Zagazig University Medical Journal
www.zumj.journals.ekb.eg

Manuscript ID ZUMJ-2201-2450
DOI **10.21608/zumj.2022.114058.2450**

Volume 28, Issue 3, May 2022, Page 612 -621

ORGINAL ARTICLE

Signature of Visfatin mRNA Expression and its Serum Level in Correlation with Risk and Severity of Non-Alcoholic Fatty Liver Disease among Obese Patients

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Submit Date 2022-01-05
Revise Date 2022-01-20
Accept Date 2022-02-01

ABSTRACT

Background*:* Nonalcoholic fatty liver disease (NAFLD) has grown at an alarming rate with the rapid growth of obesity worldwide. the underlying pathological mechanism of NAFLD has not been completely explained. Visfatin is an adipocytokine that affects metabolic regulation in the body. We aimed in the current study to examine serum and relative expression level of visfatin in obese patients with NAFLD and to determine its correlation with the susceptibility and progression of NAFLD.

Methods*:* case-control study enrolled 40 obese patients had with biopsy-proven NAFLD and forty-five healthy volunteers. The enrolled cases were divided into three groups: simple steatosis (n=19), NASH (n= 13), and cirrhosis (n=8). We investigated serum visfatin by ELISA and the relative expression level of visfatin was investigated by RT-PCR

Results: Our results revealed that values of serum visfatin were significantly ($p<0.001$) higher in obese patients with NAFLD than in control subjects. Among NAFLD patients, the highest levels of serum visfatin and its relative expression were in the cirrhosis group (59.6±23.5,2.4±0.81, respectively), NASH (52.37±18.14,2.01±0.66, respectively,), simple steatosis (43.9±9.81, 1.7±0.6, respectively) compared to the control group (14.76±2.51and0.75±0.17, respectively), $p<0.05$. We detected significant positive correlations between obesity indices, metabolic parameters, and liver enzymes among patients with NAFLD. Linear regression test showed that BMI (odds ratio 0.414, C.I. 0.313-1.672), and waist/hip ratio (odds ratio 0.352, C.I. 0.010-0.066), were the main predictors of serum levels of visfatin in NAFLD. Regards expression levels of visfatin in NAFLD, BMI (odds ratio 0.440, C.I. 013.082-41.593), and waist/hip ratio (odds ratio 0.403, C.I. 0.530-1.724), were the main predictors.

Conclusion: Serum visfatin and its mRNA values are increased in NAFLD obese patients compared to controls. There are also higher levels of both markers in the cirrhosis subgroup compared to other groups.

Keywords: NAFLD; cirrhosis; visfatin; relative expression; obesity

INTRODUCTION

There is uprising evidence that the commonest worldwide chronic liver disease is NAFLD due to increasing obesity prevalence and control of viral hepatitis [1]. The prevalence of NAFLD is about 20–30% of adults in developed nations and 25% in Asian populations [2]. There is a lot of indicators emphasizing that both obesity and insulin resistance are meticulously linked with NAFLD development [3]. NAFLD is believed to be a significant risk predictor for different diseases like hepatic (both fibrosis, and

cirrhosis) and cardiovascular diseases, and also non-insulin-dependent diabetes mellitus [4].

NAFLD comprises a variety of diseases including, nonalcoholic steatohepatitis (NASH), which can evolute into cirrhosis and hepatocellular carcinoma (HCC). It also includes simple steatosis, which is characterized by having a more benign course [5]. NASH prevalence is expected to increase by about 56% through the period from 2016 and 2030 in numerous countries worldwide [6].

Obesity and insulin resistance are linked with chronic inflammation, dyslipidemia, and hypercoagulable state [7]. Interesting studies have suggested altering the terminology from NAFLD to metabolic associated fatty liver disease, however, the molecular origin of NAFLD is still blurred [8].

