

# Effect of fenofibrate on serum nitric oxide levels in patients with hypertriglyceridemia

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## Abstract

**Background.** Fenofibrate, a peroxisome proliferator-activated receptor- $\alpha$  (PPAR $\alpha$ ) agonist, is used to treat patients with hypercholesterolemia and hypertriglyceridemia in order to reduce the risk of development of the atherosclerotic cardiovascular disease. However, it exerts pleiotropic effects beyond correcting atherogenic dyslipidemia to treat hypercholesterolemia.

**Objectives.** The aim of this study was to investigate the potential effects of fenofibrate on endothelial function by analyzing the serum nitric oxide (NO) levels in patients with hypertriglyceridemia.

**Material and methods.** Lipid profiles and serum NO levels were assessed in 56 healthy adults aged 29 to 84 years, before and after 12 weeks of fenofibrate (250 mg/d;  $n = 30$ ) or placebo ( $n = 26$ ). Appropriate dietary suggestions for hypertriglyceridemia were made for all patients. This study was randomized, double-blind and placebo-controlled in design.

**Results.** Total cholesterol, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) and triglyceride levels significantly decreased; high-density lipoprotein (HDL) and NO levels significantly increased after 12 weeks of fenofibrate therapy. We observed a statistically significant correlation between the increase in serum NO levels and decrease in serum triglyceride levels ( $r = -0.42$ ,  $p = 0.02$ ) in the fenofibrate group.

**Conclusions.** The positive effect of short-term fenofibrate treatments on vascular endothelial functions in patients with hypertriglyceridemia has been demonstrated by increasing the serum NO levels. Agents such as fenofibrate targeting PPAR $\alpha$ -associated signaling pathways show promise as an alternative treatment of vascular dysfunction related to advanced age and hyperlipidemia.

**Key words:** fibrate, hypertriglyceridemia, nitric oxide

## Cite as

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## Introduction

The endothelium plays a major role in not only regulation of the function but also the protection of the normal structure of vascular tissue mainly by the production of nitric oxide (NO). Endothelium-derived NO is a strong endogenous vasodilator, acting through the activation of the soluble guanylate cyclase resulting in cyclic guanosine monophosphate (cGMP) production.<sup>1–3</sup> Nitric oxide takes a role in regulating vascular tone; on the other hand, some important steps, such as smooth muscle proliferation in vascular tissue, platelet accumulation and endothelial cell-leukocyte interaction in the development of atherosclerosis and thrombosis, are also inhibited by NO.<sup>4–9</sup> The presence of cardiovascular risk factors may lead to impaired endothelial integrity as a result of decreased levels of NO released from endothelium.<sup>10</sup> Hypercholesterolemia, an important cause of atherosclerosis formation and progression, also results in decreased vascular NO activity.<sup>11,12</sup>

In animal studies, the inhibition of NO synthesis in hypercholesterolemia gives rise to the progression of development of atherosclerosis, while the increase in NO levels slows down or even regresses it.<sup>13–16</sup> The mechanism underlying the impairment of endothelial NO syntheses by hypercholesterolemia has remained unclear; however, it is essential to define new treatment modalities for improving vascular endothelial function by increasing vascular NO activity in patients with hyperlipidemia.

Fenofibrate, a peroxisome proliferator-activated receptor (PPAR)- $\alpha$  agonist, exerts several pleiotropic effects beyond treating atherogenic dyslipidemia by lowering plasma triacylglycerides and consequently modifying the morphology of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) particles. Fatty acids and derivatives activate the PPAR nuclear receptors. In experimental studies, it has been demonstrated that PPAR- $\alpha$  receptor activation plays an important role in all stages of the development of atherosclerosis such as vascular inflammation, suggesting that the antiatherogenic actions of PPAR- $\alpha$  occur at the level of the vascular wall.<sup>17</sup> Fenofibrate improves endothelium-dependent dilation (EDD) in the microcirculation (i.e., small mesenteric arteries) in old rats, and increases brachial artery flow-mediated dilatation (FMD) in patients with type 2 diabetes mellitus.<sup>18,19</sup> Impairment of the NO synthase (NOS) pathway contributes to the inhibition of EDD.<sup>20</sup> Fenofibrate induces an increase in endothelial NOS expression in humans, as well as in cultured endothelial cells and the aorta of rats.<sup>21–23</sup> However, plasma levels of malondialdehyde and nitrate in humans were not changed by therapy with fenofibrate.<sup>24</sup>

The objective of this study was to investigate the effect of fenofibrate therapy on serum NO level in hypertriglyceridemia.

