The relationship between the use of nucleos(t)ide analogs and metabolic parameters in patients with chronic hepatitis B

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Abstract. – OBJECTIVE: In the treatment of chronic hepatitis-B (CHB), although viral replication load is reduced with the use of nucleos(t)ide analogs, the risk of cirrhosis and hepatocellular carcinoma (HCC) remains. We aimed to investigate the relationship between metabolic syndrome (MetS) and CHB of nucleos(t)ide analogs, which are effective in mortality-morbidity.

PATIENTS AND METHODS: In patients who applied to the gastroenterology outpatient clinic between 2021 and 2022, we compared inactive HBsAg-positive patients who did not receive treatment with nucleos(t)ide analogs [entecavir (ETV), lamivudine (LAM), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF)] and medical treatment. Demographic characteristics of the patients were recorded. Lipid profile, Hemoglobin A1c (HbA1c), and HOMA-IR were recorded. The presence of hepatosteatosis was graded ultrasonographically. APRI, Forns Index, and FIB-4 score, which are indicators of non-invasive liver fibrosis, were evaluated.

RESULTS: Of the 265 patients, 55.5% (n=147) were males and 44.5% (n=118) were females. The ages of the participants ranged from 18 to 80, with a mean age of 46.54±14.03. It was observed that 62.3% (n=165) of the cases received medical treatment. When the drugs used by those receiving medical treatment were examined, 70.3% (n=116) TDF, 6.1% (n=10) TAF, 3% (n=5) LAM, and 20.6% (n=34) ETV, LDL, HDL, and total cholesterol measurement values of those who received medical treatment were lower, while HOMA-IR values were higher compared to those who did not receive the medical treatment. While the HbA1c value of the patients using ETV was found to be high, the liver stiffness indicator scores of those using TDF were found to be significantly higher.

CONCLUSIONS: In this study, in patients with CHB, it has been shown that medical treatment also affects MetS parameters.

Key Words:
   Chronic hepatitis B, Nucleos(t)ide analogs, APRI score, Forns Index, FIB-4 score, Lipid profile, HOMA-IR.

Introduction

Chronic liver disease causes an estimated 2 million deaths worldwide each year[1]. The destruction and regeneration of liver cells due to inflammation leads to progressive deterioration of liver function as a result of adaptive decompensation. Fibrosis of liver cells leads to complications such as cirrhosis and hepatocellular carcinoma (HCC). The World Health Organization estimates that 3.5% of the world's population are carriers of chronic hepatitis B (HBV), 68% of these infected patients are in the Western Pacific (115 million) and sub-Saharan Africa (60 million)[2]. Although its prevalence has decreased with universal childhood hepatitis B vaccination programs, former HBV carriers are still at risk for chronic liver disease. On the other hand, there is an increasing burden of metabolic syndrome (MetS) worldwide. Individuals with MetS have an accumulation of fat or triglycerides in liver cells due to components of MetS, such as insulin resistance, abnormal lipid metabolism, and dysregulation of cytokines and adipokines. The destruction that begins at this cellular level causes an irreversible spectrum and progresses to chronic liver disease[3]. Although the mechanistic relationship between CHB and MetS is not fully resolved, evidence suggests that MetS may have an additive effect on CHB-induced liver damage. It has been suggested[4] that MetS may be associated with the continuation of mortality and morbidity despite the anti-viral treatment given to people infected with HBV.

Patients and Methods

Work and Population

In this retrospective descriptive study, the results of 265 patients with CHB with and without

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delta agents who applied to the gastroenterohepatology outpatient clinic were evaluated over one year. This study was approved by the local Ethics Committee (Turgut Ozal University Ethics Committee, accepted: decision dated 04.04.2022 and numbered 2022/68) and followed the guidelines of the Declaration of Helsinki.

