

Evaluation of Metabolic Changes in Patients Initiated on Tenofovir Alafenamide Fumarate Therapy

Tenofovir Alafenamid Fumarat Tedavisi Başlanan Hastalarda Metabolik Değişikliklerin Değerlendirilmesi

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ABSTRACT

Introduction: Hepatitis B virus (HBV) infection remains a common global health issue affecting millions and may lead to severe complications. The choice of antiviral drugs for effective HBV treatment plays a critical role in patient outcomes, although the side effects of these drugs must also be considered.

Materials and Methods: This retrospective study included 57 patients who either started antiviral treatment for HBV or switched to tenofovir alafenamid fumarate (TAF) therapy between February 1, 2020, and February 1, 2023. The patients' medical records were retrospectively reviewed.

Results: Among the 57 patients included, 34 were male (59.6%) with a mean age of 60.8±11.3 years. Seven patients (12.3%) had a history of solid organ transplantation. TAF therapy was initiated following a switch from entecavir in 3 patients (5.3%) and from tenofovir disoproxil fumarate in 46 patients (80.7%). Although there were numerical increases in body weight and fasting blood glucose, these changes were not statistically significant ($p=0.44$, $p=0.28$, respectively). The mean baseline triglyceride (TG) level was 128.7±18.69 mg/dL, while the mean follow-up level increased to 148.8±14.6 mg/dL, a statistically significant change ($p=0.043$).

Conclusion: TAF therapy was associated with increased serum TG levels. However, these findings should be interpreted with caution due to the relatively small sample size ($n=57$), which limits the generalizability of the results. However, further long-term prospective studies with larger cohorts are needed to assess the metabolic effects of TAF, both in treatment-naïve and previously treated patients.

Keywords: metabolic dysfunction, hypertriglyceridemia, hepatitis B treatment, chronic liver disease

ÖZET

Amaç: Hepatit B virüsü (HBV) enfeksiyonu milyonlarca kişiyi etkileyen yaygın bir küresel sağlık sorunu olmaya devam ediyor ve ciddi komplikasyonlara yol açabiliyor. Etkili HBV tedavisi için antiviral ilaçların seçimi hasta sonuçlarında kritik bir rol oynar, ancak bu ilaçların yan etkileri de dikkate alınmalıdır.

Materyaller ve Yöntemler: Bu retrospektif çalışmaya 1 Şubat 2020 ile 1 Şubat 2023 tarihleri arasında HBV için antiviral tedaviye başlayan veya tenofovir alafenamid fumarat (TAF) tedavisine geçen 57 hasta dahil edildi. Hastaların tıbbi kayıtları retrospektif olarak incelendi.

Sonuçlar: Dahil edilen 57 hastadan 34'ü erkekti (%59,6) ve ortalama yaşları 60,8±11,3 yıldır. Yedi hastanın (%12,3) solid organ nakli öyküsü vardı. TAF tedavisi 3 hastada (%5,3) entekavir'den ve 46 hastada (%80,7) tenofovir disoproksil fumarat'tan geçişin ardından başlatıldı. Vücut ağırlığında ve açlık kan şekerinde sayısal artışlar olmasına rağmen, bu değişiklikler istatistiksel olarak anlamlı değildi (sırasıyla $p=0,44$, $p=0,28$). Ortalama başlangıç trigliserit (TG) seviyesi 128,7±18,69 mg/dL iken, ortalama takip seviyesi 148,8±14,6 mg/dL'ye yükseldi, bu istatistiksel olarak anlamlı bir değişikliği ($p=0,043$).

Sonuç: TAF tedavisi serum TG seviyelerinde artışla ilişkilendirildi. Ancak, hem tedavi görmemiş hem de daha önce tedavi görmüş hastalarda TAF'ın metabolik etkilerini değerlendirmek için daha büyük kohortlara daha uzun vadeli prospektif çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Metabolik disfonksiyon, hipertrigliseridemi, hepatit B tedavisi

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Introduction

Hepatitis B Virus (HBV) remains a widespread infection that continues to affect millions of people despite ongoing vaccination efforts, and it can lead to significant complications(1). The primary goals of antiviral agents used in treatment are to prevent hepatocellular damage, halt the progression to life-threatening liver failure, reduce the risk of hepatocellular carcinoma (HCC), and even reverse disease progression (1,2). However, as with any treatment, therapies administered for chronic HBV infection also have side effects. In recent years, increasing attention has been directed toward the metabolic safety profiles of antiviral agents used in chronic HBV management.

