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ORIGINAL ARTICLE

Mac-2-Binding Protein Glycosylation Isomer as a Biomarker of Non Alcoholic Fatty Liver Disease in Type 2 Diabetic Patients

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ABSTRACT:

Background: The rising incidence of diabetes also contributes to the rise in nonalcoholic fatty liver disease (NAFLD). There is mounting evidence that the levels of the serum Mac-2-binding protein glycosylation isomer (M2BPGi) reflect the build-up of fat in the liver. This study assessed the clinical utility of blood M2BPGi levels in patients with type 2 diabetes who also had non-alcoholic fatty liver disease (NAFLD). Methods: This case-control study included 23 subjects who serve as apparently healthy control, 23 type 2 diabetic patients without NAFLD, and 23 type 2 diabetic patients with NAFLD. Fatty liver was diagnosed by abdominal ultrasound scan. Serum M2BPGi level was determined by ELISA. Results: M2BPGi was significantly higher in diabetic group without NAFLD when compared to controls and in diabetic group with NAFLD when compared to diabetic patients without NAFLD and controls. A significant positive correlation was detected between M2BPGi and ALT, HbA1c, FLI score and ACR in diabetic patients with NAFLD. M2BPGi showed an area under the curve (AUC) of 0.886, 86.9% sensitivity, and 78.2% specificity for diagnosing of NAFLD in diabetic patients, according to receiver operating characteristic (ROC) curve analysis. In combination with FLI, the sensitivity was 95.8% and specificity was 100%. Conclusions: M2BPGi might act as a non-invasive marker for nonalcoholic fatty liver either alone or in combination with FLI. Also, it was correlated with steatosis grades and associated with microalbuminuria.

Keywords: Type 2 diabetes mellitus, Non-alcoholic fatty liver disease, Mac-2- binding protein glycosylation isomer

INTRODUCTION

The most common form of chronic liver disease worldwide and the primary cause of liver-related death and morbidity is non-alcoholic fatty liver disease (NAFLD) [1]. Patients are more likely to have poor outcomes since the condition can develop to substantial liver damage such as cirrhosis, fibrosis, hepatocellular carcinoma, and death [2].

With prevalence estimates increasing from about 25% in the early 2000s to 32% in the previous ten years, NAFLD affects up to two billion people worldwide, reflecting diabetes and obesity epidemics [3]. Over one-third of people in Egypt have NAFLD, making it one of the countries with the greatest prevalences of the condition [4].

The risk is increased for those who have type 2 diabetic mellitus (T2DM). than those without diabetes of developing NAFLD and proceeding to cirrhosis. The incidence of NAFLD was 68.71% in type 2 diabetic patients. According to the GBD-2019 dataset, the North Africa and the Middle East (MENA) area is expected to have 141.51 million cases. Egypt was projected to have the most instances (25.71 million) [5].

Furthermore, NAFLD raises the risk of diabetes's chronic vascular disorders and

complicates its management, according to mounting data [6]. In the diabetic subjects, NAFLD screening is crucial for early detection and avoiding from progressing to more advanced stages[7]. A significant underdiagnosis occurs in real-world settings, where most patients are incidentally diagnosed with NAFLD after cirrhosis has already progressed [8]. In order to reduce the progression to fatal and irreversible stages, early detection is essential [9].

During the evolution of fibrosis, hepatic stellate cells (HSCs) release the glycosylation isomer of the Mac-2 binding protein (M2BPGi), which acts as a messenger between Kupffer cells and HSCs via Mac-2 (Galectin-3) [10]. M2BPGi is being used more and more in clinical settings to identify liver fibrosis in patients with nonalcoholic fatty liver disease (NAFLD), chronic hepatitis C, and chronic hepatitis B, as well as to forecast the risk of hepatocellular carcinoma in these patients [11].

The purpose of this study was to assess the clinical value of blood M2BPGi levels in individuals with non-alcoholic fatty liver disease and type 2 diabetes.