Patients and Laboratory Tests

Demographic characteristics, blood tests, medical treatment, non-invasive liver fibrosis indicators, ultrasonography, and metabolic parameters of all CHB patients with and without delta agents were analyzed from the hospital automation system. Nucleoside analogs [entecavir (ETV), lamuvudine (LAM), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF)], anti-diabetic drugs [insulin, oral anti-diabetics (OAD)] used in medical treatment were recorded. Hepatosteatosis levels of the patients were graded ultrasonographically. In blood controls of patients with CHB, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), hemogram, glucose, uric acid, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, and insulin values were measured. Based on the results of these blood tests, HOMA-IR, which is an indicator of insulin resistance in metabolic syndrome, was calculated. Total cholesterol/HDL value, which is also associated with atherosclerotic disease as a result of metabolic syndrome, was calculated. APRI, Forns Index, and FIB-4 score, which are non-invasive indicators of liver fibrosis, were calculated. The HOMA-IR value was calculated as HOMA-IR=Fasting Glucose(mg/dL) x Fasting Insulin(uIU/mL)/405. Patients with a HOMA score of ≥2.7 were considered positive for insulin resistance.

Non-Invasive Liver Tests

AST/Platelet ratio index (APRI),
Forns Index, FIB-4
- APRI=([Upper reference limit value of AST/AST]/Platelet count [10^9/L]) × 100,
- Forns Index = 7.811-3.131 × ln (platelet count) + 0.781 × In (GGT) + 3.467 × ln (age)- 0.014 × cholesterol (mg/dL),
- FIB-4 = Age (years) × AST (U/L)/[Platelet count (10^9/L) × (ALT)1/2 (U/L)

Statistical Analysis

While evaluating the findings obtained in the study, NCSS (Number Cruncher Statistical System) 2020 Statistical Software (NCSS LLC, Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, quantitative variables were shown with mean, standard deviation, median, min, and max values, and qualitative variables were shown with descriptive statistical methods such as frequency and percentage. Shapiro-Wilks test and Box Plot graphics were used to evaluate the conformity of the data to the normal distribution. Student-*t* test was used in quantitative two-group evaluations with normal distribution, one-way ANOVA test was used in the comparison of three groups and above, and the Bonferroni test was used to determine the group that caused the difference. Paired Sample *t*-test was used for in-group evaluations. Mann-Whitney U test for the evaluation of non-normally distributed variables according to two groups, the Kruskal-Wallis' test was used in the comparison of three groups and above, and the Dunn test was used to determine the group that caused the difference. Fisher's Exact test was used to compare qualitative data. The results were evaluated at the 95% confidence interval, and the significance level was $p<0.05$.

Results

The study was carried out between 2021 and 2022. It was conducted with a total of 265 cases, 55.5% (n=147) male and 44.5% (n=118) female. The ages of the participants ranged from 18 to 80, and the mean age was found to be 46.54±14.03.

It was observed that 21.9% (n=58) of the patients participating in the study were positive for HBV DNA. It was observed that 9.1% (n=58) of the cases were HDV RNA positive. It was observed that 29.1% (n=77) of the patients were co-infected. 62.3% (n=165) of the patients received medical treatment. Nucleoside analogs were used in medical treatment; 70.3% (n=116) had TDF, 6.1% (n=10) TAF, 3% (n=5) LAM, 20.6% and (n=34) ETV. When the patients participating in the study were examined metabolically; 12.5% (n=33) had a diagnosis of diabetes mellitus (DM). 4.9% (n=13) of these patients were receiving insulin therapy. It was observed that 10.9% (n=29) used OAD, while 11.3% (n=30) of the cases were receiving HL treatment (Table I).

LDL cholesterol measurement values of patients who received medical treatment were found to be statistically significantly lower than those of patients who did not receive medical treatment

(p=0.045; p<0.05). HDL cholesterol measurement values of the subjects who received medical treatment were found to be statistically significantly lower than those who did not receive medical treatment (p=0.001; p<0.01). The total cholesterol values of the patients who received medical treatment were found to be statistically significantly lower than those who did not receive medical treatment (p=0.001; p<0.01). The HOMA-IR measurement values of the patients who received medical treatment were found to be statistically significantly higher than those who did not receive medical treatment (p=0.019; p<0.05) (Table II).

