Effect of Raloxifene on Serum Triglycerides in Women With a History of Hypertriglyceridemia While on Oral Estrogen Therapy

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OBJECTIVE — Raloxifene hydrochloride is a selective estrogen receptor modulator that to date has not been shown to cause hypertriglyceridemia in normal, diabetic, or hypertriglyceridemic women. This study was designed to assess the effect of raloxifene on serum triglycerides in postmenopausal women who have a history of increased hypertriglyceridemia with oral estrogen therapy.

RESEARCH DESIGN AND METHODS — This was a single-center, uncontrolled, open-label study investigating the effects of 8 weeks of raloxifene (60 mg/day) therapy on plasma lipids. The study subjects were 12 postmenopausal women, ages 49–73 years, with a documented history of oral estrogen–induced hypertriglyceridemia (serum triglycerides ≥3.39 mmol/l [≥300 mg/dl]).

RESULTS — At week 2 of the study, three (25%) of the subjects withdrew from the trial because they developed marked hypertriglyceridemia (≥11.3 mmol/l [≥1,000 mg/dl]) during raloxifene therapy. These three women had higher baseline triglyceride and glucose levels, were not being treated with lipid-lowering agents, and were more likely to have diabetes than the other study subjects. The remaining nine patients (75%) completed the 8-week trial and experienced a nonsignificant increase in mean triglyceride levels from baseline to end point. Raloxifene treatment also resulted in a significant 16% decrease in hepatic lipase activity and a 26% increase in HDL₂ levels (P = 0.013 and 0.03, respectively).

CONCLUSIONS — Patients with a previous history of hypertriglyceridemia on oral estrogen therapy should have serum triglyceride levels monitored closely after beginning raloxifene therapy and may even require fibrate therapy before beginning raloxifene.

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Raloxifene hydrochloride is a benzo-thiophene derivative that binds to the estrogen receptor and has estrogen agonist effects on bone (1,2) and some cardiovascular risk factors (i.e., lipid metabolism and inflammatory markers) (3), but also has anti-estrogenic effects on the breast and uterus (4,5). Several large trials in normal and diabetic postmenopausal women have shown that raloxifene does not significantly affect serum triglyceride levels (1,3,6–8); however, there are no data on raloxifene’s effects on serum triglyceride levels in women with a history of oral estrogen–induced hypertriglyceridemia.

Oral (but not transdermal) estrogen has been shown to increase serum triglycerides, but in most cases the increased level does not surpass the normal range (9–12). However, in some women with baseline hypertriglyceridemia, oral estrogen therapy can cause markedly increased serum triglyceride levels and pancreatitis that require discontinuation of therapy (13–15).

The present study was designed to assess the effect of raloxifene, a selective estrogen receptor modulator, on serum triglyceride levels in 12 postmenopausal women with a known history of marked elevations of serum triglycerides in response to oral estrogen or combination hormone replacement therapy (HRT).

RESEARCH DESIGN AND METHODS — This was a single-center, uncontrolled, open-label study investigating the effects of 8 weeks of raloxifene therapy (60 mg/day) on plasma lipids and lipoproteins. The study was performed at the request of the U.S. Food and Drug Administration Advisory Board. For the study, 12 postmenopausal women, ages 49–73 years (mean age 58.1 years) with a documented clinical history of oral estrogen–induced hypertriglyceridemia (serum triglycerides ≥3.39 mmol/l [≥300 mg/dl] in response to oral estro-
Raloxifene in hypertriglyceridemic women

...gen) were invited to participate. The women had all previously been evaluated and treated at the University of Washington lipid clinic for oral estrogen–associated hypertriglyceridemia. As part of their treatment at the clinic, oral estrogen had been discontinued and transdermal estrogen had been initiated several years before the current study. This switch to transdermal estrogen was made because transdermal estrogen does not lead to exacerbations in triglycerides in hypertriglyceridemic women, whereas oral estrogen can lead to marked elevations in triglycerides (16,17). All patients were taking transdermal estrogen immediately before the trial and were studied at the first baseline visit on transdermal estrogen (on-patch baseline). They discontinued transdermal estrogen 4 weeks before beginning raloxifene therapy and were studied again at a second baseline (off-patch baseline). Some of the study participants were no longer taking lipid-lowering medications as they had self-discontinued these medications or were under the management of outside physicians. No changes to lipid-lowering or diabetes medications were made before the start of or during the 8-week raloxifene trial and the women continued their baseline lipid-lowering medication regimen throughout the 8-week raloxifene trial without changes. Of the 12 women enrolled in the trial, 4 were using statin monotherapy, 4 were using no lipid-lowering medications, 2 were using fibrate monotherapy, and 2 were using a combination of statin plus fibrate medications. The women did not receive dietary instructions as part of the study.