It may be assumed that adipose tissue, which is considered an endocrine organ that secretes adipokines, has the main role in metabolic homeostasis [9]. Adipokines, are polypeptides with biological activities. Some of them are hormones, whereas others are inflammatory and immune-related cytokines. These cytokines provide the molecular link between obesity and different related diseases [10]. Prior studies specified that numerous adipokines as leptin, visfatin, fetuin-A, and adiponectin are strongly linked with the development of obesity, type 2 diabetes, metabolic syndrome (MetS), and NAFLD [11].

Visfatin was detected in visceral fat depots. It parallels a protein formerly recognized as a pre-β-cell colony-enhancing factor (PBEF), that is produced in all of the adipose tissue, skeletal muscle, bone marrow, liver, and lymphocytes [12]. Visfatin owes insulin-like metabolic properties in numerous rodent models of in vivo insulin resistance and obesity. There is growing evidence that visfatin mediates its metabolic effects by attaching to and stimulating the insulin receptor [13].

There is little and controversial data regarding the associations between both serum and visfatin gene expression and NAFLD. To our knowledge, this study is the first Egyptian one that investigates the associations of visfatin gene expression with the risk and severity of NAFLD obese patients. The study aimed to investigate the relationship between serum visfatin and its relative expression levels with the risk of NAFLD in Egyptian obese adults.

SUBJECTS AND METHODS

The present study included 40 obese patients with NAFLD and 45 age-matched healthy individuals. NAFLD cases were selected according to ultrasonographic results by an expert according to the standard criteria of the American Gastroenterology Association [14]. All included patients underwent confirmatory liver biopsy after written consent was obtained. Then NAFLD patients were divided into three groups: simple steatosis (n=19), NASH (n= 13), and cirrhosis (n=8). All patients were subjected to thorough history taking, full clinical assessment, and anthropometric measures of obesity. A Dual-energy X-ray absorptiometry (DEXA) scan was done for assessment of fat mass index (FMI) and fat-free mass index (FFMI). Study design, inclusion, and exclusion criteria are shown in figure 1. All enrollment subjects have given their written informed consent. The current study was approved by the committees of Ethics Faculties of **Medicine, Zagazig University (IRB #9206-19-1-2022)**. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Routine laboratory investigations including fasting plasma glucose (FPG), fasting lipid profile (TC, LDL, HDL, and TG, as well as ALT and AST were measured by Cobas 8000, Roche diagnostics, Germany. While Hba1c was measured by Cobas 6000, Roche diagnostics. Exclusion of other causes of liver diseases was done through investigation of serum alpha-fetoprotein (AFP) levels and viral markers including hepatitis B surface antigen (HBsAg) and HCV antibodies (HCV-Ab were measured by Cobas 8000. Serum visfatin was measured using an enzyme-linked immunosorbent assay kit (USCN Life Science Inc., Wuhan, China), with a lower limit of sensitivity of 0.78 ng/ml (range: 3.12–200 ng/ml). The interassay and

https://dx.doi.org/10.21608/zumj.2022.114058.2450
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intra-assay coefficients of variation were less than 14 and less than 5%, respectively

GENE EXPRESSION ANALYSIS

The RNA was extracted from EDTA peripheral blood samples, according to the company's instructions. The clarity of the extracted RNA was evaluated using a NanoDrop spectrophotometer. The RNA was reverse transcribed into cDNA by SCRIPT Reverse Transcriptase Kit (Jena Bioscience, Germany) using Oligo-(dT) primers. The mRNA expression of visfatin was investigated by Real-time PCR using Roche light cycler system (Roche Molecular Biochemical, Mannheim, Germany). We used the following visfatin primer: sense, 5′-AAGAGA CTGCTGGCATAG GA-3′, and antisense, 5′- ACCACAGATACAG GCACTGA-3′ and beta-actin 5 were used as reference. The relative visfatin mRNA expression was calculated by the $\Delta\Delta C_T$ technique.

2.5. Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 23 (Armonk, NY, USA, IBM Corp). Data were expressed as mean ± standard deviation (SD)and analyzed an independent t-test or one-way analysis of variance (ANOVA). In the current study, we evaluated our results by Pearson and linear correlations and the power of diagnostic markers, serum and relative visfatin mRNA expression by ROC analysis for all statistical calculations, P < 0.05 was considered statistically significant.