ALT and AST measurement values of the subjects who received medical treatment were statistically significantly higher than those of patients who did not (p=0.001; p=0.001; p<0.01). The APRI scores of the subjects who received medical treatment were statistically significantly higher than those of patients who did not (p=0.001; p<0.01). A statistically significant difference was found between the % APRI scores of the cases according to their medical treatment status (p=0.001; p<0.01). While the rate of F0-F1 % APRI measurements of those who did not receive medical treatment was higher than those of patients who received medical treatment, the rate of F2, F3-F4 was lower. The FIB-4 scores of the subjects who received medical treatment were statistically significantly higher than those of patients who did not (p=0.001; p<0.01). A statistically significant

Table I. Distributions of descriptive characteristics.

		n (%)
Gender	Male	147 (55.5)
	Female	118 (44.5)
Age	Mean±Sd	46.54±14.03
	Median (Min-Max)	46 (18-80)
HBV DNA	Mean±Sd	2441920.43±1476172.70
	Median (Min-Max)	0 (0-100.000.000)
	Negative	207 (78.1)
	Positive	58 (21.9)
HDV RNA	Mean±Sd	9.07±28.75
	Median (Min-Max)	0 (0-100)
	Negative	241 (90.9)
	Positive	24 (9.1)
HBV DNA + HDV RNA	Negative	188 (70.9)
	Positive	77 (29.1)
Medical treatment status and drugs used in treatment	Absent	100 (37.7)
	Existent	165 (62.3)
	TDF	116 (70.3)
	TAF	10 (6.1)
	LAM	5 (3.0)
	ENT	34 (20.6)
DM	Absent	232 (87.5)
	Existent	33 (12.5)
Insulin	Absent	252 (95.1)
	Existent	13 (4.9)
OAD	Not Used	236 (89.1)
	Used	29 (10.9)
Cancer History	Absent	253 (95.5)
	Existent	12 (4.5)
INF treatment	Absent	251 (94.7)
	Existent	14 (5.3)
CAD	Absent	249 (94.0)
	Existent	16 (6.0)
HL treatment	Absent	235 (88.7)
	Existent	30 (11.3)
Liver Transplantation	Absent	260 (98.1)
	Existent	5 (1.9)

HBV DNA: Hepatitis B virus Deoxyribo nucleic acid, HDV RNA: Hepatitis D virus Ribonucleic acid, DM: Diabetes mellitus, OAD: Oral anti-diabetic, INF: Interferon, CAD: Coronary artery disease, HL: Hyperlipidemia.

Table II. Comparison of metabolic variables by medical treatment reception status.

| | | Total | Medical Treatment | | |
			Absent (n=100)	Existent (n=165)	p
Ultrasound Hepatosteatosis	**Grade 0**	214 (80.8)	81 (81.0)	133 (80.6)	a0.376
	Grade 1	45 (17.0)	15 (15.0)	30 (18.2)	
	Grade 2	5 (1.9)	3 (3.0)	2 (1.2)	
	Grade 3	1 (0.4)	1 (1.0)	0 (0)	
Uric acid	Mean±Sd	4.53±1.27	4.52±1.18	4.54±1.32	b0.888
	Median (Min-Max)	4.5 (1-9.4)	4.5 (1-7.9)	4.5 (1.9-9.4)	
HbA1c	Mean±Sd	5.92±3.41	6.05±5.28	5.84±1.34	c0.412
	Median(Min-Max)	5.5 (3.9-58)	5.4 (4.4-58)	5.5 (3.9-13.5)	
LDL	Mean±Sd	92.52±29.8	97.23±28.16	89.66±30.48	b0.045*
	Median (Min-Max)	91.7 (27-238.1)	93.3 (54.3-212.5)	89.3 (27-238.1)	
HDL	Mean±Sd	47.02±14.38	51.62±15.03	44.23±13.25	b0.001**
	Median (Min-Max)	45.9 (9.3-129.8)	51 (26.9-129.8)	43.7 (9.3-88.6)	
Cholesterol	Mean±Sd	164.99±34.52	174.66±32.58	159.14±34.44	b0.001**
	Median (Min-Max)	164 (78.3-295)	171 (106-295)	159 (78.3-295)	
Triglyceride	Mean±Sd	127.80±70.97	131.13±72.66	125.79±70.07	b0.554
	Median (Min-Max)	112.2 (11.8-566.2)	116.5 (28.3-566.2)	110.8 (11.8-549)	
HOMA-IR	Mean±Sd	6.03±8.93	4.68±7.30	6.85±9.72	c0.019*
	Median (Min-Max)	2.8 (0.4-77.5)	2.3 (0.6-63.6)	3.3 (0.4-77.5)	

