Evaluation of Insulin Resistance of Individuals with MAFLD

MAFLD'lı Bireylerin İnsülin Rezistansı'nın Değerlendirilmesi

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Abstract

Introduction MAFLD is a new diagnosis that has been brought to the terminology in the last 2 years, and it is thought that the main mechanism underlying its development is Insulin Resistance (IR). In our study, it is planned to research the role of IR level in the etiology of patients with MAFLD.

Materials and Methods 265 individuals with MAFLD are included in the study by examining their sub-parameters of case diagnosis. While 85 patients have T2DM, 180 patients are found to be PreDiabetic. IR is calculated with HOMA-IR. The value of 2.5 and above is considered as high, and below 2.5 is considered as normal. The ratios of HOMA-IR levels and their relationship between waist circumference and BMI were examined.

Results The value of HOMA-IR was found high in 60.6% of prediabetic MAFLDs, while it was normal in 39.4% of them. Age ((p=0.001; p<0.01) and waist circumference (p=0.028; p<0.05) in the T2DM group were found to be higher than the PreDiabetic group. Very weak positive correlation was found between HOMA-IR and BMI (r=0.223; p=0.003; p<0.01) and waist circumference (r=0.205; p=0.006; p<0.01) in the prediabetic group. In the T2DM group, there was a very weak positive correlation between BMI and HOMA-IR (r=0.254; p=0.019; p<0.05).

Conclusion : In our study, IR was not detected in 39.4% of patients with MAFLD. This result leads us to think that insulin sensitizing agents may not be effective in this patient group in patients with normal IR levels. We think that these agents will not be effective in patients with normal IR levels. Our study should be supported with experimental and histological MAFLD studies.

Keywords MAFLD, Prediabetes, Insulin Resistance

Özet

Amaç MAFLD son 2 yılda terminolojiye kazandırılmış yeni bir tanı olup, gelişiminde altta yatan ana mekanizmanın İnsülin Rezistansı(IR) olduğu düşünülmektedir. Çalışmamızla MAFLD'lı hastaların IR düzeyinin etyolojideki rolünü incelemeyi planladık.

Gereç ve Yöntemle Method: Çalışmaya 265 MAFLD'lı vaka tanı alt parametreleri incelenerek dahil edildi. 85 hastada T2DM varken, 180 hasta Prediyabetik'ti. HOMA-IR ile IR hesaplandı. 2.5 ve üzeri yüksek, 2.5 altı normal olarak değerlendirildi. HOMA-IR düzeyi oranları ve bel çevresi ve BMI ile ilişkisi incelendi.

Bulgular Prediyabetik MAFLD'ların %60.6'sında HOMA-IR yüksek iken, %39.4'ünde normaldir. T2DM grubunun yaş((p=0,001; p<0,01) ve bel çevresi(p=0,028; p<0,05) prediyabetik gruptan yüksek tespit edildi. Prediyabetik grupta HOMA-IR ile BMI arasında(r=0,223; p=0,003; p<0,01), bel çevresi arasında(r=0,205; p=0,006; p<0,01) çok zayıf pozitif ilişki tespit edilmiştir. T2DM grubunda ise BMI ile HOMA-IR arasında çok zayıf düzeyde pozitif ilişki tespit edilmiştir(r=0,254; p=0,019; p<0,05).

Sonuç Çalışmamızda MAFLD'lı hastaların %39.4'ünde IR saptanmamıştır. Bu sonuç bize IR düzeyi normal hastalarda insülin duyarlaştırıcı ajanların bu hasta grubunda işe yaramayabileceğini düşündürmektedir. IR seviyesi normal hastalarda bu ajanların işe yaramayacağını düşünmekteyiz. Çalışmamızın deneysel ve histolojik düzeyde MAFLD çalışmaları ile desteklenmesi gerekmektedir.