3. RESULTS

In the current study, we evaluated the clinical, anthropometric, and laboratory results of all enrolled subjects, case (n=40) and control group(n=45). NAFLD patients were significantly metabolic dysfunction compared to the healthy age-matched control group as shown in table 1, P <0.001*.

CHARACTERISTICS OF NAFLD SUBGROUPS

We found statistically significant differences between studied groups regards, systolic blood pressure, obesity indices, and dyslipidemia profile as well as FPG, ALT, and AST, as demonstrated in table 2, P <0.001*.

Serum and relative visfatin mRNA expression in studied patients.

Our results revealed that there was a significant difference between studied groups as regard serum visfatin and its relative expression level and the highest level in cirrhosis 59.6±23.5, 2.4±0.81, respectively), NASH (52.37±18.14,2.01±0.66, respectively), simple steatosis(43.9±9.81, 1.7±0.6, respectively) compared to control group (14.76±2.51and 0.75±0.17 , respectively). P <0.001*, figure 2. the p-value of post hoc analysis was p<0.001 between all groups except (simple steatosis and NASH, p=0.038 as well as NASH and cirrhosis=0.146) regards serum visfatin. Regards visfatin relative expression levels, the p-value was p<0.001 except (simple steatosis and NASH,p=0.211 as well as NASH and cirrhosis=0.120)

Pearson Association of serum and relative visfatin mRNA expression in obese NAFLD patients

There were significant positive correlations between serum and relative visfatin mRNA expression levels and obesity indices as well as metabolic dysfunction parameters and liver enzyme, P <0.001*, (Table 3).

Linear regression test in NAFLD groups

We further studied our results by linear regression test. We included all significant correlators with the studied marker. Interestingly, we found among studied parameters,BMI and waist/hip ratio were the main predictors of serum and relative visfatin mRNA expression among other studied parameters, as presented in table 4, P <0.001*. The main predictors of serum levels of visfatin in NAFLD were BMI (odds ratio 0.414, C.I. 0.313-1.672), and waist/hip ratio (odds ratio 0.352, C.I. 0.010-0.066), were. Regards expression levels of visfatin in NAFLD, BMI (odds ratio 0.440, C.I. 013.082-41.593), and waist/hip ratio (odds ratio 0.403, C.I. 0.530-1.724), were the main predictors.

The diagnostic power of circulating serum and relative visfatin mRNA expression for identification of NAFLD by ROC analysis

We investigated our findings to assess the power of serum visfatin, the AUC was

https://dx.doi.org/10.21608/zumj.2022.114058.2450
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0.863 (95% CI = 0.769–0.957) with sensitivity = 87.5.%, specificity = 94.5%, and the cutoff values (21.3), (Fig. 3a). regards the relative visfatin mRNA,the AUC was 0.923 (95% CI = 0.786 –0.978) with sensitivity = 77.5.%, specificity = 87.7%, and the cutoff values (1.3), (Fig. 3a)

The accuracy of serum and relative visfatin mRNA expression for differentiating NASH from simple steatosis

We studied the power of serum visfatin for differentiating NASH from simple steatosis, the AUC was 0.756 (95% CI = 0.606–0.908) with sensitivity = 75%, specificity 70%, and the cutoff values (40.3), (Fig. 3b). regards the relative visfatin mRNA, the AUC was 0.646 (95% CI = 0.477–0.836) with sensitivity = 75.5.%, specificity = 83.7%, and the cutoff values (1.9), (Fig. 3b)

The accuracy of serum and relative visfatin mRNA expression for differentiating cirrhosis from NASH

We further investigated power of serum visfatin in diagnose NAFLD the AUC was 0.570 (95% CI = 0.386–0.574) with sensitivity = 60.5.%, specificity = 68.5%, and the cutoff values (36.3), (Fig. 3c). Regards relative visfatin mRNA,the AUC was 0.656 (95% CI = 0.476–0.837) with sensitivity = 67.5.%, specificity = 85.7%, and the cutoff values (1.34), (Fig. 3c)

Table 1: clinical, anthropometric and laboratory characteristics of studied groups.

