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Interaction of newly developed markers of insulin resistance and liver fibrosis

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Abstract

Aim: Insulin resistance is one of the most common causes of liver fibrosis. Instead of the Homeostatic Model Assessment- Insulin Resistance (HOMA-IR) index, which has been used to indicate insulin resistance for many years, Triglyceride-Glucose index (TyG) has recently been used, which is thought to be more predictive. (AST) to Platelet Ratio Index (APRI) and Fibrosis-4 Index (FIB-4) are newly developed markers to indicate liver fibrosis. In this study, we aimed to examine the relationship between TyG and HOMA-IR and APRI and FIB-4.

Materials and Methods: 8.618 patients who applied to Turgut Özal Medical Center internal medicine outpatient clinic between March 2019 and March 2024 were retrospectively examined. APRI and FIB-4 levels were compared in patients by grouping them by age and as having/not having insulin resistance according to TyG and HOMA-IR.

Results: There was a statistically significant positive correlation between TyG with APRI and FIB4 (ρ=0.041, p<0.001 for APRI and ρ=0.109, p<0.001 for FIB4). There was a significant difference in APRI and FIB-4 in the grouping made according to the presence of insulin resistance. In the grouping made according to glycemic status, FIB-4 was significantly different among all subgroups (p<0.001 for each), while there was no significant difference in APRI.

Conclusion: Insulin resistance is one of the conditions that should be closely monitored not only because it predisposes to diabetes but also because it causes dysfunction in liver. Newly diagnosed indexes may be useful to follow-up these patients before any symptoms ocur. Widespread use of these indices especially FIB-4 index which we claim that it is more predictive than others, in clinical practice may be beneficial due to their predictive effects and noninvasiveness.

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Introduction

Insulin resistance is a condition that occurs as a result of the insensitivity of cells in tissues to the insulin hormone and causes dysfunctions in various systems [1]. Gold standard for measuring insulin resistance is the hyperinsulinemic-euglycemic glucose clamp technique [2]. However, since it is an invasive method, non-invasive methods have been sought over time. An index called Homeostatic Model Assessment- Insulin Resistance (HOMA-IR) which is formulized with fasting insulin and glucose levels has been used for a long time [3]. In recent years, there has been a growing interest in the development of new indexes that are claimed to be more effective than the HOMA-IR index [4]. Among these, the Triglyceride glucose (TyG) index stands out in terms of both reliability and ease of measurement [5].

Liver fibrosis is one of the most common causes of liver failure which is characterized by irreversible impairment of hepatocytes [1]. It often develops secondary to nonalcoholic fatty liver disease, which is generally seen in diabetic or prediabetic patients [6]. Liver biopsy is the gold standard test for diagnosing liver fibrosis [7]. There are many studies in the literature mentioning the non-invasive diagnostic methods for liver fibrosis [8]. Among these Aspartate aminotransferase (AST) to Platelet Ratio Index (APRI) and Fibrosis-4 Index (FIB-4) are standing out recently [9].

There are various of studies in the literature evaluating the association between insulin resistance and liver fibrosis [10-12]. In this study we aimed to investigate the relation-

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ship between insulin resistance indexes and liver fibrosis indexes.

Materials and Methods

Study population

This study was approved by the Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee with the decision number 2024/6088. After obtaining ethics committee approval, patients between 18-80 ages who applied to the Internal Medicine outpatient clinic of our Turgut Ozal Medical Center between March 2019 and March 2024 were retrospectively examined. AST, ALT, Platelet, Fasting Plasma Glucose, Insulin, HbA1c and Triglyceride levels were recorded. After patients whose liver function tests increased 2 times or more above the upper limit were excluded from the study, a total of 8618 patients were included in the study.

Grouping the patients

For insulin resistance, patients were grouped as present or absent according to TyG and HOMA-IR.

For glycemic status, patients were divided into 3 groups as:

- Normoglycemic (fasting blood glucose < 100 mg/dl)
- Impaired fasting glucose (fasting blood glucose between 100 – 126 mg/dl)
- Hyperglycemic (fasting blood glucose > 126 mg/dl)

For age groups patients were divided in 3 groups as Group 1 is between 18-39 aged, Group 2 is between 40-64 aged and Group 3 is 65 and older aged.

Laboratory evaluation

Insulin resistance and liver fibrosis indicators were measured from the patients' peripheral venous blood taken in the morning after an 8-hour fasting.

For insulin resistance

- HOMA-IR index: Fasting glucose * Fasting insulin / 405 (>2.5 insulin resistance is present) [3]
- Triglyceride Glucose index (TyG): ln [fasting triglyceride * fasting glucose] / 2 (>4.49 there is insulin resistance) [13].
- HbA1c < 5.7 is normal, 5.7 - 6.5 is prediabetes, ≥6.5 is diabetes [14].