aFisher-Freeman Halton test. bStudent-t test. cMann-Whitney U test. **$p<0.01$, *$p<0$.

difference was found between the % FIB-4 scores of the cases according to their medical treatment status ($p=0.001$; $p<0.01$). While the percentage of F0-F1 % FIB-4 scores of those who did not receive medical treatment was higher than those of patients who received medical treatment, the rate of F3-F4 was lower. Forns index scores of the cases who received medical treatment were found to be statistically significantly higher than those of patients who did not receive medical treatment ($p=0.001$; $p<0.01$). A statistically significant difference was found between the % Forns index scores of the cases, according to their medical treatment status ($p=0.001$; $p<0.01$). While the percentage of F0-F1 Forns index scores of those who did not receive medical treatment was higher than those of patients who received medical treatment, F2-F3-F4 was lower (Table III).

A statistically significant difference was found between the HbA1c measurement values of the cases according to the drugs used in medical treatment ($p=0.018$; $p<0.05$). As a result of the pairwise comparisons made in order to determine the source of the difference, HbA1c measurement values of those using the ETV drug were sig-

nificantly higher than those of patients using the LAM drug ($p=0.010$; $p<0.05$) (Table IV).

A statistically significant difference was found between the ALT measurement values of the cases according to the drugs used in medical treatment ($p=0.038$; $p<0.05$). As a result of the pairwise comparisons made in order to determine the source of the difference, the ALT values of the patients using TDF medication were significantly higher than those of patients using LAM medication ($p=0.025$; $p<0.05$). A statistically significant difference was found between the FIB-4 scores of the cases according to the drugs used in medical treatment ($p=0.001$; $p<0.01$). As a result of pairwise comparisons, the FIB-4 scores of patients using TDF drugs were significantly higher than those of patients using TAF and ETV drugs ($p=0.026$; $p=0.004$; $p<0.05$). A statistically significant difference was found between the FIB-4 % scores of the cases according to the drugs used in medical treatment ($p=0.001$; $p<0.01$). The FIB-4 % scores of the cases using the TDF drug were higher than those of patients using the ETV drug. The FIB-4 % scores of the cases using TAF drugs were lower than those of patients using TDF,

LAM, and ETV drugs. The FIB-4 % scores of the cases using TDF drugs were F2-F3 higher than those of patients using TAF and ETV drugs. The FIB-4 % scores of those who use LAM drugs are lower than those of patients who use TDF, TAF, and ETV drugs. A statistically significant difference was found between the Forns Index scores of the cases according to the drugs used in medical treatment ($p=0.001$; $p<0.01$). As a result of pairwise comparisons, the Forns Index scores of patients using TDF drugs were significantly higher than those of patients using TAF and ETV drugs ($p=0.038$; $p=0.003$; $p<0.05$). A statistically significant difference was found between the % Forns Index scores of the cases according to the drugs used in medical treatment ($p=0.006$; $p<0.01$). The percentage of Forn Index % scores F0-F1 of the cases using the TDF drug was higher than those of the patients using the ETV drug. The percentage of F2-F3-F4 percent of Forns Index scores of the cases using TDF drugs is lower than those of patients using TAF and ETV drugs. The percentage of F2-F3-F4 percentage scores in the Forns Index of the cases using the LAM drug is lower than those of patients using other drugs (Table V).

The uric acid, HbA1c, and HOMA-IR measurement values of the cases with DM were found to be statistically significantly higher than those of patients without DM ($p=0.017$; $p=0.001$; $p=0.016$; $p<0.05$). The HbA1c measurement values of the cases with HBV DNA (+) were found to be statistically significantly higher than those of patients with HBV DNA (-) ($p=0.001$; $p<0.01$).

