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Retrospective Study

Dynamic Changes of Estimated Glomerular Filtration Rate are Conversely Related to Triglyceride in Non-overweight Patients

Si-Qi Liu, Xiu-Jun Zhang, Yuan Xue, Rui Huang, Jian Wang, Chao Wu, Yi-Shan He, Ya-Ru Pan, Long-Gen Liu

Abstract

BACKGROUND

Correlation between Triglyceride (TG) and estimated glomerular filtration rate (eGFR) remains largely unknown in overweight and non-overweight patients.

AIM

To investigate the dynamic changes of eGFR and lipid profiles during 3-year tenofovir disoproxil fumarate (TDF) treatment in patients with chronic hepatitis B (CHB) and overweight.

METHODS

A total of 202 CHB patients who received TDF treatment at the Third People's Hospital of Changzhou (Changzhou, China) and Nanjing Drum Tower Hospital (Nanjing, China) between January 2016 and May 2018 were retrospectively enrolled. According to the body mass index (BMI) at the initiation of TDF treatment, CHB patients were divided into overweight (BMI ≥ 25 kg/m²) and non-overweight (BMI < 25 kg/m²) groups. Logistic regression was applied for the analysis of risk factors for eGFR < 90 mL/(min $\cdot 1.73$ m²).

RESULTS

There is no significant difference in hepatitis B virus DNA (HBV DNA) negativity and hepatitis Be antigen (HBeAg) loss between patients with overweight and non-overweight (both $P > 0.05$). More patients in non-overweight group achieved alanine aminotransferase (ALT) normalization compared with those in overweight group ($\chi^2 = 11.036$, $P < 0.01$). In non-overweight patients, the eGFR significantly declined in the 1st year ($P < 0.01$), then remained at a relatively lower level. TG significantly declined in the 2nd year ($P = 0.02$) and increased in the 3rd year. Moreover, TG was negatively correlated with GFR at the four-time points ($P = 0.002, 0.030, 0.007, 0.008$, respectively). In overweight patients, eGFR and TG remained relatively stable during the 3-year treatment, and eGFR showed no significant relationship with TG. Moreover, multivariate analysis showed that age ($P < 0.01$, 95%CI [0.97–1.005]) and baseline eGFR ($P < 0.01$, 95%CI [5.056–33.668]) were independent risk factors for eGFR $< 90 \text{ mL}/(\text{min } 1.73 \text{ m}^2)$ at the 3rd year.

CONCLUSION

Dynamic changes in renal function were conversely related to TG during TDF treatment in patients with CHB and normal BMI, but not with overweight.

³ INTRODUCTION

Approximately 296 million people worldwide are chronically infected with hepatitis B virus (HBV), while an estimated 820 000 patients die on a yearly basis^[1]. In addition, liver cirrhosis (LC) and hepatocellular carcinoma (HCC) have been identified as the main causes of death. Previous studies have shown that ⁶antiviral therapy can slow the progression of LC and reduce the incidence of HCC caused by HBV infection^[2].

Tenofovir disoproxil fumarate (TDF) is recommended as one of the first-line antiviral agents. In phase III clinical trial, TDF was showed to be well tolerated during more than 7 years of follow-up^[3]. In addition, the estimated glomerular filtration rate

(eGFR) remained stable in patients with impaired kidney function during 3-year real-world studies conducted in Europe^[4]. Our previous study also showed that eGFR remained stable irrespective of prior LC or age >65 years old in a two-year real-world study^[5]. However, potential nephrotoxicity during long-term treatment of TDF remains a concern in clinical practice. A real-world observational study reported that eGFR significantly declined during 48-month TDF treatment, and the cumulative incidence of renal function impairment was significantly higher in the TDF group^[6]. TDF therapy and underlying chronic kidney diseases were identified as independent risk factors for renal dysfunction^[6]. Another study with a 10-year follow-up showed that the cumulative incidence of renal impairment was higher during TDF treatment as compared with entecavir^[7].