For liver fibrosis

- AST APRI score (AST-Platelet ratio index): (AST/Upper limit of normal 40 IU/L)/platelet count (platelet × 10^9/L) × 100 (<0.5 normal, 0.5-1.5 high, ≥ 1.5 obvious fibrosis) [9].
- FIB-4 index (age x AST)/platelet value x (ALT) 1/2 (<1.5 no fibrosis, ≥3.5 significant fibrosis) [9] indexes have been measured.

Statistical analysis

Numerical data will be expressed as mean ± standard deviation, and categorical data will be expressed as a ratio. It was evaluated whether the data were normally distributed using the Kolmogorov-Smirnov test. T-test was used for statistics of data conforming to normal distribution, and Mann-Whitney U test with Bonferoni correction after Kruskall Wallis was used to compare data that did not comply with normal distribution. Categorical data will be compared with the chi-square test. Pearson correlation test was used to correlate data with normal distribution, and Spearman correlation test was used to correlate data that did not comply with normal distribution.

Results

There was a statistically significant positive correlation between TyG with APRI and FIB4. (ρ=0.041, p<0.001 for APRI and ρ=0.109, p<0.001 for FIB4). There was no statistically significant correlation between the HOMA index with APRI and FIB4 (p=0.764, p=0.129 respectively).

When grouped as presence or absence of insulin resistance according to TyG, there was a statistically significant difference between the groups in terms of APRI and FIB4 (Table 1). When divided into groups with and without insulin resistance according to the HOMA index, there was no statistically significant difference between the groups in terms of FIB-4 and APRI scores. (p=0.636 and p=0.942 respectively).

Correlation of TyG with APRI and FIB4 is shown in Table 2 when patients were divided into subgroups as normoglycemic, impaired fasting glucose and hyperglycemic. There was a statistically significant positive correlation between Tyg and APRI and between TyG and FIB-4 in both normoglycemic patients and patients with impaired fasting

Table 1. Comparison of fibrosis indicators in groups with and without insulin resistance according to the Triglyceride-Glucose index.

	TyG		
	<4.49	≥4.50	p
APRI median (min-max)	0.180 (0.029 – 6.330)	0.227 (0.025 - 4.340)	<0.001
FIB-4 median (min-max)	0.59 (0.07 - 20)	0.83 (0.12 -29.23)	<0.001

TyG: Triglyceride-glucose index, APRI: AST to Platelet Ratio Index, FIB-4: Fibrosis-4 Index.

Table 2. Correlation of TyG with APRI and FIB-4.

	Normoglycemic n=8618		Impaired Fasting Glucose n=2630		Hyperglycemic n=1564	
	ρ	p	ρ	p	ρ	p
APRI	0.073	**<0.001**	0.055	**0.001**	0.009	0.637
FIB-4	0.140	**<0.001**	0.046	**0.006**	-0.026	0.197

TyG: Triglyceride-glucose index, APRI: AST to Platelet Ratio Index, FIB-4: Fibrosis-4 Index.

Table 3. Comparison of APRI and FIB-4 according to glycemic status.

	Normoglycemic n=8618	Impaired Fasting Glucose n=2630	Hyperglycemic n=1564	p
APRI median (min-max)	0.183 (0.007 – 6.330)	0.191 (0.024 – 3.729)	0.185 (0.036 – 13.37)	<0.001
FIB-4 median (min-max)	0.61 (0.05 – 29.23)	0.82 (0.07 – 35.52)	0.93 (0.14 – 13.37)	<0.001

APRI: AST to Platelet Ratio Index, FIB-4: Fibrosis-4 Index.

Table 4. Comparison of APRI and FIB-4 according to age.

	Group 1 n=5883	Group 2 n=5171	Group 3 n=1808	p
APRI median (min-max)	0.177 (0.033 – 6.203)	0.191 (0.007 – 6.456)	0.196 (0.029 – 6.330)	<0.001
FIB-4 median (min-max)	0.46 (0.07 – 5.75)	0.87 (0.05 – 13.37)	1.38 (0.24 – 32.52)	<0.001

APRI: AST to Platelet Ratio Index, FIB-4: Fibrosis-4 Index.

glucose. In hyperglycemic patients, TyG had no significant correlation with APRI and FIB-4.