Variables	Normal group (mean ± SD) (n=45)	NAFLD (mean ± SD) (n=40)	P
Age (years)	41.04± 6.37	41.42±6.91	0.789
Female, n (%)	34(75.5%)	31(77.5%)	0.519
Systolic blood pressure (mm Hg)	123.3± 3.07	131.3± 13.1	<0.001*
Diastolic blood pressure (mm Hg)	87.1±6.96	88.9±7.30	0.06
Body mass index (kg/m2)	23.6±2.940	36.3±3.126	<0.001*
Waist/hip ratio	0.82±0.194	1.3±0.26	<0.001*
FMI (kg/m2)	4.6±0.625	7.9±0.98	<0.001*
FFMI (kg/m2)	18.6±2.50	28.14± 3.95	<0.001*
Total cholesterol (mg/dL)	140.3± 26.54	176.6± 56.48	<0.001*
Triglycerides (mg/dL)	132.6± 12.51	149.6± 32.01	<0.001*
LDL cholesterol (mg/dL)	122.9± 22.9	156.2± 44.79	<0.001*
HDL cholesterol (mg/dL)	53.1±6.67	40.9±6.775	<0.001*
Fasting plasma glucose (mg/dL)	87.9±7.97	156.1± 51.1	<0.001*
AST(IU/L)	33.3±3.126	65.5±20.6	<0.001*
ALT (IU/L)	33.06± 2.5	84.5±20.67	<0.001*

FMI, fat mass index; FFMI, fat free mass index; AST; aspartate aminotransferase, ALT; alanine aminotransferase *P < 0.05 .

Table 2: clinical, anthropometric and laboratory characteristics of NAFLD groups.

Variables	Simple steatosis N=19	NASH N=13	Cirrhosis N=8	
Systolic blood pressure (mm Hg)	123.9± 15.5	147.1± 10.4	128.5± 3.37	<0.01*
Diastolic blood pressure (mm Hg)	85.1±8.31	95.6±6.17	87.1 ±5.16	0.765
Body mass index (kg/m2)	34.5±2.33	38.06±5.98	36.6±4.71	<0.01*
Waist/hip ratio	1.26±0.21	1.5±0.18	1.6±0.14	<0.01*
FMI (kg/m2)	6.8±1.26	7.61±0.59	7.52±034	<0.01*
FFMI (kg/m2)	27.01±5.06	30.4±2.38	29.9±1.36	<0.01*
Total cholesterol (mg/dL)	176.4±61.9	164.4±22.89	216.1±16.5	<0.01*
Triglycerides (mg/dL)	132.5±38.2	190.1±20.7	160. ±12.9	<0.01*
LDL cholesterol (mg/dL)	160.4±53.8	130.9±19.91	181.9±14.3	<0.01*

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Variables	Simple steatosis N=19	NASH N=13	Cirrhosis N=8	
HDL cholesterol (mg/dL)	40.4±4.299	44.6±6.178	35.6±8.08	<0.01*
Fasting plasma glucose (mg/dL)	126.9±11.9	187.4±19.89	197.1±52.5	<0.01*
AST(IU/L)	23.6±14.13	76.2 ±24.4	52.9±26.3	<0.01*
ALT (IU/L)	29.4±12.7	87.6±23.3	64.3±28.2	<0.01*

FMI, fat mass index; FFMI, fat free mass index; , AST; aspartate aminotransferase, ALT; alanine aminotransferase GGTP, gamma-glutamyl transpeptidase ,*P < 0.05.

Table 3: Pearson correlation of serum visfatin (ng/ml) and its mRNA expression with clinical, anthropometric, and biochemical characteristics in NAFLD groups.