Overweight is a global pandemic associated with dyslipidemia. The accumulation of triglycerides leads to the development of hepatic steatosis (HS), resulting in a high incidence of non-alcoholic fatty liver (NAFLD)^[8]. Individuals may concomitantly suffer from two liver diseases, which in turn may have a synergistic effect on the risk of HCC, cirrhosis, and death^[9]. Compared with non-overweight patients, those suffering from overweight and dyslipidemia had significantly lower average eGFR^[10].

In addition, lipid profiles were regulated by TDF in patients with HIV or HBV infection. Triglyceride (TG), total cholesterol, and high-density lipoprotein cholesterol (HDL-C) significantly increased after switching from TDF to TAF, thus significantly worsening the lipid profile^[11-14]. For patients with CHB, TDF but not entecavir significantly decreases serum lipoprotein, including HDL-C, low-density lipoprotein cholesterol (LDL-C), and total cholesterol (CHOL)^[15]. However, the effects of TDF on eGFR and lipid profiles in patients CHB and obese remain largely unknown.

Herein, we investigated the dynamic changes of eGFR and lipid profiles during 3-year TDF treatment and their correlations in patients with CHB and overweight.

MATERIALS AND METHODS

Patients

A total of 355 HBV-infected patients who received TDF treatment at the Third People's Hospital of Changzhou (Changzhou, China) and Nanjing Drum Tower Hospital (Nanjing, China) between January 2016 and May 2018 were retrospectively enrolled. CHB and LC were diagnosed according to the Chinese guidelines for the prevention and treatment of CHB (2019 version)^[16]. Patients with immunodeficiency diseases, autoimmune diseases, alcohol abuse, and co-infection with other hepatitis viruses, were excluded. After 3-year follow-up, 153 patients with poor compliance, TDF discontinuation, or missing data were additionally excluded (**Figure 1**).

Demographic and clinical data including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), CHOL, TG, creatinine (Cr), calcium (Ca), phosphorus (P), and HBeAg were collected., complete response rates for HBV DNA suppression and ALT normalization were calculated. According to the International Obesity Task Force, Asians with body mass index (BMI) ≥ 25 kg/m² were diagnosed with overweight^[17].

The study was approved by the Ethics Committee of the Third People's Hospital of Changzhou according to the Declaration of Helsinki 1975. The retrospective study was non-interventional, anonymous and harmless to the patients, the written informed consents were exempt according to the ethic approval.

Estimated glomerular filtration rate (eGFR) calculation

eGFR was calculated based on the chronic kidney disease Epidemiology Collaboration equation (CKD-EPI_{cr}). Decreased eGFR was defined as eGFR < 90 mL/(min 1.73m²).

Statistical analysis

All data were analyzed using SPSS26.0 (Chicago, IL, USA). For continuous variables, data were expressed as median (interquartile range, IQR) and compared using the Mann-Whitney U test. Categorical variables are expressed as frequencies and compared using the Chi-square test. Spearman correlation was used to analyze the correlation between eGFR and lipid profiles. Multivariate logistic regression was used to analyze

the risk factors for decreased eGFR at the end of a 3-year follow-up. A two-sided $P < 0.05$ indicated statistical significance.

RESULTS

Baseline characteristics of patients

Among the 202 CHB patients, 44 patients (21.8%) were overweight (BMI ≥ 25 kg/m²). As shown in **Table 1**, there were more male patients in the overweight group (88.6% vs. 70.3%, $P = 0.01$). TG and CHOL levels were comparable between two groups ($P = 0.13$ and 0.98 , respectively). ⁴ There was no significant difference in ALT, AST, TBIL, eGFR between the two groups (all $P > 0.05$).