When APRI and FIB-4 values were examined according to glycemic status, there was a statistically significant difference in all groups (Table 3). In subgroup analyses, APRI and FIB-4 were significantly different between the normoglycemic and impaired fasting glucose groups ($p<0.001$, $p<0.001$). When comparing normoglycemic and hyperglycemic groups, FIB-4 was significant ($p<0.001$), while the difference between APRI groups was not significant statistically ($p=0.306$). When the group with impaired fasting glucose was compared with the hyperglycemic group, there was a statistically significant difference in FIB-4 ($p<0.001$), while there was no statistically significant difference in APRI values ($p=0.101$).

According to TyG, patients with insulin resistance were grouped as normoglycemic, impaired fasting glucose and hyperglycemic according to their glycemic status. When the differences in terms of FIB-4 and APRI were examined, FIB-4 was found to be statistically different in normoglycemic-impaired fasting glucose subgroups ($p<0.001$), normoglycemic-hyperglycemic subgroups ($p<0.001$) and impaired fasting glucose-hyperglycemic subgroups ($p<0.001$). There was no statistically significant difference between subgroups in terms of APRI levels.

In the analyses performed by grouping the patients according to their ages, a statistically significant difference was found between all age groups in terms of APRI and FIB-4 values when grouped as 18-39 years (age group 1), 40-64 years (age group 2) and over 65 years (age group 3) (Table 4). When the subgroups were compared with each other in terms of FIB-4, a statistically significant difference was found between Group 1 and Group 2, Group 2 and Group 3, and Group 1 and Group 3 ($p<0.001$ for each). When compared in terms of APRI levels, a statistically significant difference was found between Group 1 and Group 2 ($p<0.001$) and between Group 1 and Group 3 ($p<0.001$), while no statistically significant difference was found between Group 2 and Group 3 ($p=0.120$).

Discussion

While APRI and FIB-4 indexes have a weak correlation with TyG, they do not have a correlation with the HOMA index. In addition while there is a statistically significant difference between groups in terms of APRI and FIB-4 levels when they were grouped according to TyG, there is no difference when they were grouped according to HOMA-IR. Depending on this finding we assumed that TyG is more sensitive index than HOMA-IR. Our thought on this subject were supported by the studies in the literature [15,16]. Furthermore, the rise in liver fibrosis indicators in patients with high TyG levels led us to consider the possibility that insulin resistance may have an impact on liver tissue from an early stage. Lebensztejn at all showed molecular effects of insulin resistance on hepatocytes [17].

It was an unexpected finding that while TyG had a correlation with APRI and FIB-4 in normoglycemic and impaired fasting glucose subgroups, there was no correlation in hyperglycemic subgroup with both indexes. The most likely reason for this finding may be that the deterioration in tissues due to the increase in blood glucose level may affect the reliability of the parameters obtained from laboratory tests. When subgroups were analyzed according to glycemicstatus, there was a statistically significant difference in FIB-4 levels between all groups. However APRI levels were statistically significantly different only in the normoglycemic and impaired fasting glucose groups. We assume that FIB-4 may be a more sensitive indicator than APRI. In a recent study, it was shown that both indexes were effective in showing fibrosis, while FIB-4 had a higher predictive effect [18].

When examining the impact of glycemic status on APRI and FIB-4 in patients with insulin resistance, it became evident that FIB-4 was influenced by glycemic conditions across the board, whereas APRI values remained largely

unaffected. This led us to consider the possibility that insulin resistance may have an impact on liver tissue, regardless of the patient's glycemic status. It also led us to believe that the FIB-4 value may be a useful indicator of this. We hope that further research on this subject will help to clarify the existing literature.

There was a significant difference when all age groups were compared in terms of APRI and FIB-4. This finding was similar to studies suggesting that liver fibrosis indicators tended to increase with increasing age [19]. When APRI and FIB-4 values were compared by age groups, FIB-4 was significantly different in all age groups, whereas APRI was not significantly different in patients aged 40 years and older, which led us to think that APRI levels are affected more with age and FIB-4 may be a more effective indicator in elderly patients. Further studies may be useful to clarify the literature on this subject.

Our study has some limitations. First of them is this is a retrospective study. Second limitation is that the patients were not subjected to liver biopsy or liver ultrasound for the detection of liver fibrosis.

Conclusion

Insulin resistance is one of the conditions that should be closely monitored not only because it predisposes to diabetes but also because it causes dysfunction in many systems. Liver failure is one of the most feared outcomes. Thanks to the recently developed indices that are predictive of both insulin resistance and liver fibrosis, patients can be followed up more closely and if there is an increased risk, further examinations can be performed without wasting time and detected at early stages. We believe that the widespread use of these indices especially FIB-4 index which we claim that it is more predictive than others, in clinical practice will be beneficial due to their predictive effects and noninvasiveness.

Ethical approval

This study was approved by the Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee with the decision number 2024/6088.

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