## Material and methods

### Subjects and study design

The Ethics Committee of the Ankara University Faculty of Medicine approved the study and all procedures were carried out according to the Declaration of Helsinki. All participants gave written informed consent. The study was funded by the Association of Turkish Clinical Vascular Biology.

This study was randomized, prospective and placebo-controlled in design. Sixty-eight hypertriglyceridemic patients who were admitted to our outpatient clinic in the Cardiology Department of the Ankara University School of Medicine between February 2014 and February 2015 were evaluated to enroll in the study. A total of 8 patients, of whom 3 patients declined to participate the study and 5 patients did not meet the inclusion criteria, were excluded from the study. The study population consisted of 60 patients who were allocated to the 2 arms (Fig. 1). The exclusion criteria included known vascular disease, stable angina pectoris, smoking, serum creatinine >1.5 mg/dL, abnormal liver or muscle enzymes, alcohol consumption, or use of antioxidant or lipid-regulating therapy. The past medical history of all participants was examined in detail and 12-lead electrocardiography, and a physical examination with measurement of liver enzymes, renal function test, fasting lipid profile, and glucose were performed. Sixty patients were randomly assigned to receive either oral treatment with 250-mg micronized fenofibrate ( $n = 30$ ) or placebo capsules ( $n = 30$ ) once daily for 12 weeks. A computer-generated table of random numbers (1:1) was used for accurate randomization. Four patients in the placebo group dropped out of treatment on their own decision during the study after randomization, so 26 patients reached the final analyses in the placebo group. Both investigators and patients were blinded to the treatment. A physician was assigned to count the pills to assess treatment compliance. Minor adverse effects that did not require drug withdrawal, such as abdominal pain in 2 patients, dyspepsia in 1 patient, and dizziness in 1 patient, were observed in the treatment group during the follow-up period. In our study, appropriate dietary suggestions for hypertriglyceridemia were made for all patients with no objective follow-up of participants' compliance with diet.

### Laboratory assays

Venous blood samples were taken in the morning after overnight fasting to study the biochemical parameters at the beginning and at the end of both treatment periods.

It is recommended that patients take fenofibrate treatment with their evening meal. Patients were reviewed every 2 weeks to assess compliance with the treatment, adverse effects, body weight, and blood pressure. Plasma liver and muscle enzymes were monitored at 6-week intervals.