In non-overweight group, the median HBV viral load at baseline was 5.06 Log₁₀IU/mL, 152 (96.2%) patients had undetectable HBV DNA at week 144, and 138 (87.3%) patients achieved ALT normalization. For patients with overweight, 41 (93.2%) patients had undetectable HBV DNA at week 144, and 29 (65.9%) patients achieved ALT normalization. At week 144, among the 112 patients with positive HBeAg in non-overweight group, 50 (44.6%) and 6 (5.4%) experienced HBeAg loss and seroconversion. In overweight patients, 33 (75%) were HBeAg-positive at baseline, 14 (42.4%) and 2 (6.1%) experienced HBeAg loss and seroconversion. No patient had HBsAg loss in either non-overweight or overweight patients during 144-week follow-up. There is no significant difference in HBV DNA negativity and HBeAg loss between patients with overweight and non-overweight (both $P > 0.05$). More patients in non-overweight group achieved ALT normalization compared with those in overweight group ($\chi^2 = 11.036$, $P < 0.01$).

As shown in **Figure 2**, in non-overweight patients, eGFR significantly declined in the 1st year and remained as such until the 3rd year. Among the 136 patients who had eGFR ≥ 90 mL/(min \cdot 1.73m²) at baseline, 20 (14.7%) had decreased eGFR at the 3rd year. While in overweight patients, eGFR remained relatively stable during the 3-year treatment. Among the 34 patients who had eGFR ≥ 90 mL/(min \cdot 1.73m²) at baseline, two

(5.9%) patients had decreased eGFR at the 3rd year, and the difference was not significant from patients in non-obese group ($P = 0.25$).

In non-overweight patients, CHOL significantly decreased in the 1st year ($P < 0.05$), after which it slowly increased. Unexpectedly, CHOL returned to the baseline level in the 3rd year. In overweight patients, CHOL significantly decreased in the 2nd year ($P < 0.05$) and then returned to the baseline level at the 3rd year.

In non-overweight patients, TG significantly declined in the 2nd year ($P < 0.05$) and increased at the 3rd year, while in overweight patients, TG remained relatively stable during the 3-year follow-up.

Correlation between eGFR and lipid profiles in patients with and without overweight

In all the patients, baseline eGFR was positively correlated with eGFR at the 1st, 2nd, and 3rd year. There were also positive relationships between TG at the four-time points. Similar relationships were found in CHOL.

In non-overweight patients, eGFR was negatively correlated with TG at each time point (all $P < 0.05$) (**Figure 3A**). In addition, eGFR did not correlate with CHOL at each time-point, except for the 2nd year, while in overweight patients, eGFR showed no significant relationship with TG or CHOL at any time-point.

Risk factors for decreased eGFR at the end of the 3rd year

Univariate and multivariate logistic regression analyses were performed to analyze the risk factors for decreased eGFR at the end of the 3rd year. For the 202 patients, age, LC, TBil, and baseline $\text{eGFR} < 90 \text{ mL}/(\text{min} \cdot 1.73 \text{ m}^2)$ were associated with decreased eGFR in the 3rd year. Next, multivariate analysis showed that age ($P < 0.01$) and baseline $\text{eGFR} < 90 \text{ mL}/(\text{min} \cdot 1.73 \text{ m}^2)$ ($p < 0.01$) were independent risk factors for $\text{eGFR} < 90 \text{ mL}/(\text{min} \cdot 1.73 \text{ m}^2)$ in the 3rd year (**Table 2**).

For 158 non-overweight patients, univariate analysis showed that age, LC, TBil, and baseline $\text{eGFR} < 90 \text{ mL}/(\text{min} \cdot 1.73 \text{ m}^2)$ were associated with decreased eGFR in the 3rd year. Moreover, multivariate analysis showed that age ($P < 0.01$) and baseline $\text{eGFR} < 90 \text{ mL}/(\text{min} \cdot 1.73 \text{ m}^2)$ ($P < 0.01$) were independent risk factors for decreased eGFR in the 3rd year (**Table 3**).

For 44 overweight patients, age, LC, and baseline $\text{eGFR} < 90 \text{ mL}/(\text{min} \cdot 1.73 \text{ m}^2)$ (all $P < 0.01$) were associated with decreased eGFR in the 3rd year, and baseline $\text{eGFR} < 90 \text{ mL}/(\text{min} \cdot 1.73 \text{ m}^2)$ was the independent risk factor for decreased eGFR in the 3rd year (**Table 4**).