Anahtar Kelimeler MAFLD, İnsülin Rezistansı, Prediyabet

INTRODUCTION

Metabolic Syndrome (MetS) and its main sub-components which is Insulin Resistance (IR), and the presence of HepatoSteatosis with obesity have been defined as Metabolic Disfunction-Associated Fatty Liver Disease (MAFLD)(1,2) recently. Even though it has similar aspects with Non-Alcoholic Fatty Liver Disease (NAFLD), the diagnosis of MAFLD does not exclude viral hepatitis and alcohol consumption above a certain level. Evidence of metabolic disorder (presence of Type 2 Diabetes Mellitus (T2DM), obesity or metabolic disorder) must be present for the diagnosis of MAFLD at the same time. However, these criteria are not required for NAFLD. It is required for diagnosis to show fat in the liver in Ultrasonographic (USG) imaging or histologically show 5% or more fat in hepatocytes. As a new terminology, MAFLD is more inclusive and its diagnosis depends on more precise criteria in comparison with NAFLD (3).

It is still a common idea nowadays that IR is the most important mechanism underlying metabolic effects and lipoidosis in the liver. The fact that HepatoSteatosis is seen more common in T2DM and rare in Type 1 Diabetes Mellitus (T1DM) also encourages this thesis. Moreover, glucotoxicity and lipotoxicity are among the other important factors that contribute to the development of lipidosis in the liver(4).

In this study, we have the purpose to analyze the frequency of IR and its relationship with the components that comprises MAFLD in cases diagnosed with MAFLD.

MATERIAL and METHODS

A study group of 265 cases aging 18 years and over who applied to 3 different internal diseases policlinic between the dates June and September 2022 and complied with the MAFLD criteria were constituted. The data were evaluated retrospectively. T1DM, pregnant women and patients with gestational diabetes mellitus were excluded from the study. Cases were included in the study if the HbA1c value was between 5.7-6.4% in the aspect of PreDiabetes. The livers evaluated in all cases were interpreted by radiology specialists with Voluson Simens G60 S brand USG device, and were included in the study in case grade 1 or higher HepatoSteatosis were seen. In order to make standardization among the cases, any level of alcohol consumption and the presence of viral hepatitis were excluded from the study. PreDiabetic patients using any antidiabetic agents were not included in the study. Waist circumference, height and weight values of all cases were measured and Body Mass Index (BMI) values were calculated. Individuals who have BMI values of 30 kg/m2 and above were considered as obese. Blood pressure values were measured manually with an Omron brand mercury sphygmomanometer. HbA1c level, Fasting Plasma Glucose (FPG) levels and lipid parameters were evaluated in all cases.

A homeostasis model evaluation HOMA-IR (fasting insulin(microU/L)xFPG(nmol/L)/22.5) was used to evaluate IR (5). HOMA-IR level of 2.5 and above was evaluated as IR.

Ethics committee approval was granted (desicion no:2022/514/234/1).

Statistical Method

For statistical analysis and calculations, IBM SPSS Statistics 26 (IBM-SPSS, Turkey) licensed program was used. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used in the evaluation of the data. The quantitative data's conformity to normal distribution was tested with Kolmogorov-Smirnov, Shapiro-Wilk test, Skewness-Kurtosis test and graphical evaluations. Independent Samples t-Test was used for the comparison of normally distributed quantitative data between two groups, and the Mann Whitney U test was used for two-group comparisons of data that were not normally distributed. Pearson Chi-Square test was used for the comparison of qualitative data. In order to evaluate the relationships between variables, Spearman's Correlation Analysis was used. Significance level was determined at least $p<0.05$.

Table 1: Distribution of Demographic Characteristics

		n	%
Age (years)	Median(Min-Max); Mean±Sd	49(18-74)	48,4±10,7
Gender	Male	66	24,9
	Female	199	75,1
BMI(kg/m^2)	Median(Min-Max); Mean±Sd	31(19-53)	31,9±5,71
	Obese(-)	111	41,9
	Obese(+)	154	58,1
Waist circumference (cm)	Median(Min-Max); Mean±Sd	104(75-141)	105±11,3
T2DM	PreDiabetes	180	67,9
	T2DM	85	32,1
HbA1c(%)	Median(Min-Max); Mean±Sd	5,9(5,1-15,3)	6,5±1,4
FPG(mg/dL)	Median(Min-Max); Mean±Sd	96(64-327)	111,9±48,5
HOMA-IR	Median(Min-Max); Mean±Sd	3(0,4-32,6)	3,9±3,5
	Normal	98	37
	High	167	63

FPG: Fasting Plasma Glucose
BMI: Body Mass Index

RESULTS

The study was conducted with a total of 265 cases, with the participants of which 24.9% (n=66) were male and 75.1% (n=199) were female. The ages of the participants ranged from 18 to 74, with a mean of 48.4±10.7 years old.