Variables	Serum visfatin		Visfatin mRNA expression	
	r	p	r	p
Body mass index (kg/m2)	0.633	<0.001*	0.728	<0.001*
Waist/hip ratio	0.665	<0.001*	0.605	<0.001*
FMI (kg/m2)	0.610	<0.001*	0.610	<0.001*
FFMI (kg/m2)	0.343	<0.001*	0 .512	<0.001*
Total cholesterol (mg/dL)	0.514	<0.001*	0.424	<0.001*
Triglycerides (mg/dL)	0.492	<0.001*	0.692	<0.001*
LDL cholesterol (mg/dL)	0.387	<0.001*	0.527	<0.001*
HDL cholesterol (mg/dL)	-0.108	0.125	-0.068	0.095
Fasting plasma glucose (mg/dL)	0.591	<0.001*	0.331	<0.001*
AST(IU/L)	0.435	<0.001*	0.627	<0.001*
ALT (IU/L)	0.443	<0.001*	0.479	<0.001*

FMI, fat mass index; FFMI, fat free mass index; AST; aspartate aminotransferase, ALT; alanine aminotransferase; *P < 0.05

Table 4: linear regression analyses in NAFLD women to test the influence of the main independent variables against serum visfatin (ng/ml) and its mRNA expression (dependent variable) in NAFLD patients

Model		Unstandardized Coefficients		Standardized Coefficients	t	P value	95% C.I.	
		B	Std. Error	Beta			Lower Bound	Upper Bound
serum visfatin	Constant	-1.008	0.286		-3.524	<0.001*	-1.577	-.439
	BMI	0.993	00.341	0.414	2.907	<0.001*	0.313	1.672
	Waist/hip ratio	0.038	0.014	0.352	2.656	<0.001*	0.010	0.066
	FMI	0.001	0.001	0.039	0.497	0.621	-0.002	.003
	TC	0.001	0.003	0.022	0.169	0.866	-0.006	0.007
	ALT	0.002	0.005	0.044	0.314	0.754	-0.008	0.011
	Constant	-30.251	6.000		-5.042	<0.001*	-42.193	-18.308
	BMI	27.337	7.162	0.440	3.817	<0.001*	13.082	41.593
visfatin	Waist/hip ratio	1.127	0.300	0.403	3.756	<0.001*	0.530	1.724
mRNA expression	FMI	-0.031	.029	-0.070	-1.094	.277	-00.089	.026
	TC	0-.016	0.073	-0.024	-0.224	0.823	-0.161	0.128
	ALT	.131	.102	.143	1.276	0.206	-0.073	0.335

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FMI, fat mass index; FFMI, fat free mass index; AST; aspartate aminotransferase, ALT; alanine aminotransferase; *P < 0.05