Tenofovir alafenamide fumarate (TAF), introduced in 2016 for the treatment of chronic HBV, offers greater plasma stability and ensures antiviral efficacy through lower systemic exposure (3). TAF is preferred over TDF, especially in cases of osteoporosis and chronic kidney disease (CKD) (3-6). Moreover, it may be considered as a first-line treatment option in newly diagnosed cases of chronic HBV. TAF therapy can offer patients a better safety profile and improved long-term tolerability (7).

There are publications reporting occurrences of hyperlipidemia or weight gain in patients who have switched to TAF therapy (8,9). However, the effect of TAF on hyperlipidemia remains an important area of ongoing research. This study aimed to investigate the metabolic side effect profile in chronic HBV patients monitored at our center who switched to TAF from TDF or entecavir (ETV) due to side effects, as well as in treatment-naïve chronic HBV patients initiated on TAF.

Materials and Methods

This study included patients who presented to the Gastroenterology outpatient clinic at XXX Hospital between February 1, 2020, and February 1, 2023, who were under regular follow-up every 3 to 6 months, and who either newly initiated antiviral therapy for chronic HBV infection or had previously been on antiviral treatment and subsequently switched to TAF therapy. Patients included in the study had

received TAF treatment for at least 6 months. Laboratory results obtained during follow-up between months 6 and 12, specifically those closest to the 12th month, were used in the analysis.

During initial and follow-up evaluations, patients' height and current weight, complete blood count, AST, ALT, creatinine, HbA1c, fasting serum glucose, LDL, HDL, and triglyceride levels were recorded in patient files. Based on available laboratory data, A1c, APRI, and FIB-4 scores were calculated. Serum AST and ALT levels were assessed only in patients who had a change in antiviral therapy. Patients diagnosed with familial hypercholesterolemia, those without lipid panel results or body weight records, and those who had started new antilipidemic agents for less than one year or medications that could cause lipid dysregulation during the follow-up period were excluded from the study. Hepatic steatosis was evaluated by ultrasonography and graded according to the hepatorenal echogenicity comparison (grades 1–3). Grade 1 steatosis was defined as a mild increase in hepatic echogenicity with preserved visualization of intrahepatic vessels and diaphragm; grade 2 as a moderate increase in echogenicity with slightly impaired visualization; and grade 3 as a marked increase in echogenicity with poor visualization of vascular structures and the diaphragm.

The study was approved by the Ethics Committee for Clinical Research No. 1 of XXX Hospital (Date: 26/04/2023, Approval No: E1-23-3495). It was conducted in accordance with the principles of the Declaration of Helsinki. As the study was retrospective, written informed consent was not obtained. However, verbal consent was obtained when patients were contacted for missing data and updated weight information.

Results

Of the 57 patients included in the study, 23 were female (40.4%) and 34 were male (59.6%). The mean age was 60.8±11.3 years (range: 29–80). Seven patients (12.3%) had a history of organ transplantation. Three patients (5.3%) had switched from ETV and 46 patients (80.7%) from TDF to TAF therapy. Among the total cohort, 23 patients had osteoporosis, 25 had

Table-1: Comparison of Parameters Before and After TAF Treatment

Parameter	Before TAF treatment	After TAF treatment	P value
BMI (kg/m ²)	27.6 ± 4.9	27.9 ± 4.2	.466
Body weight (kg)	77.8 ± 13.7	78.5 ± 12.8	.442
Serum triglycerides (mg/dL)	104 (33-972)	126 (46-171)	.004*
Serum LDL (mg/dL)	99.4 ± 35.1	99.2 ± 37.2	.942
Serum HDL (mg/dL)	45.2 ± 14.2	46.2 ± 17.1	.708
Fasting blood glucose (mg/dL)	103 ± 32	109 ± 48	.283
Glycated HbA1c (%)	6.2 ± 1.4	6.3 ± 1.1	.695
Serum creatinine (mg/dL)	1.14 ± 0.62	1.07 ± 0.48	.069
Serum AST (IU/L)	27.6 ± 14.7	23.2 ± 10.5	.033*
Serum ALT (IU/L)	29.2 ± 23.5	26.3 ± 13.4	.315
Platelets (x10 ⁹ /L)	218.5 ± 89.1	203.2 ± 63.3	.118
Hemoglobin (g/dL)	13.7 ± 2.08	14.1 ± 1.8	.083
FIB-4	0.48 ± 0.34	0.41 ± 0.21	.110
APRI	0.73 ± 0.68	0.69 ± 0.61	.389
TC/HDL ratio	3.96 ± 1.22	4.05 ± 1.43	.532
LDL/HDL ratio	2.30 ± 0.75	2.29 ± 0.90	.892

Abbreviations: BMI, body mass index; TAF, tenofovir alafenamide fumarate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HbA1c, glycated hemoglobin; FIB-4, fibrosis-4 index; APRI, aspartate aminotransferase-to-platelet ratio index.