ALT, AST measurement values, and APRI scores of cases with HBV DNA (+) were found to be statistically significantly higher than those of patients with HBV DNA (-) ($p=0.049$; $p<0.05$).

According to HBV DNA positivity, AST/ALT measurements, FIB-4 scores and percentages, Forns Index scores and percentages, total cholesterol/HDL values, ALP and GGT measurement values do not show a statistically significant difference ($p>0.05$).

Discussion

Studies on CHB and MetS have been carried out from many different centers around the world, and no clear results could be obtained when look-

Table III. Comparison of values associated with liver stiffness by receiving medical treatment.

			Medical treatment		
		Total	Absent (n=100)	Existent (n=165)	p
ALT	Mean±Sd	51.89±153.04	25.67±18.85	67.78±191.87[c]	0.001**
	Median (Min-Max)	24 (8-1928)	20 (8-123)	27 (8-1928)	
AST	Mean±Sd	42.21±103.28	21.67±7.65	54.65±129.32[c]	0.001**
	Median (Min-Max)	21 (7-1227)	20 (11-49)	22 (7-1227)	
AST/ALT	Mean±Sd	0.99±0.41	1.01±0.32	0.98±0.46[b]	0.646
	Median (Min-Max)	0.9 (0.3-4.9)	1 (0.3-1.8)	0.9 (0.4-4.9)	
APRI	Mean±Sd	0.70±2.04	0.25±0.13	0.98±2.54[c]	0.001**
	Median (Min-Max)	0.2 (0.1-20.5)	0.2 (0.1-1)	0.3 (0.1-20.5)	
% APRI	F0-F1	207 (78.1)	94 (94.0)	113 (68.5)[a]	0.001**
	F2	36 (13.6)	6 (6.0)	30 (18.2)	
	F3-F4	22 (8.3)	0 (0)	22 (13.3)	
FIB-4	Mean±Sd	1.65±2.52	0.89±0.46	2.11±3.09[c]	0.001**
	Median (Min-Max)	0.9 (0.3-19.3)	0.8 (0.3-2.2)	1 (0.3-19.3)	
% FIB-4	**F0-F1**	128 (48.3)	59 (59.0)	69 (41.8)[a]	0.001**
	F0-F1-F2	76 (28.7)	32 (32.0)	44 (26.7)	
	F2-F3	38 (14.3)	9 (9.0)	29 (17.6)	
	F3-F4	23 (8.7)	0 (0)	23 (13.9)	
FORNS Indeksi	Mean±Sd	4.48±2.4	3.52±1.78	5.05±2.54[b]	0.001**
	Median (Min-Max)	4.1 (0-12)	3.4 (0-8.9)	4.5 (0.2-12)	
% FORNS Indeksi	**F0-F1**	135 (50.9)	67 (67.0)	68 (41.2)[a]	0.001**
	F2-F3-F4	41 (15.5)	3 (3.0)	38 (23.0)	
	NS	89 (33.6)	30 (30.0)	59 (35.8)	
Cholesterol/ HDL	Mean±Sd	3.82±1.50	3.60±1.07	3.96±1.69[b]	0.056
	Median (Min-Max)	3.5 (1.5-15.1)	3.4 (1.8-6.4)	3.6 (1.5-15.1)	

[a]Fisher-Freeman Halton test. [b]Student-*t* test. [c]Mann-Whitney U test. **$p<0.01$.

Table IV. Comparison of metabolic variables by medical treatment receiving status.