METHODS:

Study population:

Sixty-nine participants were split up into three groups for this case-control study, matched by age and sex: 23 people with type 2 diabetes who did not have non-alcoholic fatty liver disease, 23 people with type 2 diabetes who did, and 23 individuals who seemed to be in good health. Between September 2023 and March 2024, patients were gathered from Zagazig University Hospital's Internal Medicine Department outpatient clinics. After obtaining approval from our Institutional Review Board (ZU-IRB# 10843-14/6-2023), each participant provided written informed consent. The World Medical Association's code of ethics (Declaration of Helsinki 1979) was followed when conducting the study.

The same operator used a high resolution B-mode scanner (SDD-550, Aloka, Tokyo, Japan) with a 3.5 MH2 transducer to perform an abdominal ultrasound scan in order to diagnose hepatic steatosis. Participants with chronic liver diseases (hemochromatosis, autoimmune hepatitis, viral hepatitis, Wilson disease, or hepatocellular carcinoma), recent cerebrovascular stroke, recent acute coronary syndrome (within the last three months), and excessive alcohol consumption (>210g per week for men and >140g per week for women) were excluded from the study. Pregnancy and the use of steatogenic medications (such as amiodarone, tamoxifen, oestrogens, and steroids) were excluded.

Methods:

Each participant had a thorough history taking, clinical examination, abdominal ultrasound scan, and laboratory tests which included complete blood count (CBC) using a Siemens Sysmex XN-2000; liver function tests, ALP, GGT, AST, ALT, total protein, albumin, total bilirubin, and direct bilirubin ; kidney function tests (serum creatinine, BUN); fasting plasma glucose; lipid profile (total cholesterol, HDL-cholesterol (HDL-C), triglycerides, LDL-cholesterol (LDL-C))(Cobas 8000, Roche Diagnostics) and glycosylated hemoglobin (HbA1c) (Cobas 6000, Roche Diagnostics). Fatty liver index (FLI) [12]; fibrosis-4 index (FIB-4) [13]; body mass index (BMI) [14] and estimated glomerular filtration rate (eGFR) [15] were calculated. To determine the albumin creatinine ratio (ACR), urine samples were taken in the morning. Two out of the three urine samples showed evidence of albuminuria. Using an enzyme-linked immunosorbent test (ELISA) kit, serum M2BPGi levels were determined (SunRed, Shanghai; Catalogue no.: 201-12-8411).

Statistical Analysis

To ascertain how many volunteers are required for the study, Epi-Info 6 software was employed, utilizing a 95% confidence level and 80% statistical power. Data analysis was performed using SPSS version 28. Categorical variables were compared and described using the chi-square test, focusing on absolute frequencies. Depending on the type of data, means, standard deviations, medians, and interquartile ranges were used to summarize continuous variables. For comparisons involving more than two groups, either the ANOVA (F-test) or the Kruskal-Wallis (KW) test was applied. If a significant difference was found, pairwise comparisons using Tukey HSD were conducted. The

association between M2BPGi and other factors was investigated using correlation analysis. The best cutoff values for particular quantitative measurements were determined using receiver operating characteristic (ROC) curves. The independent variables that affected the outcome variable were found using regression analysis. A p-value of less than 0.05 was considered statistically significant, whereas a p-value of 0.001 or less denoted a highly significant difference.

RESULTS

The demographics, clinical criteria, and anthropometric data for all groups are outlined in Table 1. The laboratory findings for these groups are presented in Table 2. Diabetes patients with NAFLD had significantly greater M2BPGi levels than both diabetic patients without NAFLD and healthy controls, and diabetic patients without NAFLD also had higher M2BPGi levels than healthy controls. (Table 2). In the diabetic group with NAFLD, M2BPGi showed a significant positive correlation with ALT, ACR, HbA1c, and FLI score; however, it did not correlate statistically with other evaluated parameters in diabetic patients (Table 3). A significant correlation was found between M2BPGi levels and the severity of steatosis as measured by ultrasound. Patients with severe steatosis had notably higher mean of M2BPGi levels (639.11±59.2) compared to those with mild (450.88±48.13) and moderate (403.0±55.25) steatosis, with statistical significance noted. Regression analysis revealed that M2BPGi was independently associated with ACR (unstandardized β=5.259, $p<0.001$) and ALT (unstandardized β=0.597, $p=0.044$) in diabetics with NAFLD (Table 4). In order to distinguish diabetic individuals with and without non-alcoholic fatty liver disease (NAFLD), the M2BPGi area under the ROC curve (AUC) was determined to be 0.886. Accuracy was 82.6% overall, with sensitivity of 87%, specificity of 71.7%, positive predictive value of 69.8%, and negative predictive value of 91.7% at a cut-off point of ≥385.5 pg/mL. (Table 5, Figure 1). When both M2BPGi and FLI scores were used to identify NAFLD in diabetic patients, the overall accuracy reached 97.8%, and sensitivity was 95.8%, negative predictive value was 95.7%, and both specificity and positive predictive value were 100% (Table 5, Figure 1).