CKD, and 1 patient had both osteoporosis and CKD, all of whom were switched to TAF due to these complications. Additionally, 8 patients (14%) were treatment-naïve and started directly on TAF.

Although there was a numerical increase in patients' baseline body weight (77.8 ± 1.8 kg vs. 78.5 ± 1.7 kg) and fasting blood glucose (103.2 ± 4.8 mg/dL vs. 109.8 ± 6.4 mg/dL), the differences were not statistically significant (p=0.44 and p=0.28, respectively). Nine patients (15.7%) were receiving treatment for hyperlipidemia both before and after TAF initiation, with no change in dosage. The mean baseline triglyceride (TG) level was 128.7 ± 18.69 mg/dL, while the follow-up mean TG level was 148.8 ± 14.6 mg/dL. This increase was statistically significant (p=0.043). Fasting blood glucose levels showed a statistically significant increase during follow-up in the treatment-naïve group compared to the pre-treated group (p=0.005).

Even when the treatment-naïve group was excluded from the analysis, a statistically significant increase in TG levels persisted (p=0.039). This change was shown to be independent of antilipidemic drug use.

Pre-TAF evaluation revealed that 35% of patients had grade 1 or higher hepatic steatosis. During follow-up, hepatic steatosis decreased by at least one grade in 15% of patients, increased by at least one grade in 17%, and remained stable in the remaining patients. There was no statistically significant association between changes in hepatic steatosis and the switch in antiviral medication (p=0.645).

When hypertriglyceridemia was defined as TG ≥150 mg/dL, a significant increase was observed after switching to TAF. Paired analysis using the McNemar test showed that patients were more likely to develop hypertriglyceridemia after TAF therapy (OR 10.85, 95% CI 1.93–60.93; p=0.043).

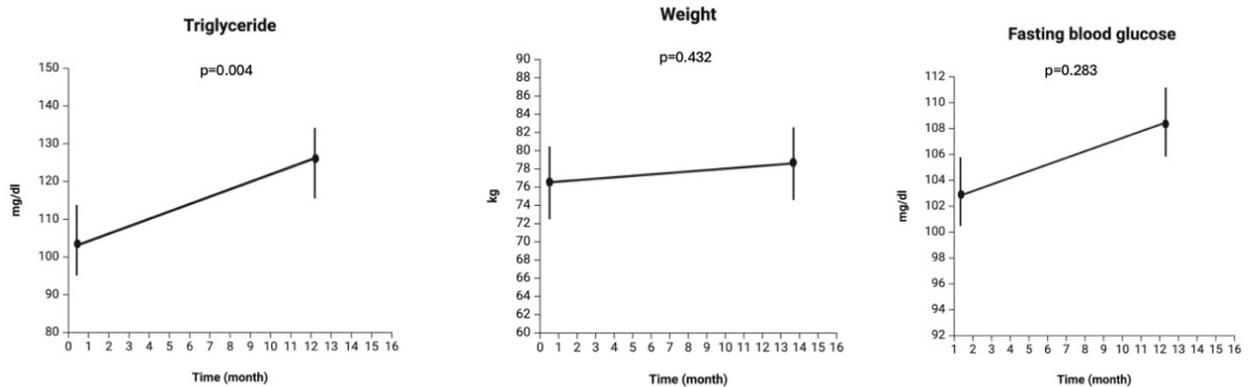


Figure 1. Changes in Triglyceride, Body Weight, and Fasting Blood Glucose Levels During 12 Months of TAF Therapy (* $p < 0.05$)

Discussion

In our study, patients who initiated TAF therapy or were switched from TDF to TAF showed increases in body weight and fasting blood glucose levels; however, these changes were not statistically significant. In contrast, serum triglyceride levels demonstrated a significant increase following TAF initiation.