BMI measurements vary between the values of 19 and 53 kg/m2, with a mean value of 31.9±5.7 kg/m2. While 58.1% (n=154) of the participants are obese, 41.9% (n=111) of them do not have the obesity. Waist circumference measurements vary between the values of 75 and 141 cm, with a mean value of 105±11.3 cm. While 67.9% (n=180) of the cases participating in the study were PreDiabetes, 32.1% (n=85) of them were T2DM patients.

HbA1c measurements vary between the values of 5.1% and 15.3%, with a mean value of 6.5±1.4%. FPG measurements vary between the values of 64 mg/dL and 327 mg/dL, with a mean value of 111.9±48.5 mg/dL. Homa-IR measurements ranged from the values 0.4 to 32.6, with a mean value of 3.9±3.5; Homa-IR level was found to be normal in 37% (n=98) of the cases, while Homa-IR level was evaluated as high in 63% (n=167) of the cases.

It was determined that there was a statistically significant difference between the ages of the cases in regard to the groups (p=0.001; p<0.01); The ages of the group with T2DM is higher than the group with prediabetes.

A statistically significant difference was found between the gender distribution of the cases in regard to the groups (p=0.001; p<0.01); The rate of incidence of T2DM is higher in women than in men.

There could not be seen a statistically significant difference between BMI measurements and obesity prevalence rates of the cases in regard to the groups (p>0.05).

It was observed that there was a statistically significant difference between the waist circumference measurements of the cases in regard to the groups (p=0.028; p<0.05); Waist circumference measurements of the group with T2DM are higher than the group with Prediabetes.

Homa-IR measurements and Homa-IR level ratios of the cases did not show a statistically significant difference in regard to the groups (p>0.05).

For PreDiabetes Group;

It was found that there was a positive and statistically significant very weak correlation between the BMI measurements of the cases and the HOMA-IR measurements (r=0.223; p=0.003; p<0.01).

A positive and statistically significant very weak correlation was found between the waist circumference measurements of the cases and the HOMA-IR measurements (r=0.205; p=0.006; p<0.01).

Table 2: Evaluations according to the Existence of Diabetes

		PreDiabetes (n=180)	T2DM (n=85)	p
Age(years)	Median(Min-Max)	46,5(18-74)	53(32-74)	[a]0,001**
	Mean±Sd	45,8±10,79	54±8,4	
Gender; n (%)	Male	32(17,8)	34(40)	[b]0,001**
	Female	148(82,2)	51(60)	
BMI(kg/m^2)	Median(Min-Max)	31(19-53)	31(21-49)	[a]0,641
	Mean±Sd	32,1±5,7	31,7±5,7	
Obesity; n (%)	No	74(41,1)	37(43,5)	[b]0,710
	Yes	106 (58,9)	48(56,5)	
Waist circumference (cm)	Median(Min-Max)	103(75-136)	106(75-141)	[a]0,028*
	Mean±Sd	103,9±11,1	107,2±11,7	
HbA1c(%)	Median(Min-Max)	5,8(5,1-6,4)	7,2(5,6-15,3)	[a]0,001**
	Mean±Sd	5,8±0,2	7,8±1,9	
FPG(mg/dL)	Median(Min-Max)	91(64-137)	134(69-327)	[a]0,001**
	Mean±Sd	92,3±11,3	153,6±67,4	
HOMA-IR	Median(Min-Max)	2,9(0,4-32,6)	3,2(0,4-21)	[c]0,499
	Mean±Sd	3,8±3,6	4±3,3	
HOMA-IR level; n (%)	Normal	71(39,4)	27(31,8)	[b]0,227
	High	109(60,6)	58(68,2)	

aIndependent Samples t Test *bPearson Chi-Square Test*
cMann Whitney U Test ***p<0,01* **p<0,05*

For the T2DM Group;

It was found that there was a positive and statistically significant very weak correlation between the BMI measurements of the cases and the HOMA-IR measurements (r=0.254; p=0.019; p<0.05).