Patients returned to the clinic every 2 weeks for blood draws. Blood was collected after a 12- to 16-h fast for lipoproteins and chemistries. A heparin bolus of 60 units/kg was then given and blood was collected 10 min later in lithium heparin tubes for the measurement of lipase activity. For safety reasons, patients were required to withdraw from the study if their serum triglycerides were ≥11.3 mmol/l (1,000 mg/dl).

At the two baseline visits (on- and off-patch baseline) and the end point (after 8 weeks or at the last visit), the following were tested in all patients: triglycerides; total, HDL, and LDL cholesterol; HDL subfractions; apolipoproteins A-1 and B; lipoprotein(a) (Lp[a]); hepatic lipase (HL) activity; lipoprotein lipase (LPL) activity; insulin and glucose levels; liver function tests; and ex-vivo LDL cholesterol oxidation. In addition, the following laboratory tests were performed at every visit (2-week intervals): total cholesterol, triglycerides, and HDL cholesterol and subfractions. The triglyceride levels on oral estrogen were historical values obtained upon referral to the University of Washington Lipid Clinic.

Inclusion criteria included 1) age 42–80 years; 2) postmenopausal status, defined as no menstrual period for 2 years or estradiol <73 pmol/l and follicle-stimulating hormone >30 IU/l if hysterectomized or age <50 years; 3) a documented history of enhanced hypertriglyceridemia (≥ 3.39 mmol/l [≥300 mg/dl]) in response to oral estrogen or HRT therapy, which declined upon withdrawal of therapy; 4) freedom from chronic, disabling conditions; 5) being likely to remain ambulatory throughout the study; and 6) being able to give informed consent. The major exclusion criteria included 1) known or suspected history of breast carcinoma; 2) a history of cancer within the previous 5 years, except excised superficial basal cell or squamous cell carcinoma of the skin; 3) a history of deep venous thrombosis; 4) baseline serum triglyceride levels ≥11.3 mmol (≥1,000 mg/dl); 5) active endocrine disorders requiring treatment, except treated hypothyroidism and type 2 diabetes; 6) acute or chronic liver disease or impaired renal function; 7) abnormal uterine bleeding or any coagulation disorder; or 8) use of androgens, systemic corticosteroids, estrogens, cholestyramine, heparin, or coumarin derivatives. The current study participants were not prescreened for the presence of prothrombotic risk factors (i.e., factor V Leiden or prothrombin); some have suggested that patients should be screened for these risk factors before initiating raloxifene therapy due to the increased risk of thromboembolism (18,19).

The University of Washington’s Human Subjects Review Committees approved the study protocol and all participants gave informed consent. Raloxifene hydrochloride (Evista) 60 mg was provided by Eli Lilly (Indianapolis, IN).

Lipids were analyzed at the Northwest Lipid Research Laboratories (University of Washington, Seattle, WA). Lipid separation was performed using ultracentrifugation (Beta Quantification) (20). HDL subclasses were analyzed by a double-precipitation procedure and apolipoproteins A-1 and B were determined immunochemically using Dade Behring reagents on a Dade Behring (Newark, DE) nephelometer autoanalyzer (21). LDL cholesterol was measured directly by the enzymatic method (Boehringer Mannheim Diagnostics, Indianapolis, IN) and calculated by the Friedewald equation (22). The Lp(a) concentration was measured by a double monoclonal antibody–based enzyme-linked immunosorbent assay, as previously reported (23). Glucose was measured by the hexokinase method and insulin was measured by an Abbott IMX analyzer (Abbott Park, IL) at a central laboratory (Covance, Indianapolis, IN). Oxidation of LDL was induced by CuSO4 (2 μmol/l) and assayed, as described previously (24).

The total lipolytic activity was measured in plasma after the heparin bolus, as previously described (25). Glycerol tri[1–14C]oleate (Amersham, Arlington Heights, IL) and lecithin were incubated with postheparin plasma for 60 min at 37°C, with LPL activity calculated as the lipolytic activity removed from plasma by incubation with the specific 5D2 monoclonal antibody against LPL, and HL activity was determined as the activity remaining after incubation with the LPL antibody. The intra- and interassay coefficients of variation of HL activity were 2.7 and 10.4%, respectively.

Statistical analyses were performed using SigmaStat 3.0 (SPSS, San Ramon, CA). The serum triglyceride concentrations at the on- and off-patch baseline, week 2, and week 8 (end point) are given as means ± SD. Baseline and 2- and 8-week measurements in women were compared using a paired t test or Wilcoxon’s signed-rank test if data were not normally distributed. Comparisons of baseline characteristics between the women who discontinued raloxifene secondary to hypertriglyceridemia (n = 3) versus those who completed study (n = 9) were performed using unpaired t tests or Mann-Whitney rank-sum test (Table 2). The study was 88% powered to detect a 10% change in serum triglycerides from baseline to end point.