These findings are consistent with data from a large Swiss cohort, where switching from TDF to TAF was associated with greater mean weight gain and a higher incidence of newly developed overweight or obesity over an 18-month period. Moreover, TAF use resulted in significant increases in total cholesterol, LDL, HDL, and triglyceride levels compared to continued TDF use. These metabolic alterations further support growing concerns about the adverse lipid and weight-related effects of TAF therapy (8). Similarly, our study observed an increase in body weight, although this was not statistically significant—likely due to the limited sample size.

Further evidence supporting a drug-related metabolic effect of TAF comes from a cohort study including 385 patients, in which 168 individuals were switched back from TAF to TDF after a median of 96 weeks of TAF exposure. Following the switch back to TDF, both total cholesterol and triglyceride levels showed marked reductions. These findings suggest that lipid alterations observed during TAF therapy may be at least partially reversible and are likely attributable to the pharmacological effects of TAF rather than irreversible metabolic changes. Notably, patients who had experienced greater increases in total cholesterol during TAF treatment showed more

pronounced reductions after switching back to TDF (9). These findings strongly support the hypothesis that these metabolic alterations are drug-related. Therefore, any increase in total cholesterol in patients receiving TAF should initially be considered treatment-associated.

In the OPERA cohort, switching from TDF to TAF was associated with rapid and significant increases in LDL cholesterol and triglyceride levels, particularly during the first 9–16 months. These lipid changes paralleled early weight gain and occurred even in patients who maintained all other antiretroviral agents, indicating a direct metabolic impact of TAF. Importantly, lipid levels did not return to baseline, despite a plateau or modest decline beyond 16 months of TAF therapy (10). As our study covers only 6–12 months of follow-up, these findings suggest that the observed elevations may represent early-phase changes. However, since no long-term data are available in our study, it remains uncertain whether these changes persist or progress over time. Based on previous literature, normalization of lipid parameters during continued TAF treatment is not expected.

In a multicenter cohort of patients with chronic hepatitis B, TAF therapy was significantly associated with increased triglyceride and total cholesterol levels compared to TDF. The incidence of dyslipidemia was notably higher in the TAF group, and these associations remained significant after propensity score matching. These findings emphasize the importance of regular lipid monitoring in patients with chronic hepatitis B receiving TAF therapy (11).

Furthermore, in a real-world cohort of treatment-naïve patients with chronic hepatitis B, TAF use was consistently associated with significant increases in total cholesterol, triglycerides, LDL, and atherogenic lipid ratios (LDL/HDL and TC/HDL) over 48 and 96 weeks. In contrast, TDF demonstrated lipid-lowering effects, particularly reducing total cholesterol and TC/HDL ratio. These findings highlight the importance of assessing cardiovascular risk when choosing antiviral therapy for chronic hepatitis B management (12). In our study, although TC/HDL and LDL/HDL ratios were evaluated, no statistically significant changes were observed.

Despite observed increases in triglycerides, fasting glucose, and body weight, no progression in hepatic steatosis was detected via ultrasound in our cohort. However, since the post-TAF evaluation was limited to 12 months, these changes may be too early to manifest as measurable hepatic steatosis.

The limitations of our study include its retrospective design and relatively small sample size. Although most patients had been previously treated with TDF, the inclusion of treatment-naïve individuals introduced a degree of heterogeneity. Although several potential confounders, including chronic kidney disease, osteoporosis, transplantation status, and concurrent medications, were carefully considered in the study design, residual confounding cannot be entirely excluded. In particular, unmeasured lifestyle-related factors such as dietary habits, physical activity, and alcohol consumption may have influenced metabolic outcomes. These factors should be taken into account when interpreting the results. However, this is not believed to have significantly impacted the primary outcomes of the study.

Although the association between TAF therapy and hypertriglyceridemia remains an area of ongoing debate, accumulating evidence—including the findings of the present study—suggests that TAF may increase triglyceride levels. Therefore, when initiating TAF as a first-line antiviral agent, particularly in patients with an elevated baseline metabolic risk profile, this potential adverse metabolic effect should be taken into consideration. Clinicians should be aware of the possible risk of hypertriglyceridemia

and provide patients with appropriate counseling regarding lifestyle modifications, including dietary interventions and regular physical activity. In selected patients, closer metabolic monitoring and timely initiation of lipid-lowering therapy may be warranted.

In conclusion, despite the limited number of patients, our study demonstrates that TAF therapy is associated with deterioration in lipid profiles. Therefore, before switching to TAF, patients should be carefully evaluated for metabolic risk factors. Close monitoring of cardiovascular and metabolic dysfunction risk is essential in this population.

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Informed consent: Written informed consent was obtained from all patients before inclusion.

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