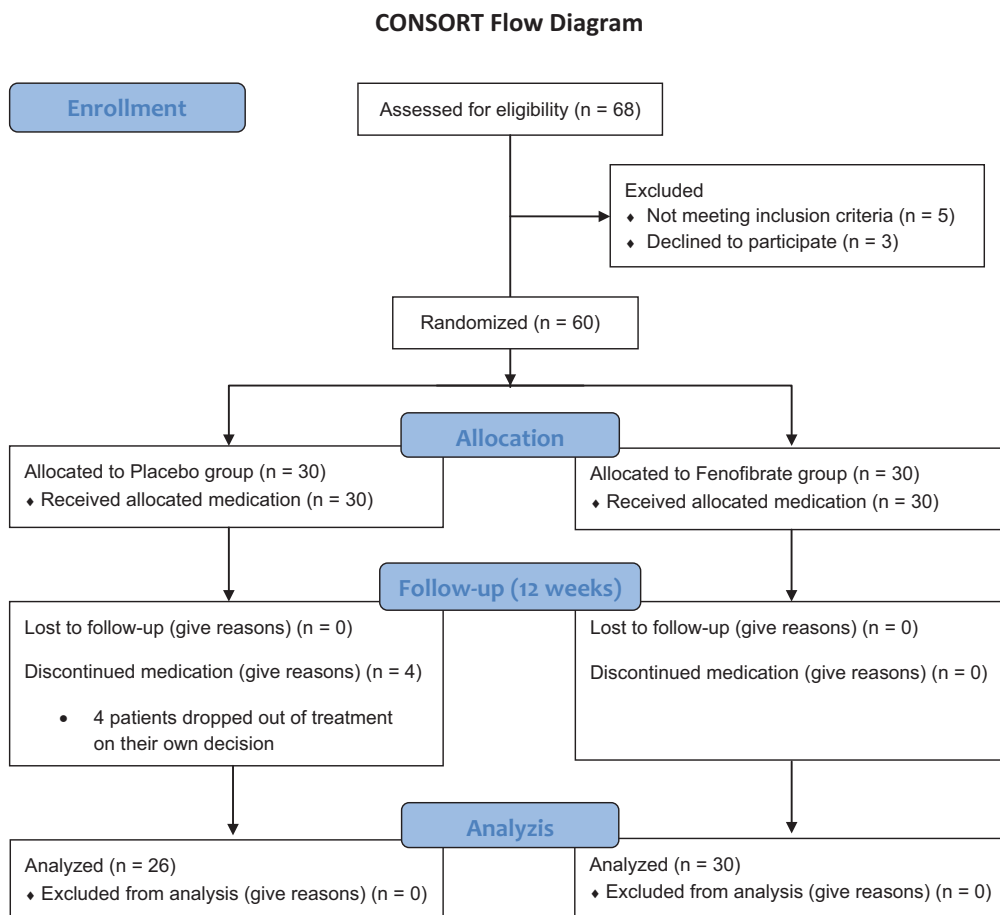


Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of patients enrolled in the study

Fasting triglyceride, HDL cholesterol and total cholesterol were examined using enzymatic kits (Roche Diagnostics, Risch-Rotkreuz, Switzerland), and LDL-cholesterol was calculated using the Friedewald formula. Serum creatinine and CK were measured using Roche Diagnostics reagents and a Hitachi 917 analyzer (Hitachi Ltd., Tokyo, Japan).

For the vast majority of convenient methods, it is impossible to detect NO because of its volatile and transient character. However, as a result of NO oxidizing to nitrite (NO<sub>2</sub><sup>-</sup>) and nitrate (NO<sub>3</sub><sup>-</sup>), we used these anions' concentrations as a quantitative measurement of NO production. We performed the spectrophotometric measurement of NO<sub>2</sub><sup>-</sup> by performing the Griess reaction after the conversion of NO<sub>3</sub><sup>-</sup> to NO<sub>2</sub><sup>-</sup>. Nitric oxide can be determined with this assay, which is achieved by nitrate reductase activity converting nitrate to nitrite. After the reaction, the nitrite is detected with colorimetric methods as an azo dye product of the Griess reaction. Nitric oxide concentration is indirectly measured by identifying both nitrite and nitrate levels in the specimen.

### Statistical analysis

We analyzed the data with the Statistical Package for the Social Sciences (SPSS) v. 20.0 for Windows (IBM Corp., Armonk, USA). Categorical variables were summarized as percentages; continuous variables are presented

as mean ± standard deviation (SD) or median with interquartile range according to normal distribution. The data was analyzed with the Shapiro–Wilk test for normal distribution. Groups were compared with  $\chi^2$  tests with Yates's correction or Fisher's exact test for categorical variables and the independent sample t-test or Mann–Whitney U test according to the distribution of data for continuous variables. Pre- and post-treatment parameters were compared using paired sample t-test for normally distributed variables, and the Wilcoxon signed rank test was used for non-normally distributed variables. Changes in serum NO levels and the changes in blood lipid parameters were distributed normally, therefore the Pearson test was used to analyze correlations. A value of  $p < 0.05$  was considered statistically significant.