Compliance was determined by counting the number of pills returned at each visit. A subject was regarded as noncompliant if she took >120% or <80% of...
The study drug in the interval between visits.

**RESULTS**

**Patient disposition and compliance**

All of the 12 women enrolled in the study had a history of hypertriglyceridemia on oral estrogen (2,226 ± 2,809 mg/dl, median 756 mg/dl, range 309–10,000 mg/dl). Of the 12 subjects, 9 completed the 8-week study and 3 discontinued the study early (at week 2 of raloxifene treatment) because they developed severe hypertriglyceridemia (triglyceride concentrations ≥11.3 mmol/l [≥1,000 mg/dl] and 9 completed the 8-week trial. LDL measurements were determined by the direct enzymatic method. LDL-2 was calculated by the Friedewald equation. P values determined by the paired t test. *P < 0.05 for baseline (off HRT) to 2 weeks on raloxifene; †P < 0.05 for baseline on-patch HRT vs. baseline off-patch HRT; ‡P < 0.05 for baseline (off HRT) to 8 weeks on raloxifene; §time between start of incubation with CuSO4 and beginning of propagation phase of oxidation reaction (lag time) is given. ND, not done.

**Characteristics of women with raloxifene-associated hypertriglyceridemia.** To identify the characteristics that predisposed some women to develop raloxifene-associated hypertriglyceridemia (≥11.3 mmol/l [≥1,000 mg/dl] and discontinue the trial at week 2 of raloxifene (n = 3), we compared their characteristics at off-patch baseline with those who did not develop hypertriglyceridemia with raloxifene treatment (n = 9) (Table 2). At the off-patch baseline, the women with raloxifene-associated hypertriglyceridemia had significantly higher mean triglyceride (range 454–945 mg/dl; P = 0.002) and glucose (P = 0.014) levels than the women who completed the entire study (range 141–488 mg/dl). Among the nine patients completing the trial, three had a history of borderline diabetic glucose levels or a family history of type 2 diabetes, one had type 2 diabetes with well-controlled glucose levels, and eight were actively using lipid-lowering medications at baseline (Table 2). In comparison, two of the three women who dis-

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**Table 1—Lipids and lipoproteins before and after raloxifene treatment in study subjects**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Raloxifene</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>On patch estrogen</td>
<td>Off patch estrogen</td>
</tr>
<tr>
<td>n</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>210 ± 27</td>
<td>214 ± 41</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>352 ± 199 (319)</td>
<td>387 ± 256 (291)</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>113 ± 30</td>
<td>112 ± 34</td>
</tr>
<tr>
<td>LDL-2 (mg/dl)</td>
<td>99 ± 29</td>
<td>100 ± 33</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>40 ± 8</td>
<td>40 ± 9</td>
</tr>
<tr>
<td>HDL₃ (mg/dl)</td>
<td>5.0 ± 2.5</td>
<td>3.9 ± 1.6†</td>
</tr>
<tr>
<td>HDL₄ (mg/dl)</td>
<td>34.5 ± 6.7</td>
<td>35.6 ± 7.7</td>
</tr>
<tr>
<td>Apolipoprotein A-1 (g/l)</td>
<td>144 ± 16</td>
<td>143 ± 19</td>
</tr>
<tr>
<td>Apolipoprotein B (g/l)</td>
<td>108 ± 15</td>
<td>111 ± 22</td>
</tr>
<tr>
<td>Lp(a) (g/l)</td>
<td>18 ± 31</td>
<td>18 ± 35</td>
</tr>
<tr>
<td>HL activity (nmol ⋅ min⁻¹ ⋅ ml⁻¹)</td>
<td>462 ± 220</td>
<td>448 ± 220</td>
</tr>
<tr>
<td>LPL activity (nmol ⋅ min⁻¹ ⋅ ml⁻¹)</td>
<td>247 ± 98</td>
<td>249 ± 86</td>
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<tr>
<td>LDL oxidation (min)§</td>
<td>83 ± 30</td>
<td>84 ± 28</td>
</tr>
<tr>
<td>Fasting insulin (µU/ml)</td>
<td>19 ± 10</td>
<td>21 ± 11</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>ND</td>
<td>124 ± 43</td>
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<td>Alanine aminotransferase (unit/l)</td>
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<td>Aspartate aminotransferase (unit/l)</td>
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<td>ND</td>
</tr>
<tr>
<td>Alkaline phosphatase (unit/l)</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Data are means ± SD (median, where given). Of the 12 women enrolled in the study, 3 women discontinued at week 2 after developing marked hypertriglyceridemia (triglycerides ≥11.3 mmol/l [≥1,000 mg/dl]) and 9 completed the 8-week trial. LDL measurements were determined by the direct enzymatic method. LDL-2 was calculated by the Friedewald equation. P values determined by the paired t test. *P < 0.05 for baseline (off HRT) to 2 weeks on raloxifene; †P < 0.05 for baseline on-patch HRT vs. baseline off-patch HRT; ‡P < 0.05 for baseline (off HRT) to 8 weeks on raloxifene; §time between start of incubation with CuSO4 and beginning of propagation phase of oxidation reaction (lag time) is given. ND, not done.