No statistically significant correlation was determined between the waist circumference measurements of the cases and the HOMA-IR measurements (p>0.05).

DISCUSSION

There are some studies in the literature that shows the relationship between NAFLD-HOMA-IR(6,7). The existence of IR is also one of the diagnostic criteria for MAFLD. In the absence of T2DM or obesity, it can be diagnosticated directly if at least one of the other minor criteria (prediabetes, being overweight, hypertension, hypertriglyceridemia, low HDL level, waist circumference that is 102 cm and above in men and 88 cm and above in women) exists with IR(8).

In this study, the cases were separated as T2DM and PreDiabetes. Because of the fact that almost all of the cases with T2DM use Metformin, some of the T2DM cases also use Pioglitazone as well. Both of the agents augment insulin sensitivity in liver and muscle tissues and facilitate the use of glucose of the tissues, and regulate plasma glucose levels (9,10). Pioglitazone has shown improvements significantly IR and related diseases which is one of the NAFLD indices in T2DM even at low dose levels, and it regulates this effect independent from the control of glucose (11). It has been found that there is a decrease in steatosis and inflammation in hepatocytes after the use of Pioglitazone in NAFLD in animal experiments (12). Whilst Metformin has positive effects on IR and weight loss (13); though there are controlled studies on HepatoSteatosis in MAFLD, these studies have not reached out to the conclusion or the final stage yet (14). As mentioned before, the fact that the existence of IR is the main issue on HepatoSteatosis and other metabolic effects is still kept up-to-date (4). PreDiabetics using Metformin currently were not included in the study, while PreDiabetic MAFLDs were included in the study. However, Pioglitazone is not within the cover of payback and cannot be used currently in PreDiabetics and/or MAFLD/NAFLD patients in our country. The reason why the Metformin users were excluded from the study is to ensure that IR could be evaluated accurately and wit-

Table 3: The Relationship between BMI and Waist Circumference Measurements and HOMA-IR Measurements

		PreDiabetes (n=180)	T2DM (n=85)
BMI & HOMA-IR	r	0,223	0,254
	p	0,003**	0,019*
Waist circumference & HOMA-IR	r	0,205	0,130
	p	0,006**	0,237

r: Spearman's Correlation Coefficient **p<0,01 *p<0,05

hout intervention. Since there will be changes in FPG and Fasting Insulin values in the use of Metformin, HOMA-IR measurement changes as well. Prediabetic MAFLDs were evaluated additionally, because IR measurements of MAFLDs with T2DM cannot reflect the baseline IR value at this point. In this group of 180 people, 60.6% (n=109) of them were determined with HOMA-IR value of 2.5 and above, while 39.4% (n=79) of them had a HOMA-IR measurement below 2.5 and this was considered as normal. One of the trend topics of the recent period which is the approach to MAFLD and its treatment is not very clear. There has not given a clear answer to the question yet, whether Pioglitazone has an effect on lipoidosis and inflammation in hepatocytes in the approximately 40% population with normal HOMA-IR values, or it is only clinically and histologically beneficial to Pioglitazone in MAFLDs with high IR values. Pharmacological treatment decision in MAFLD cases may create reservations for the physicians when the side effects that limit the use of Pioglitazone were considered. Even though MAFLD is a new subject which has been in our practice for 2 years, studies evaluating the effects of Pioglitazone in cases with NAFLD do not show such a distinction, and there is not enough data on this subject.