		Drugs used in medical treatment				
		TDF (n=116)	TAF (n=10)	LAM (n=5)	ETV (n=34)	*p*
Ultrasound	Grade 0	96 (82.8)	8 (80.0)	4 (80.0)	25 (73.5)	0.627[a]
Hepatosteatosis	Grade 1	19 (16.4)	2 (20.0)	1 (20.0)	8 (23.5)	
	Grade 2	1 (0.9)	0 (0)	0 (0)	1 (2.9)	
Uric acid	Mean±Sd	4.48±1.27	5.08±1.24	4.06±1.66	4.64±1.48	0.439[d]
	Median (Min-Max)	4.4 (1.9-9)	4.9 (3.6-8)	3.7 (2.2-6.2)	4.5 (2-9.4)	
HbA1c	Mean±Sd	5.64±1.04	6.11±1.36	5.16±0.24	6.54±1.96	0.018[e]*
	Median (Min-Max)	5.4 (3.9-13.5)	5.6 (5.1-9.4)	5.1 (4.9-5.5)	5.8 (4-12.5)	
LDL	Mean±Sd	89.90±31.58	79.30±28.44	77.20±18.07	93.71±28.45	0.461[d]
	Median (Min-Max)	89 (30.5-238.1)	81.2 (27-137)	76 (51.4-95)	92.3(56.8-156.3)	
HDL	Mean±Sd	44.14±13.27	51.63±16.59	48.58±14.97	41.71±11.44	0.180[d]
	Median (Min-Max)	43.5 (13-88.6)	49.4 (33.2-79.5)	45.7 (32-67.9)	41.3 (9.3-60.5)	
Cholesterol	Mean±Sd	159.24±34.96	150.72±36.04	150.4±35.58	162.54±32.88	0.744[d]
	Median (Min-Max)	158.5 (78.3-295)	136 (99-212)	161 (104-187)	159 (109-231)	
Triglyceride	Mean±Sd	125.49±73.69	98.75±35.03	122.08±45.80	135.32±67.62	0.549[d]
	Median (Min-Max)	110.2 (11.8-549)	99.1(57.6-160.7)	112.2(74.6-196.4)	115.5(53.4-334.4)	
HOMA-IR	Mean±Sd	6.55±8.79	6.03±5.12	3.52±3.57	8.61±13.66	0.345[e]
	Median (Min-Max)	3.2 (0.4-54.5)	4 (0.9-16.5)	1.4 (0.6-8.6)	4.8 (0.8-77.5)	

[a]Fisher-Freeman Halton test. [d]One-Way ANOVA test. [e]Kruskal-Wallis test & Dunn-bonferroni test. *$p<0.05$.

ing at the data. Studies[5,6] in sub-Saharan Africa found that the combined prevalence of MetS in people with CHB ranged from 5.0% to 30.1%. Although researchers reported these data, two studies[7,8] conducted in Europe suggested that there was no relationship between them, citing a profound lack of data on CHB and MetS. In our study, we found a high HbA1c rate in patients with high HBV DNA. HBV DNA positivity in patients increases the susceptibility to DM. On the other hand, many nucleoside analogs that we use in treatment have an effect on metabolic parameters. In our study, we observed that while total cholesterol, LDL and HDL levels decreased with the use of nucleoside analogs in patients diagnosed with CHB, HOMA-IR levels increased. HbA1c was found to be higher in patients using ETV compared to those using other nucleoside analogs. We cannot directly determine the comparison of CHB and MetS due to multifactorial factors. While no correlation was found between CHB and MetS in a case series conducted in Taiwan[9], an inverse correlation was reported between CHB and MetS in two other cross-sectional studies from Taiwan[10,11]. A large population-based study conducted in the United States (NHANES III study) found a significantly lower prevalence of MetS in CHB patients compared to controls (10.4% *vs.* 25.6%, *p*=0.019). This inverse correlation between MetS and CHB, classified by gender, was found to persist in men, but not in women. CHB patients with