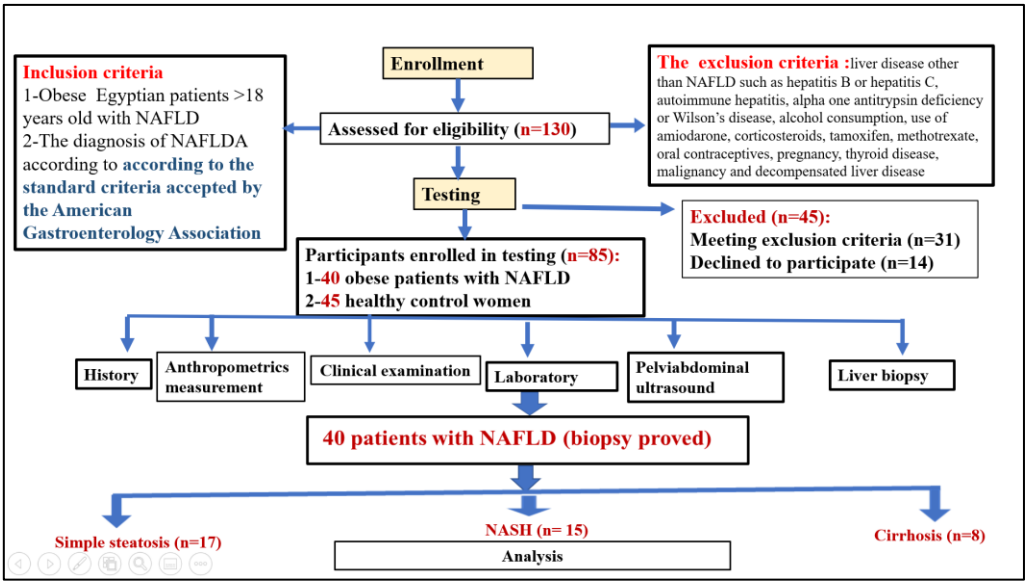

Figure (1): Flowchart of the study

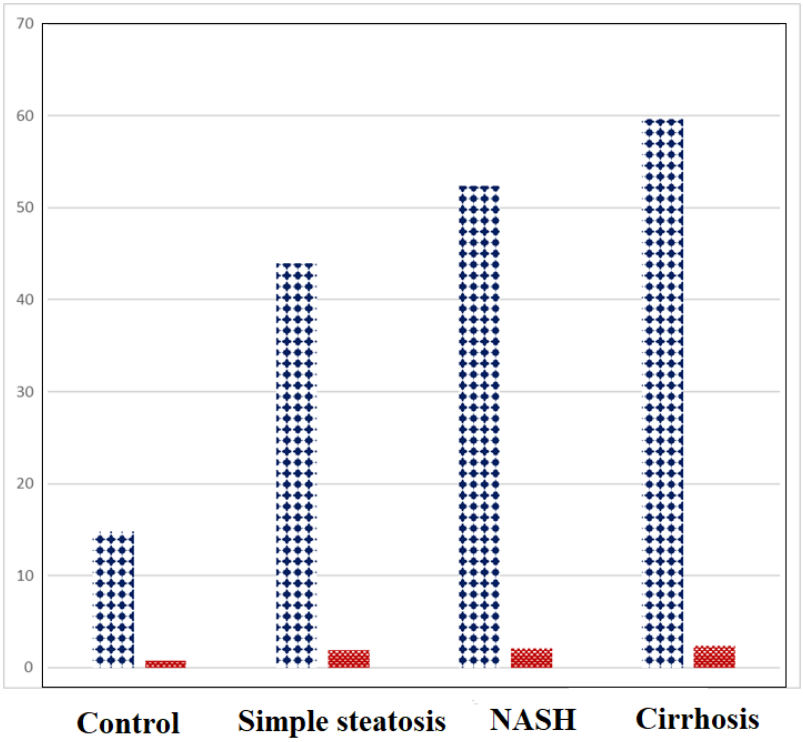

Figure (2): Comparison between serum visfatin and its mRNA expression level

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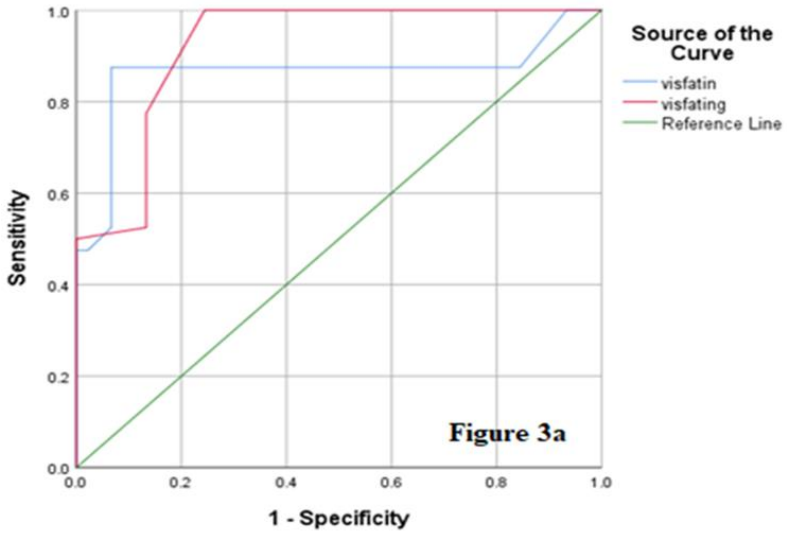

Fig.3a :Receiver operating characteristic curve of serum visfatin and its relative expression for diagnosis of NAFLD.