DISCUSSION

Data from the present study indicated that it was not sufficient to withdraw TDF according to fluctuations in eGFR. As the dynamic changes of eGFR and lipid profile were different in patients with overweight or non-overweight, BMI and lipid profiles should also be taken into consideration. eGFR remained stable during the 3-year treatment, which is especially true for overweight patients. However, BMI was not an independent risk factor for decreased eGFR at the end of 3-year TDF treatment, BMI should be monitored during treatment. As there is evidence that TDF may be associated with weight loss in patients with HIV infection^[18], it would be interesting to monitor the weight in patients with HBV infection and TDF treatment. However, BMI was not calculated during the follow-up in the present study.

While there is increasing evidence supporting the regulation of lipid profiles by TDF^[19-21], the mechanisms remain largely unknown. Recently, Suzuki *et al.* reported that TDF, but not ETV, reduced supernatant total CHOL, LDL-C, HDL-C, and TG by up-regulating hepatic CD36 in HepG2 cells^[22]. Other mechanisms remain to be elucidated, regardless of food intake. It has been reported that increased LDL-C is associated with eGFR decline and the development of chronic kidney deficiency in men without hypertension or diabetes^[23]. To the best of our knowledge, there are still barriers to the implementation of LDL-C in many rural areas. Moafi *et al.* reported that CHOL, HDLC, and TG were negatively correlated with eGFR after adjusting BMI, blood pressure, and blood glucose^[24]. In the present study, it was interesting to find that TG was negatively correlated with eGFR in non-overweight. Thus, TG regulation may be beneficial for reducing the renal toxicity of TDF.

A Korean study showed that advanced age was associated with reduced renal function at week 144. In addition, comorbidities including diabetes or hypertension showed the tendency toward renal impairment^[25]. Similar results were found in the present study, where age and baseline eGFR $<90\text{mL}/(\text{min}\cdot1.73\text{m}^2)$ were independent risk factors for reduced renal function. In clinical practice, it is worrisome to administer TDF in patients with impaired eGFR. Unexpectedly, patients with impaired baseline eGFR had relatively stable eGFR during 3-year TDF treatment. This result suggest that TDF remains a useful alternative in patients with decreased eGFR, although routine tests are recommended.

This study has several limitations. First, lipid indicators, including LDL and HDL, are lacking. Second, other indicators, including urine protein quantitation Cystatin C, which may be more sensitive, were not detected during TDF treatment.

CONCLUSION

In conclusion, dynamic changes in renal function were associated with TG during TDF treatment in CHB patients without overweight, but not with overweight.

ARTICLE HIGHLIGHTS

Research background

TDF is recommended as one of the first-line antiviral agents. The effects of TDF on lipid profiles in patients with CHB and overweight are largely unknown.

Research motivation

Overweight is a global pandemic associated with dyslipidemia. Correlation between Triglyceride (TG) and eGFR remains largely unclear.

Research objectives

To determine the impact of 3-year TDF treatment on lipid metabolism profiles and renal function in Chinese patients with CHB and overweight.

Research methods

This multi-centre, retrospective cohort study included CHB patients who received TDF treatment. According to the BMI at the initiation of TDF treatment, CHB patients were divided into different groups. Changes of lipid profiles and renal function , as well as the risk factors for $\text{eGFR} < 90 \text{ mL}/(\text{min} \cdot 1.73\text{m}^2)$ were analyzed. Spearman correlation was used to analyze the correlation between eGFR and lipid profiles.

Research results

In non-overweight patients, TG was negatively correlated with GFR at the four-time points ($P = 0.002, 0.030, 0.007, 0.008$, respectively).

Research conclusions

There is a negative relation between TG and changes in eGFR during TDF treatment in patients with CHB and normal BMI.

Research perspectives

TG regulation may be beneficial for reducing the renal toxicity of TDF.

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