high ALT levels had a significantly lower rate of MetS compared to controls (2.1% *vs.* 49.8%, *p*<0.001). In light of these findings, Janicko et al[7] and Jarčuška et al[8] suggested that chronic liver inflammation rather than HBV itself may be responsible for metabolic derangements in CHB patients[12]. Studies[7,8] conducted in Europe and Slovakia report MetS prevalence rates of 24.6% in populations with CHB[8]. No significant association was found between MetS and HBV infection in either study in Slovakia[7,8]. Instead, other studies[12] showed that CHB patients with MetS showed significantly higher HBV-DNA viral load and elevated liver enzymes, including ALT and GGT, compared to those without MetS[12]. This suggested that MetS has an additive effect on CHB-induced liver injury[7,8]. In contrast, a positive association between an occult HBV infection and MetS [hazard ratio (HR) = 2.27. 95% CI: 1.52-3.38] was demonstrated in a 2014 retrospective Chinese cohort study[13]. Zhou et al[13] suggested that occult HBV infection may be a risk factor for the development of MetS. It is understood from these data that the mechanistic relationship between CHB and MetS is not fully resolved. The reason for the conflicting findings may be the differences in the diagnostic criteria of MetS used in various studies[14-18]. Several studies[5,19-21] have shown that underlying MetS increases the risk and progression of liver fibrosis, cirrhosis, and HCC in patients with CHB. A longitudinal population-based study[21], with 1,690 out of 2,979 par-

ticipants aged 40-65 years diagnosed with CHB, found that the presence of three or more metabolic risk factors, compared to no factor, increased the risk of HCC by two to threefold. It was observed that the risk of HCC increased exponentially in CHB patients. This association continued after controlling for high HBV-DNA ($\geq$ 10,000 copies/mL), viral factors, and other known risk factors for HCC. Among these metabolic risk factors, insulin resistance and central obesity were independently associated with liver damage and the development of HCC. In the cohort conducted by Shyu et al[22], 2,966 CHB patients with Type 2 diabetes (T2DM) and 2,966 CHB patients without T2DM were followed up for an average of 11.4 years. In CHB patients with T2DM, the HCC incidence (13.3% *vs.* 10.0%; *p*<0.001) and HCC-related mortality (4.7% *vs.* 7.5%; *p*<0.001) were significantly higher. Here, elevated serum adiponectin levels may also play a role in the increased risk of liver fibrosis, cirrhosis, and HCC[23,24]. It has been reported[11,12,25,26] that total cholesterol and triglyceride levels are significantly lower in patients with CHB. Similar to the literature, no significant difference was found in triglyceride values in our study, while total cholester-

ol, HDL, and LDL values were low. Although the heterogeneity in lipid profiles among CHB patients is not fully understood, some virus-specific risk factors have been associated[26] with lipid abnormalities observed in the CHB diagnosed population. It has also been shown[25,27] that viral antigens reduce serum triglyceride levels by inhibiting the secretion of apolipoprotein B, a necessary component for multi-LDL and LDL formation, and cause hepatic triglycerides to accumulate.

Joo et al[28], in their research, found that patients with HBV infection were associated with a lower risk of non-alcoholic fatty liver disease (NAFLD) cases. By investigating the lipid profiles in these patients, they reported a significant reduction in total cholesterol levels over time in CHB patients compared to controls. This suggested that HBV infection may protect against the development of NAFLD, possibly through its effect on lipid metabolism. Our study is the first in the literature to find that HOMA-IR was high in patients with CHB and using nucleos(t)ide analogs. Patients in the study were using ETV, LAM, TDF, and TAF as nucleos(t)ide analogs. APRI, Forns Index, and FIB-4 scores evaluated for liver stiffness were

Table V. Comparison of values associated with liver stiffness by receiving medical treatment.