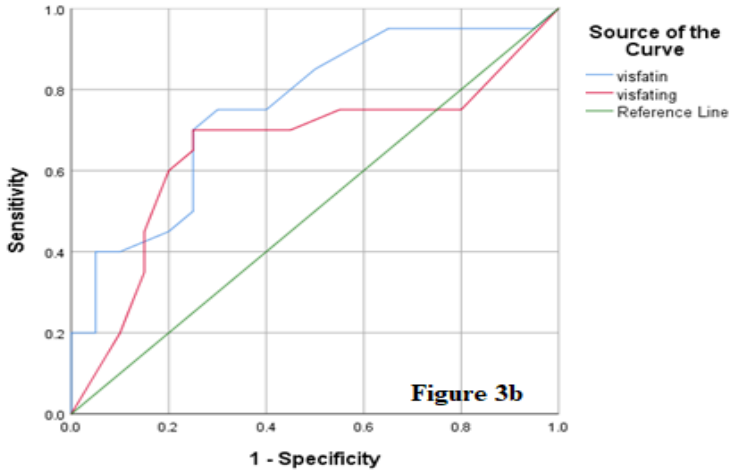

Fig.3b :Receiver operating characteristic curve of serum visfatin and its relative expression for differentiate NASH from simple steatosis

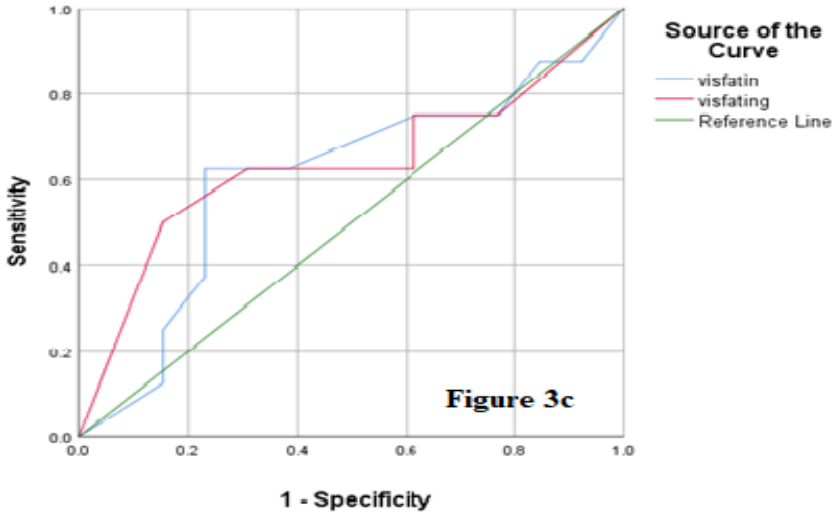

Fig.3c :Receiver operating characteristic curve of serum visfatin and its relative expression for differentiate cirrhosis from NASH.

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DISCUSSION

NAFLD has currently deemed the most common liver disease in developed countries [15]. Substantial evidence implicates that the prevalence of NAFLD worldwide is varying according to ethnicity [16], as genetic and epigenetic dysregulation influence the pathological and clinical features of NAFLD. The prevalence of NAFLD has grown at an alarming rate with the rapid growth of obesity worldwide and the underlying pathological mechanism of NAFLD has not been completely explained [17].

Accumulating studies have reported that visfatin is a complex protein, as it has endocrine, autocrine, and paracrine functions thus regulating many metabolic functions in the body functions [18]. Moreover, emerging data have demonstrated that higher serum levels of visfatin are associated with inflammation and endothelial dysfunction. There is compelling evidence suggesting visfatin is expressed in many cells all over the body, adipocytes, immune cells, hepatocytes, myoblasts [19].

This study aimed to investigate the associations of visfatin and its mRNA with susceptibility and progression of NAFLD in Egyptian obese adults.

In the current research, we investigated 40 NAFLD patients proved biopsy and age, sex-matched 45 health control as expected, our results revealed that obesity indices, metabolic parameters, and liver enzymes were significantly high in NAFLD compared to control.