Table (1): Demographic, clinical criteria and anthropometric measures of the studied groups:

	Control	Diabetic patients without NAFLD	Diabetic patients with NAFLD	p
	n=23	n=23	n=23	
Gender: Female Male	 9 (39.1) 14 (60.9)	 7 (30.4) 16 (69.6)	 12 (52.2) 11 (47.8)	0.319
Age (years)*	41.61 ± 11.48	43.91 ± 2.73	43.39 ± 6.59	0.579
Duration of diabetes mellitus (years)*	-	4.22 ± 1.76	5.74 ± 2.42	0.209
Hypertension (n)	-	4 (17.4)	7(30.4)	0.491
Waist circumference (cm) *	90.96 ± 7.76	99.04 ± 8.39$^{\infty}$	106.78 ± 8.50$^{\infty}$	<0.001
BMI (body mass index) *	22.83±2.42	25.12 ± 2.13$^{\infty}$	28.15 ± 4.49$^{\infty}$	<0.001
US steatosis grades: Mild Moderate Severe	-	-	 6 (26.1) 8 (34.8) 9 (39.1)$^{\infty}$	<0.001

n: number of subjects; Data are represented as number (%) or mean± SD *; P>0.05: non significant; p⩽0.00: highly significant;

∞: significant with other group;

Table (2): Laboratory findings of the studied groups

	Control	Diabetic patients without NAFLD	Diabetic patients with NAFLD	P
	n=23	n=23	n=23	
Total bilirubin (mg/dl)	0.53 ± 0.13	0.52 ±0.13	0.47 ± 0.1	0.277
Direct bilirubin (mg/dl)	0.2 ± 0.06	0.2 ± 0.07	0.17 ± 0.05	0.16
Total protein (g/dl)	7.0 ± 0.67	7.05 ±0.61	7.24 ± 0.38	0.34
Albumin (g/dl)	4.34 ± 0.43	4.12 ±0.43	4.29 ± 0.41	0.188
ALT (U/L)*	16(15 – 22)	15(13 -25)	35(27 – 46) ∞	<0.001
AST (U/L)*	16(13 – 25)	15(13 -19)	20(13 – 30)	0.369
ALP (U/L)*	35(34 – 56)	45(43 -60)	60(45 – 79) ∞	<0.001
GGT (U/L)*	29(22 – 35)	34(27 -46)	47(32 – 66) ∞	<0.001
Creatinine (mg/dl)	0.67 ± 0.14	0.71 ±0.15	0.87 ± 0.17∞	<0.001
BUN (mg/dl)	12.87 ± 4.47	11.96 ±4.5	13.22 ± 4.19	0.605
eGFR	108.96 ± 8.36	98.91±7.56∞	91.35 ± 11.24∞	<0.001
ACR (mg/g)*	14(12 – 16)	28(22 – 54) ∞	38(27 – 87) ∞	<0.001
Fasting plasma glucose (mg/dl)	79.78 ± 4.91	89.65 ±14.67∞	105.74 ± 14.11∞	<0.001
HbA1c (%)	4.98 ± 0.25	5.54 ± 0.83∞	7.26 ± 0.64∞	<0.001
Total cholesterol (mg/dl)	176.17 ± 9.63	185.57 ± 14.52	202.65 ± 31.33∞	<0.001
LDL-C (mg/dl)	88.7 ± 11.61	99.87 ± 12.9	138.96 ± 21.59∞	<0.001
HDL –C (mg/dl)	47.09 ± 6.63	45.26 ± 4.79	35.26 ± 7.98∞	<0.001
Triglycerides (mg/dl)	109.13 ± 19.47	137.65 ±28.15∞	163.13 ± 23.99∞	<0.001
FLI	19.83 ± 6.66	26.49 ± 10.03∞	45.17 ± 17.38∞	<0.001
FIB-4	0.84 ± 0.14	0.86 ± 0.19	0.91 ± 0.29	0.523
M2BPGi (pg/mL) *	300(276 – 337)	358(269 – 385) ∞	479(430 – 653) ∞	<0.001