The idea that IR is being the main mechanism of lipoidosis in hepatocytes does not comprise all the cases. Looking at MAFLD as the new terminology instead of an updated version of NAFLD, it is considered that it would be more accurate to research it as a diagnostic area with unexplained questions underlying it. There may also be divergences for the treatments of MAFLDs without IR. However, it is evaluated that this hypothesis should be tested with different data of clinical patients, different studies in which hepatocytes were interpreted histologically, and new animal experiments.

Another finding is that while a weak positive correlation was statistically seen between HOMA-IR level and BMI, it was found a weak positive correlation between waist circumference and HOMA-IR level in PreDiabetics as well. Regardless of male or female, the median of waist circumference was 104 cm in the study, while the median of BMI was 31 kg/m2. Even though, it can not be assessed about the MAFLD prevalence at the moment, we should keep in mind that Turkey has the most obese society in Europe, and it is estimated that 50% of the Turkish population will be obese by the year 2030 (15). It was shown in the results of TURDEP-2 that the T2DM prevalence in our country was 13.7%, and the prevalences of Isolated-IFG, Impaired Glucose Tolerance (IGT) and Combined Prediabetes were 14.7%, 7.9% and 8.2% respectively (16). It is seen that the prevalence stated in TURDEP-2 has increased in the past 12 years. The hypertension prevalence in our country is 30.3%(17). It is evaluated that the increase in prevalences of T2DM, PreDiabetes, Obesity, Hypertension would augment the frequency of MAFLD. On the other hand, it has been understood now that the detection of HepatoSteatosis on USG is not considered insignificant as previously determined. All the other components should be investigated as well, when any of the components of MAFLD was detected. 3 out of every 4 patients were women in the study. It is considered that women should especially be

more alert and careful about MAFLD.

Limitations of the Study

This is a retrospective study. Because of the pandemic conditions, Postprandial Plasma Glucose was not measured in patients who applied to the policlinic. Moreover, the hs-CRP level of the cases could not be evaluated due to laboratory conditions. The patients that were added to the MAFLD group were excluded from these criteria.

CONCLUSION

It is seen in the results of the study that approximately 1 out of every 3 patients diagnosed with MAFLD does not have IR. This result suggests that insulin sensitizing agents recommended to use in the treatment of MAFLD may not be useful in this group. It is evaluated that it could be more appropriate to consider each patient with MAFLD individually rather than the standard treatment approach