Similar results were confirmed in Farrell et al study, they detected that obesity, T2DM, and dyslipidemia are the best-known risk factors of NAFLD [20]. According to the current study results, in the cirrhosis subgroup, the mean age of this group was significantly higher than other studied subgroups. Similar Petersen et al observed a higher prevalence of liver cirrhosis in the elderly and they explained their findings by increasing Mitochondrial dysfunction in the elderly which could contribute to this finding [21].

The most important findings in the current research are that visfatin and its mRNA values were higher in NAFLD compared to control. Among NAFLD, patients with cirrhosis had the highest serum and relative visfatin mRNA expression compared to other studied groups. Even more importantly, regards the association of serum and relative visfatin mRNA expression with metabolic parameters, obesity indices as well as liver function in NAFLD. We detected significant positive correlations between them and body composition parameters; BMI, waist/hip ratio, FMI% and FFMI% as well as TG, LDL, and FPG, Regarding HDL, we detected significant negative correlations with serum and relative visfatin mRNA expression levels. We further investigated our results by regression test to determine the main predictors of visfatin and its mRNA levels and we found BMI and waist/hip ratio were the main interpreters.

Regarding metabolic diseases, debated results about visfatin levels have been detected. Some studies observed a high level of visfatin in obesity and its related metabolic dysfunction [22]. Against our results, few studies detected lower values of visfatin in metabolic dysfunction patients compared to healthy controls [23-25]. The controversy results between ours and the others could be due to significant differences in BMI as our study included more obese patients compared to other studies.

Regards NAFLD, research conducted by Jarrar et al detected similar results. However, they detected that visfatin levels decreased in the NASH group [26]. Additionally, Aller and his colleagues investigated the impact of visfatin on the progression of NAFLD and they found that serum visfatin level was not related to steatosis grade or severity [27]. Another study published by Halil et al detected non-significant associations between visfatin and hepatic as well as systemic inflammatory markers [28]. Against our results, Dahl, et al. observed that visfatin expression in the liver was markedly decreased in patients with

NAFLD, [29]. The difference between our results and these studies could be due to significant differences in BMI as our study enrolled more obese patients compared to other studies.

Even more importantly, we in this study attempted to pierce out the value of serum visfatin levels as diagnostic markers of NAFLD by ROC the sensitivity was 87.5% and the specificity was 94.5%. Considering NASH, the sensitivity was 75 % and the specificity was 70%. While the sensitivity was 60.5% was and the specificity was 68.5% for differentiating cirrhosis from NASH.

Regards relative mRNA expression of visfatin diagnostic value power, for diagnosis of NAFLD, the sensitivity was 77.5% and the specificity was 87.5%. Considering NASH, the sensitivity was 60.5 % and the specificity was 68.5%. While the sensitivity 67.5% was and the specificity was 85.7% for differentiating cirrhosis from NASH.

In conclusion, obese patients with NAFLD had higher values of serum and relative mRNA expression of visfatin than the control group; Moreover, among NAFLD groups, the highest values were observed in patients with cirrhosis. Additionally, they positively associated with obesity indices and metabolic parameters The diagnostic power of a serum and relative mRNA expression of visfatin were highly significant; thus, it could be a useful noninvasive diagnostic and prognostic biomarkers of NAFLD

Limitation: Some limitations should be considered. the small sample size of the study. Few studied genetic and serum markers. Thus, further future studies with alarger sample size and investigations of many serum, genetic and epigenetic markers will be done

Conflict of interest No conflict of interest.

Acknowledgments: The authors thank doctors of pathology and radiodiagnosis departments, faculty of medicine, Zagazig University for their efforts and help in this research.

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To Cite:
Rashad, N., Khalil, U., Sharafeddin, M., Hussien, M., Ibrahim, M., Sherif, M. Signature of Visfatin mRNA Expression and its Serum Level in Correlation with susceptibility and progression of Non-Alcoholic Fatty Liver Disease among Obese Patients. *Zagazig University Medical Journal*, 2022; (612 -621): -. doi: 10.21608/zumj.2022.114058.2450