n: number of subjects; Data are represented as mean± SD or Median (IQR)*; P>0.05: non significant; p≤0.00: highly significant;
∞: significant with other group;

Table (3): Correlation between M2BPGi levels and some studied parameters patients groups

	Diabetic without NAFLD		Diabetic with NAFLD	
	r	P	r	p
Age (years)	0.275	0.204	0.198	0.366
Duration of DM (years)	0.309	0.152	0.366	0.086
Waist circumference (cm)	0.254	0.242	0.199	0.362
BMI (kg/m^2)	0.339	0.114	0.253	0.243
Total bilirubin (mg/dL)	0.341	0.112	-0.039	0.861
Direct bilirubin (mg/dL)	-0.201	0.357	0.026	0.905
Total protein (g/dL)	-0.026	0.907	0.12	0.585
Albumin (g/dL)	-0.200	0.361	0.136	0.537
ALT (U/L)	-0.019	0.931	0.582	0.004
AST (U/L)	0.054	0.808	0.314	0.144
ALP (U/L)	-0.349	0.103	-0.153	0.484
GGT (U/L)	-0.031	0.889	0.403	0.057
Creatinine (mg/dL)	-0.317	0.141	-0.057	0.798
BUN (mg/dL)	0.193	0.378	0.283	0.191
eGFR (ml/min)	-0.254	0.242	-0.091	0.681
ACR(mg/g)	-0.346	0.106	0.815	<0.001
FBG (mg/dL)	-0.328	0.126	0.353	0.099
HbA1c (%)	0.369	0.083	.434	0.039
Total cholesterol (mg/dL)	-0.41	0.052	0.379	0.094
LDL-C (mg/dL)	0.326	0.129	-0.316	0.142

	Diabetic without NAFLD		Diabetic with NAFLD	
	r	P	r	p
HDL-C (mg/dL)	-0.102	0.644	0.171	0.435
Triglycerides (mg/dL)	0.168	0.444	-0.37	0.082
FLI	-0.271	.212	0.72	<0.001
FIB-4	-0.072	0.743	0.114	0.605

P>0.05: non significant; p≤0.00: highly significant

Table (4): Multiple stepwise regression analysis of variables independently associated with serum M2BPGi in patients with NAFLD

	Unstandardized coefficients		Standardized coefficients	t	P	95% Confidence Interval	
	beta	Std. error	beta			Lower	Upper
(Constant)	328.708	26.892		2.223	<0.001**	272.611	384.804
ACR	5.259	0.909	0.694	.786	<0.001**	3.363	7.154
ALT	0.597	0.223	0.322	.681	0.044*	0.133	1.062

*p<0.05 is significant; **p≤0.001 is highly significant

Table (5): Performance of M2BPGi and FLI in diagnosis of NAFLD in diabetic patients.

	Cutoff	AUC	Sensitivity%	Specificity%	PPV%	NPV%	Accuracy%	P
M2BPGi (pg/mL)	≥385.5	0.886	87%	78.3%	80%	85.7%	82.6%	<0.001
FLI	≥30	0.824	73.9%	78.3%	77.3%	75%	76.1%	<0.001
M2BPGi and FLI		.972	95.8%	100%	100%	95.7%	97.8%	<0.001