### Results

A comparison of patients with placebo (n = 26; 10 male and 16 female; mean age 53.5 ± 15.1 years) and those with fenofibrate therapy (n = 30; 8 male and 22 female; mean age 55.7 ± 7 years) regarding baseline characteristics and laboratory findings is demonstrated in Table 1. No significant differences were detected between the 2 groups in terms of sex, age, the presence of hypertension, diabetes mellitus, hypothyroidism, chronic obstructive pulmonary

**Table 1.** Baseline characteristics of the study and control group

Variable	Placebo (n = 26)	Fenofibrate (n = 30)	p-value
Age, years	53.5 ±15.1	55.7 ±7	0.19
Male gender, n (%)	10 (38.5)	8 (26.7)	0.5
Hypertension, n (%)	18 (69.2)	26 (86.7)	0.21
Diabetes mellitus, n (%)	6 (23.1)	10 (33.3)	0.58
Hypothyroidism, n (%)	2 (7.7)	–	0.21
COPD, n (%)	1 (3.8)	3 (10)	0.6
ACE-I or ARB use, n (%)	16 (61.5)	24 (80)	0.22
β-blocker use, n (%)	6 (23.1)	6 (20)	1
Diuretics use, n (%)	2 (7.7)	2 (6.7)	1
Calcium channel blockers use, n (%)	–	2 (6.7)	0.49
Total cholesterol [mg/dL]	217.1 ±28.4	238.3 ±52.8	0.09
LDL cholesterol [mg/dL]	127.5 ±22.5	141.2 ±30	0.08
HDL cholesterol [mg/dL]	39.9 ±8	40.6 ±10.7	0.81
VLDL [mg/dL]	52 (36–55)	68.7 (46–77)	0.07
Triglycerides [mg/dL]	330 ±25.4	380.9 ±139.4	0.12
NO [μM]	26.4 ±11.9	30.9 ±12.4	0.17
Creatinine [mg/dL]	0.74 (0.65–0.92)	0.83 (0.68–0.98)	0.5
Creatinine kinase [u/L]	128 (79–250)	85.5 (62.75–160.75)	0.39
Adverse effect, n (%)	–	4 (13.3)	0.12

COPD – chronic obstructive pulmonary disease; VLDL – very low-density lipoprotein; LDL – low-density lipoprotein; HDL – high-density lipoprotein; NO – nitric oxide.

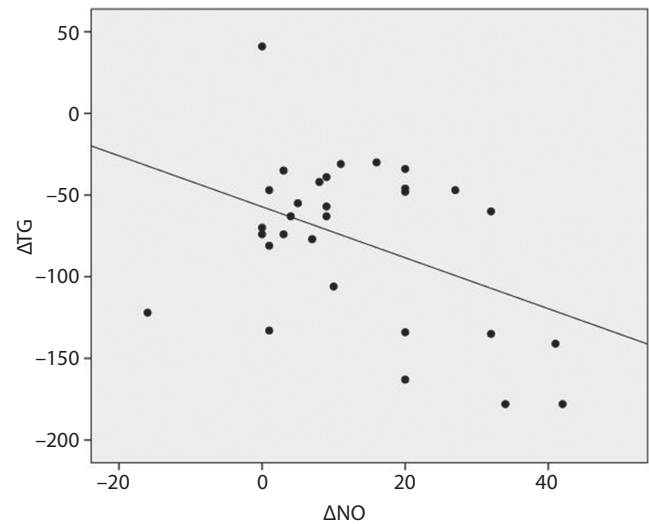
disease (COPD), cardiovascular drug use, blood lipid panel, and NO level.

Biochemical measurements recorded at baseline and after 12 weeks of fenofibrate or placebo are listed in Table 2. Baseline triglyceride levels decreased significantly after 12 weeks in the placebo group ( $p < 0.001$ ); however, there was no significant change in other types of blood lipid parameters and NO level. Total cholesterol, LDL, very low-density lipoprotein (VLDL) and triglyceride levels significantly decreased; HDL and NO levels significantly increased after 12 weeks of fenofibrate therapy. Treatment with fenofibrate

**Table 2.** Biochemical variables at baseline and 12 weeks for placebo and fenofibrate groups

Variables	Placebo group			Fenofibrate group		
	baseline	12 <sup>th</sup> week	p-value	baseline	12 <sup>th</sup> week	p-value
Total cholesterol [mg/dL]	217.1 ±28.4	213 ±36.3	0.3	238.3 ±52.8	186.7 ±36.6	$p < 0.001$
LDL cholesterol [mg/dL]	127.5 ±22.5	123.2 ±22.9	0.07	141.2 ±30	106.8 ±33.5	$p < 0.001$
HDL cholesterol [mg/dL]	39.9 ±8	41.9 ±7.8	0.15	40.6 ±10.7	43.5 ±8.6	0.001
VLDL [mg/dL]	52 (36–55)	35 (30–54)	0.89	68.7 (46–77)	38 (31–56)	0.001
Triglycerides [mg/dL]	330 ±25.4	280.4 ±38.9	$p < 0.001$	380.9 ±139.4	303.5 ±120	$p < 0.001$
Nitric oxide [μM]	26.4 ±11.9	27.1 ±12.4	0.06	30.9 ±12.4	43.9 ±15.8	$p < 0.001$

VLDL – very low-density lipoprotein; LDL – low-density lipoprotein; HDL – high-density lipoprotein.

