34]. In support of the role of S1P in the induction and progression of hepatic steatosis, in a cohort of NASH patients, expression of S1P-receptor 4 was found to be 6-fold higher than healthy controls[35].

CONCLUSION

Regardless of the existence of diabetes, high HBC may cause the onset or advancement of hepatic steatosis, particularly if it is linked to IR. The occurrence of hepatic steatosis and/or fibrosis may be predicted by the measurement of HBC and HTC, which

are straightforward normal laboratory tests. Patients with high-grade liver fibrosis can be moderately accurately identified by a high HOMA-IR score.

RECOMMENDATIONS

Even in thin patients, the development of hepatic steatosis can be prevented by using iron preparation sparingly. To determine the predictive validity of the recommended cutoff thresholds for HBC and HOMA-IR scores for hepatic steatosis status, larger-scale research is needed.

LIMITATIONS

The results obtained are limited to overweight subjects due to the absence of average and underweight subjects. Additionally, individuals who continued receiving iron supplements need to be assessed.

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No conflict of interest.

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