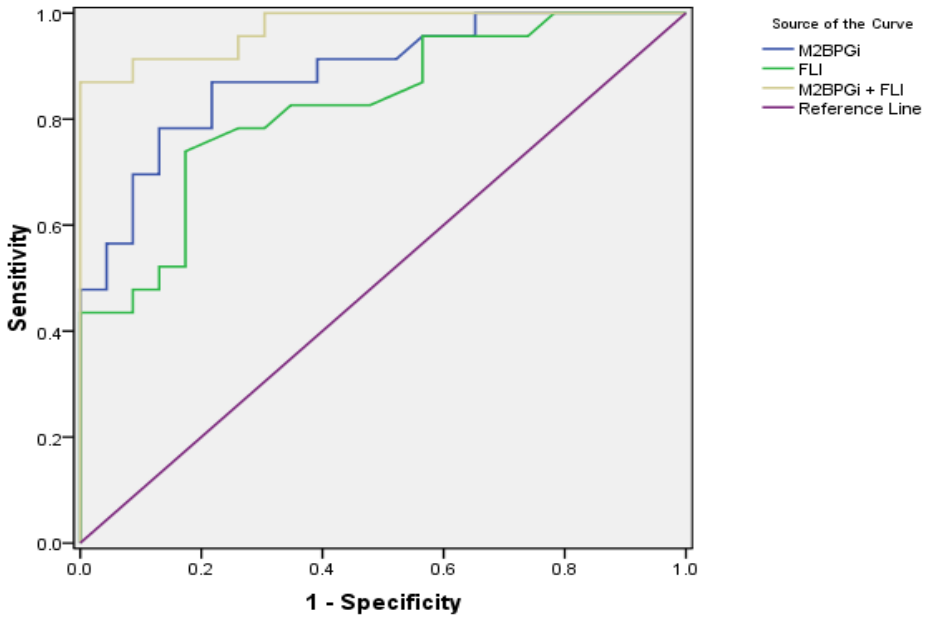

Figure (1) :ROC curve showing performance of M2BPGi and FLI in diagnosis NAFLD

DISCUSSION

NAFLD, or non-alcoholic fatty liver disease, is a growing global health concern. progressing through stages like steatosis, inflammation, fibrosis, and carcinoma [16]. It shares similar mechanisms with type 2 diabetes (T2DM), including insulin resistance and abnormal lipid metabolism [17]. T2DM with NAFLD may not exhibit obvious clinical signs in its early stages. The condition will improve with prompt and efficient treatment, this emphasizes how crucial early diagnosis is [16].

Liver histology, imaging methods, non-invasive blood biomarkers, or prediction scores can all be used for NAFLD diagnosis. The sensitivity of common imaging diagnostic techniques for identifying mild steatosis is low and they depend on the subjective assessment of physicians [18]. The gold standard for diagnosis is the liver biopsy. Nevertheless, the quest for non-invasive techniques for early diagnosis has been more intense due to possible sampling error, cost, invasiveness, and impracticability for screening [19]. Blood biomarkers and prediction scores provide a cost-effective method of diagnosing NAFLD [20].

One such biomarker is M2BPGi, generated by hepatic stellate cells (HSCs) and associated with the development of liver cancer and fibrosis [21]. M2BPGi is easily detectable in blood, and it acts as a messenger between HSCs and Kupffer cells through Mac-2 (Galectin-3) [11].

This study revealed increased M2BPGi levels in diabetic patients compared to controls, similar to previous findings that associating high M2BPGi with increased diabetes risk in other populations[22]. These results imply that inflammation and insulin resistance may be the cause of the substantial correlation between serum M2BPGi levels and an increased risk of diabetes [22].

Several studies support the theory that elevated levels of M2BPGi can promote insulin resistance and inflammation. These studies were mostly concerned with the functions of Mac-2. In human liver tissue specimens, Mac-2 expression has been proven to be induced by M2BPGi[21], which promote inflammation [23] and insulin resistance [24]. Moreover, Mac-2 antigen has been linked to diabetes incidence and prevalence [25]. These results imply that M2BPGi could contribute to inflammation, insulin resistance, and type 2 diabetes [22].

This work revealed that individuals with NAFLD exhibited significantly elevated median levels of M2BPGi compared to diabetic patients without NAFLD and controls. These results align with the findings of Li and his coworkers [26], who noted that T2DM patients with NAFLD had significantly higher serum M2BPGi levels than both the T2DM-only group and controls.