**Fig. 2.** Statistically significant correlation between the increase in serum NO levels and decrease in serum triglyceride levels ( $r = -0.42$ ,  $p = 0.02$ ). ( $\Delta$  NO: change in serum NO levels;  $\Delta$  TG: change in serum triglyceride levels)

resulted in a significant increase in serum NO levels compared to the placebo group ( $p < 0.001$  vs  $p = 0.06$ ).

Table 3 compares the magnitude of both groups' various parameter changes during the study. This comparison revealed that the increase in HDL and creatinine, and the decrease in creatinine kinase, are similar in the placebo and fenofibrate groups, but that the decreases in total cholesterol, LDL, VLDL and triglycerides, and the increase in NO, are significantly higher in the fenofibrate group.

We observed a statistically significant correlation between the increase in serum NO levels and decrease in serum triglyceride levels ( $r = -0.42$ ,  $p = 0.02$ ; Fig. 2), with a non-significant correlation for other changes in the lipid variables (HDL:  $r = 0.04$ ,  $p = 0.84$ ; VLDL:  $r = 0.12$ ,  $p = 0.55$ ; total cholesterol:  $r = 0.35$ ,  $p = 0.07$ ; and LDL  $r = 0.03$ ,  $p = 0.87$ ; Table 4) in the fenofibrate group.

## Discussion

In our study, it has been demonstrated that fenofibrate significantly decreased total cholesterol, LDL cholesterol, VLDL cholesterol and triglycerides, and increased HDL

**Table 3.** Comparison of the magnitude of the changes from baseline to 12<sup>th</sup> week follow-up evaluation in placebo and fenofibrate groups

Variables	Change in placebo group after 12 weeks (n = 26)	Change in fenofibrate group after 12 weeks (n = 30)	p-value
Total cholesterol [mg/dL]	-14.5 ± 50.1	-51.6 ± 45.1	0.02
LDL cholesterol [mg/dL]	-4.3 ± 10.9	-34.3 ± 30.3	p < 0.001
HDL cholesterol [mg/dL]	2 ± 6.2	2.9 ± 4.3	0.53
VLDL [mg/dL]	-0.5 ± 13.1	-33.9 ± 47.2	0.01
Triglycerides [mg/dL]	-49.6 ± 26.5	-77.4 ± 50.6	0.01
Creatinine [mg/dL]	0.03 ± 0.14	0.03 ± 0.09	0.87
Creatinine kinase [u/L]	-16.7 ± 7.4	-10.3 ± 18.4	0.44
Nitric oxide [μM]	0.77 ± 1.9	12.9 ± 13.7	p < 0.001

VLDL – very low-density lipoprotein; LDL – low-density lipoprotein; HDL – high-density lipoprotein.

**Table 4.** Correlation between changes in serum NO levels and changes in blood lipid parameters in the fenofibrate group

Variables	Δ NO level	
	r	p-value
Δ Triglycerides	-0.42	0.02
Δ VLDL	0.12	0.55
Δ HDL	0.04	0.84
Δ LDL	0.03	0.87
Δ Total cholesterol	0.35	0.07

r – correlation coefficient; VLDL – very low-density lipoprotein; LDL – low-density lipoprotein; HDL – high-density lipoprotein; NO – nitric oxide.