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References

1. Sanyal AJ. Past, present and future perspectives in nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol. 2019;16(6):377–386. doi: 10.1038/s41575-019-0144-8.
2. Eslam M, Sanyal AJ, George J. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020; 158:1999–2014. doi: 10.1053/j.gastro.2019.11.312.
3. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol 2020;73:202-209. doi: https://doi.org/10.1016/j.jhep.2020.03.039.
4. Cusi K, Sanyal AJ, Zhang S, Hartman ML, Bue-Valleskey JM, Hoogwerf BJ, et al. Non-alcoholic fatty liver disease (NAFLD) prevalence and its metabolic associations in patients with type 1 diabetes and type 2 diabetes. Diabetes Obes Metab 2017; 19:1630–1634. doi: 10.1111/dom.12973.
5. Vilela BS, Vasques AC, Cassani RS, Forti AC, Pareja JC, Tambascia MA; BRAMS Investigators, Geloneze B. The HOMA-Adiponectin (HOMA-AD) Closely Mirrors the HOMA-IR Index in the Screening of Insulin Resistance in the Brazilian Metabolic Syndrome Study (BRAMS). PLoS One. 2016 Aug 4;11(8):e0158751. doi: 10.1371/journal.pone.0158751. PMID: 27490249; PMCID: PMC4973901.
6. Hossain IA, Rahman Shah MM, Rahman MK, Ali L. Gamma glutamyl transferase is an independent determinant for the association of insulin resistance with nonalcoholic fatty liver disease in Bangladeshi adults: Association of GGT and HOMA-IR with NAFLD. Diabetes Metab Syndr. 2016 Jan-Mar;10(1 Suppl 1):S25-9. doi: 10.1016/j.dsx.2015.09.005. Epub 2015 Oct 9. PMID: 26482965.
7. Isokuortti E, Zhou Y, Peltonen M, Bugianesi E, Clement K, Bonnefont-Rousselot D, Lacorte JM, Gastaldelli A, Schuppan D, Schattenberg JM, Hakkarainen A, Lundbom N, Jousilahti P, Männistö S, Keinänen-Kiukaanniemi S, Saltevo J, Anstee QM, Yki-Järvinen H. Use of HOMA-IR to diagnose non-alcoholic fatty liver disease: a population-based and inter-laboratory study. Diabetologia. 2017 Oct;60(10):1873-1882. doi: 10.1007/s00125-017-4340-1. Epub 2017 Jun 29. PMID: 28660493.
8. Lin S, Huang J, Wang M, Kumar R, Liu Y, Liu S, Wu Y, Wang X, Zhu Y. Comparison of MAFLD and NAFLD diagnostic criteria in real world. Liver Int. 2020 Sep;40(9):2082-2089. doi: 10.1111/liv.14548. Epub 2020 Jul 26. PMID: 32478487.
9. Giannarelli R, Aragona M, Coppelli A, Del Prato S. Reducing insulin resistance with metformin: the evidence today. Diabetes Metab. 2003 Sep;29(4 Pt 2):6S28-35. doi: 10.1016/s1262-3636(03)72785-2. PMID: 14502098.
10. Şenyiğit, A., & Kanat, M. (2017). Physiopathological treatment approach and position of pioglitazone in type 2 diabetes. Anatolian Clinic the Journal of Medical Sciences, 22(3), 220-223. https://doi.org/10.21673/anadoluklin.284462
11. Della Pepa G, Russo M, Vitale M, Carli F, Vetrani C, Masulli M, Riccardi G, Vaccaro O, Gastaldelli A, Rivellese AA, Bozzetto L. Pioglitazone even at low dosage improves NAFLD in type 2 diabetes: clinical and pathophysiological insights from a subgroup of the TOSCA.IT randomised trial. Diabetes Res Clin Pract. 2021 Aug;178:108984. doi: 10.1016/j.diabres.2021.108984. Epub 2021 Jul 24. PMID: 34311022.
12. Xu P, Zhang XG, Li YM, Yu CH, Xu L, Xu GY. Research on the protection effect of pioglitazone for non-alcoholic fatty liver disease (NAFLD) in rats. J Zhejiang Univ Sci B. 2006 Aug;7(8):627-33. doi: 10.1631/jzus.2006.B0627. PMID: 16845716; PMCID: PMC1533756.
13. Jalali M, Rahimlou M, Mahmoodi M, Moosavian SP, Symonds ME, Jalali R, et al. The effects of metformin administration on liver enzymes and body composition in non-diabetic patients with nonalcoholic fatty liver disease and/or non-alcoholic steatohepatitis: an up-to date systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 2020;159:104799. doi: https://doi.org/10.1016/j.phrs.2020.104799.
14. Musso G, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. Diabetologia 2012; 55:885-904. doi: https://doi.org/10.1007/s00125-011-2446-4.
15. Lobstein, Tim, Hannah Brinsden, and Margot Neveux. "World Obesity Atlas 2022." (2022).
16. Satman I, Omer B, Tutuncu Y, Kalaca S, Gedik S, Dinccag N, Karsidag K, Genc S, Telci A, Canbaz B, Turker F, Yilmaz T, Cakir B, Tuomilehto J; TURDEP-II Study Group. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. Eur J Epidemiol. 2013 Feb;28(2):169-80. doi: 10.1007/s10654-013-9771-5. Epub 2013 Feb 14. PMID: 23407904; PMCID: PMC3604592.
17. Sengul S, Akpolat T, Erdem Y, Derici U, Arici M, Sindel S, Karatan O, Turgan C, Hasanoglu E, Caglar S, Erturk S; Turkish Society of Hypertension and Renal Diseases. Changes in hypertension prevalence, awareness, treatment, and control rates in Turkey from 2003 to 2012. J Hypertens. 2016 Jun;34(6):1208-17. doi: 10.1097/HJH.0000000000000901. PMID: 26991534; PMCID: PMC4856172.