The extracellular matrix produces a glycoprotein known as Mac-2 binding protein (M2BP). When M2BP's sugar chain structure is heavily glycosylated, it interacts with galectin-3, which regulates basic physiological functions like differentiation, growth, proliferation, inflammation, and interactions between cells and the matrix. M2BPGi may serve as an alternate marker for measuring hepatic stellate cells (HSCs) activation since it stimulates the production of interleukin-6, interleukin-1, and other cytokines and originates from HSCs in the liver. This indicates that HSC activation occurs as liver fibrosis progresses [27].

According to a cross-sectional study done by Kamada et al. [28], subjects with fatty liver identified byl ultrasonography had higher M2BPGi levels than subjects without fatty liver. This finding may indicate that an increase in M2BPGi concentrations is a reflection of the buildup of liver fat. By activating the PI-3-kinase pathway, lipid buildup in hepatocytes triggers the release of mediators that speed up HSC proliferation, activation, and intensification of their resistance to apoptosis. Additionally, in activated HSCs, these soluble mediators from steatotic hepatocytes increase the expression of profibrogenic and proinflammatory genes [29].

In diabetics with NAFLD, Our research revealed a favorable relationship between M2BPGi and FLI score, ALT, ACR, and HbA1c. These results are in accordance with previous studies that discovered a positive correlation between M2BPGi and ALT,

HbA1c level, and FLI score in diabetics whose abdominal sonography revealed hepatic steatosis [30,31].

This work showed a positive correlation between ACR and M2BPGi. Additionally, regression analysis revealed that among diabetics with NAFLD, ACR was independently linked to M2BPGi. These findings are consistent with a research by Hashimoto and his colleagues. [32], who found a connection between diabetic microangiopathy and M2BPGi levels in type 2 diabetic patients. Additionally, this study demonstrated an independent association between M2BPGi and a higher incidence of microalbuminuria.

In diabetics with NAFLD, the current study found an independent association between M2BPGi and ALT. Serum ALT levels have been shown to predict endothelial function in patients with NASH, and elevated ALT is a sign of oxidative stress, which may play a vital role in the evolution of both endothelial dysfunction and NASH [33].

Chronic inflammation is linked to both diabetic angiopathy and chronic liver disease (CLD). TNF-α expression is augmented in patients with CLD. Through cytotoxicity, TNF-α damages the kidneys, causing glomerular cell death and, ultimately, albuminuria [34]. Moreover, CLD causes inflammation, hypertrophy, and renal fibrosis because it triggers RAAS, which raises the production of reactive oxygen species [35]. Furthermore, intercellular adhesion molecule-1 is connected to both CLD and diabetic microangiopathy [36].

The degree of steatosis as determined by ultrasonography and the M2BPGi level were shown to be significantly correlated in the current study. The severe grade has significantly higher M2BPGi levels than the other grades. According to Nah et al. [37] who investigated the effect of tailored lifestyle modifications on NAFLD remission, M2BPGi had decreased following the 12-month intervention and was associated with hepatic fat fraction remission using magnetic resonance imaging.

The current study found that the M2BPGi ROC-AUC for distinguishing diabetic patients with NAFLD from those without was 0.886. At the cut-off of ≥385.5 pg/mL, the overall accuracy was 82.6%, 86.9% sensitivity, 78.3% specificity, the positive predictive value was 80%, and the negative predictive value was 85.7%. When used to identify NAFLD in diabetics, by combining M2BPGi and FLI score the sensitivity increased to 95.8% with 100% specificity, 97.8% total accuracy, 95.7% negative predictive value, and 100% positive predictive value.

There are some shortcomings in this study. First and foremost, the most accurate method for diagnosing non-alcoholic fatty liver disease is still liver biopsy, even if abdominal ultrasonography is a recognized technique for fatty liver identification. The tiny sample size of this study is another drawback. Consequently, a larger multicenter study is needed to validate these results.

Conclusions**:**

In conclusion, M2BPGi, either by itself or in conjunction with FLI, may be a potential non-invasive marker for nonalcoholic fatty liver. Additionally, it was linked to microalbuminuria and corresponded with steatosis grades.

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