in patients with hypertriglyceridemia. Besides being a hypolipidemic drug, there are some important molecular and metabolic pleiotropic effects of fenofibrate on the vascular endothelium. Previous studies have demonstrated the effect of fibrates on vasomotor function as a pleiotropic effect on vascular endothelium. It has been shown that 12 weeks of fenofibrate therapy improves FMD in patients with type 2 diabetes mellitus after oral fat loading.<sup>25</sup> On the other hand, 3 weeks of gemfibrozil therapy did not show similar beneficial effects in healthy volunteers.<sup>26</sup> When compared with a placebo, bezafibrate therapy increases coronary artery dilation after exercise in patients with coronary artery disease; however, FMD was not changed significantly by either gemfibrozil usage alone or combination therapy with niacin.<sup>27,28</sup> Endothelium-dependent dilation in patients with hyperlipidemia and type 2 diabetes mellitus as well as in healthy middle-aged and older normolipidemic individuals were improved by therapy with fenofibrate.<sup>19,21,24,29–32</sup>

Although the results were controversial, it was observed in most of the studies that fenofibrate therapy significantly improves FMD. It is plausible that the hypolipidemic action

of fenofibrate may account for this pleiotropic effect. From this hypothesis, it can be proposed that there was a significant correlation between the alteration in lipid levels and amelioration in FMD. On the other hand, it was also reported that improvements in EDD with fenofibrate was independent of reductions in lipids.<sup>21,32</sup> In these patients, improvements in EDD were provided by the increased activity of endothelial NOS, which plays a major role in ensuring NO release from vascular endothelial cells in healthy humans.<sup>21</sup> In another clinical trial, it was also shown that treatment with fenofibrate in patients with metabolic syndrome improved the endothelial protective effects of HDL by demonstrating the advanced ability of HDL to induce the expression of endothelial NOS on human umbilical vein endothelial cells.<sup>33</sup> Furthermore, PPAR-α agonists induced production of endothelial NOS in cell cultures, which leads to decreased oxidative stress, with increased bioactivity of NO.<sup>22,34</sup> Naturally occurring PPAR agonists can impede the inducible NOS enzyme pathway. Thus, the production of eicosanoid breakdown products as a result of inflammation may assist in its eventual resolution by activation of the PPAR pathway. In addition to these anti-inflammatory effects, PPAR-α ligands may improve endothelial NOS activity.<sup>35</sup> The activation of PPAR-α by fenofibrate in mice not only improved endothelial vasodilatation but also prevented myocardial ischemic injury, so treatment with fenofibrate ameliorated post-ischemic contractile dysfunction and decreased myocardial infarct size by an antioxidant mechanism that enhanced the bioavailability of NO.<sup>36</sup> Similarly, cardioprotection in a rat model of diabetic and acute myocardial infarction is also generated by fenofibrate + metformin combination therapy and fenofibrate therapy alone via decreased inducible NOS (iNOS) activity and increased NO bioavailability.<sup>37</sup> Additionally, fenofibrate therapy remained significantly associated with increased NO production and decreased serum asymmetric dimethylarginine level, leading to amelioration of inflammation and oxidation in rats.<sup>38</sup> However, the plasma levels of malondialdehyde and nitrate in humans were not changed by therapy with fenofibrate.<sup>24</sup>

Most of the studies showed that fenofibrate therapy significantly improved FMD, whereas serum NO levels were not measured in participants, so it had not been investigated whether there was a correlation between improved FMD and change in serum NO levels. In the literature, there was only 1 study which showed that fenofibrate therapy did not alter plasma levels of malondialdehyde and nitrate in humans, despite a significant improvement in FMD.<sup>24</sup> Thus, it is claimed that fenofibrate may not have clinically important antioxidant effects. Here, we demonstrate for the first time that compared with placebo, fenofibrate significantly increases the serum NO levels in patients with hypertriglyceridemia. These results indicate that fenofibrate targeting the PPARα-related signaling pathways shows promise for the treatment of vascular dysfunction associated with dyslipidemic status including hypertriglyceridemia, and the prevention of cardiovascular disease.

On limitation is this result is not supported by any clinical test such as FMD, etc. demonstrating the relationship between improved endothelial function and increased serum NO levels as a pleiotropic effect of fenofibrate. Additionally, the small patient population is another limitation of this study.

In conclusion, fenofibrate significantly changes lipoprotein levels by decreasing total cholesterol, LDL cholesterol, VLDL cholesterol and triglycerides, and increasing HDL-C. It also significantly increases the serum NO levels in patients with hypertriglyceridemia as a pleiotropic effect.

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