		Drugs used in medical treatment				
		TDF (n=116)	TAF (n=10)	LAM (n=5)	ETV (n=34)	*p*
ALT	Mean±Sd	73.12±220.53	59.72±63.17	14.20±4.09	59.81±108.49	**0.038**[e]*
	Median (Min-Max)	27.5 (10-1928)	40.5 (9-203)	13 (10-21)	26 (8-580)	
AST	Mean±Sd	55.99±146.46	47.99±38.52	19.2±3.27	57.26±87.92	**0.214**[e]
	Median (Min-Max)	23 (11-1227)	40 (15-140)	18 (16-24)	22 (7-328)	
AST/ALT	Mean±Sd	0.94±0.45	1.20±0.62	1.39±0.22	1.01±0.43	**0.059**[d]
	Median (Min-Max)	0.9 (0.4-4.9)	1 (0.6-2.3)	1.4 (1.1-1.7)	0.9 (0.4-2.6)	
APRI	Mean±Sd	1.02±2.91	1.00±0.81	0.28±0.18	0.96±1.55	**0.063**[e]
	Median (Min-Max)	0.2 (0.1-20.5)	0.8 (0.1-2.5)	0.2 (0.1-0.6)	0.4 (0.1-7)	
% APRI	**F0-F1**	84 (72.4)	3 (30.0)	4 (80.0)	22 (64.7)	**0.116**[a]
	F2	19 (16.4)	4 (40.0)	1 (20.0)	6 (17.6)	
	F3-F4	13 (11.2)	3 (30.0)	0 (0)	6 (17.6)	
FIB-4	Mean±Sd	3.24±2.56	1.29±0.53	2.8±3.57	2.11±3.09	**0.001**[e]**
	Median (Min-Max)	2.5 (0.4-7.9)	1 (0.8-2)	1.5 (0.5-19.3)	1 (0.3-19.3)	
% FIB-4	**F0-F1**	58 (50.0)	2 (20.0)	1 (20.0)	8 (23.5)	**0.001**[a]**
	F0-F1-F2	31 (26.7)	0 (0)	3 (60.0)	10 (29.4)	
	F2-F3	13 (11.2)	5 (50.0)	1 (20.0)	10 (29.4)	
	F3-F4	14 (12.1)	3 (30.0)	0 (0)	6 (17.6)	
FORNS Indeksi	Mean±Sd	6.79±3.02	4.56±1.59	6.26±2.16	5.05±2.54	**0.001**[d]**
	Median (Min-Max)	6.7 (2.2-11.8)	4.4 (2.3-6.5)	6.5 (2.5-9.5)	4.5 (0.2-12)	
% FORNS Indeksi	F0-F1	57 (49.1)	2 (20.0)	2 (40.0)	7 (20.6)	**0.006**[a]**
	F2-F3-F4	20 (17.2)	5 (50.0)	0 (0)	13 (38.2)	
	NS	39 (33.6)	3 (30.0)	3 (60.0)	14 (41.2)	
Cholesterol/HDL	Mean±Sd	3.05±0.72	3.17±0.49	4.37±2.27	3.96±1.69	**0.113**[d]
	Median (Min-Max)	3 (2.1-4.1)	3 (2.8-3.8)	4.1 (2.3-15.1)	3.6 (1.5-15.1)	

[a]Fisher-Freeman Halton test. [d]One-Way ANOVA test. [e]Kruskal-Wallis test and Dunn-bonferroni test. *p*<0.05, **p*<0.01.

observed in favor of increased fibrosis in those receiving medical treatment. We thought that delayed initiation of medical treatment, long-standing viral load, unknown effects of the medical treatment we used on the liver, and patient-related effects might cause this.

Limitations

Since we evaluated the patients with a single visit and we did not know the height, weight, body mass index, and family history of the patients, we could not combine this in our net research. Despite this limitation in our study, we detected high HbA1c values in patients using nucleos(t)ide analogs. Again, we detected more significant and higher HbA1c levels in patients using ETV than in those using LAM, TDF, and TAF. We also found that APRI, Forns Index, and FIB-4 scores, which we look at to evaluate liver stiffness, were significantly higher in those using TDF among nucleos(t)ide analogs.

Conclusions

We do not know the effects of CHB on MetS, and we do not know the effect of long-term nucleos(t)ide analogs on host metabolism. In our study, the effects on metabolic variability and liver stiffness in patients with inactive hepatitis B who did not receive medical treatment and CHB who received medical treatment (ETV, LAM, TDF, and TAF) were evaluated from a whole perspective. HbA1c was found to be high in patients with high HBV DNA replication. In addition, total cholesterol, LDL, and HDL were found to be lower in those using nucleoside analogs. While liver stiffness was found to be high with APRI, FIB-4, and Forns Index in patients using TDF, we found that lipid profile was low and HgA1c was high in patients using ENT. As a result, MetS was found to be multifactorial. Although CHB and nucleoside analogs increase susceptibility to MetS, we still have a lot of data to be investigated.

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