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The study drug in the interval between visits.

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**Efficacy results**

**Baseline visits.** There was no significant change in triglycerides between the on- and off-patch baseline visits (n = 12; 352 ± 199 vs. 387 ± 256 mg/dl; P = 0.35) (Table 1 and Fig. 1).

**Raloxifene trial.** All 12 women returned for their 2-week visit on raloxifene. At that visit, there was a significant increase in mean triglyceride levels from the off-patch baseline measurement in the entire group (n = 12; 387 ± 256 vs. 773 ± 830 mg/dl; P = 0.012). At week 2, three patients discontinued the study due to an increase in serum triglycerides above the preset safety threshold of 11.3 mmol/l (1,000 mg/dl) (Fig. 1). The serum triglyceride concentrations that prompted discontinuation from the trial were 11.8, 24.3, and 30.1 mmol/l (1,045, 2,152, and 2,667 mg/dl). Serum triglycerides decreased from their peak values in two of these women while they were still receiving raloxifene but before they discontinued the study (data not shown). In the 9 women who did not discontinue the raloxifene trial, there was a nonsignificant increase in fasting triglycerides between the off-patch baseline and treatment week 2 (268 ± 103 vs. 378 ± 273 mg/dl; P = 0.098). At treatment week 8, there was a nonsignificant increase in fasting triglycerides from off-patch baseline to week 8 in the nine women who completed the raloxifene trial (Table 1 and Fig. 1).

Raloxifene treatment resulted in a significant 16% decrease in HL activity and a 27% increase in HDL₃ (P = 0.013 and 0.03) (Table 1). The lag time for LDL cholesterol oxidation, a measure of the resistance of the LDL particle to oxidation, also increased with raloxifene treatment (P = 0.033). No other statistically significant changes were observed with 8 weeks of raloxifene treatment.
continued raloxifene had type 2 diabetes and none of the three women were using lipid-lowering medications. No other statistically significant baseline differences were observed between these two groups of women.

Comparison of response of women on and off lipid-lowering drugs. The women not using lipid-lowering medications ($n = 4$) during the raloxifene trial had a significant increase in triglycerides from the off-patch baseline to the 2-week visit ($614 \pm 331$ vs. $1,541 \pm 1,070$ mg/dl; $P = 0.027$). At the 2-week visit, three of these four women were required to stop taking raloxifene due to the development of hypertriglyceridemia ($\geq 11.3$ mmol/l [$\geq 1,000$ mg/dl]). The eight women who were using lipid-lowering medications during the raloxifene trial had a nonsignificant increase in triglycerides from the off-patch baseline to the 2-week visit ($273 \pm 109$ vs. $388 \pm 290$ mg/dl; $P = 0.18$) and from the off-patch baseline to the 8-week end point ($273 \pm 109$ vs. $416 \pm 196$ mg/dl; $P = 0.064$).

There were no significant changes from baseline in vital signs, liver function tests, or insulin or glucose levels during raloxifene treatment (data from weeks 2, 4, and 6 not shown). Except for the three cases of hypertriglyceridemia, no new safety concerns or adverse events were noted with raloxifene. The most commonly reported adverse event reported was hot flashes, observed in 5 of the 12 women.

CONCLUSIONS—We investigated the effects of raloxifene on lipid metabolism in a select group of hypertriglyceridemic women with a history of increased triglyceride levels while on oral estrogen therapy. Our results demonstrated three major findings. First, 25% of the enrolled women experienced increased serum triglycerides to levels $\geq 11.3$ mmol/l ($\geq 1,000$ mg/dl) and withdrew from the study, suggesting that raloxifene may increase serum triglyceride levels in women with a history of hypertriglyceridemia while they are taking oral estrogen. Second, the women with raloxifene-associated hypertriglyceridemia were more likely to have diabetes and less likely to be treated with lipid-lowering agents, making them especially susceptible to hypertriglyceridemia. Finally, we found that raloxifene led to a significant decrease in HL activity and an increase in HDL2 cholesterol levels.

Many studies have shown that raloxifene has a favorable impact on lipid metabolism. Raloxifene use is associated with a 10–20% reduction in total and LDL cholesterol (1,3,7,26–31) and an 8% reduction in Lp(a) (3). Although most studies to date have not shown changes in HDL cholesterol with raloxifene, several studies have shown that raloxifene significantly increases HDL2, the large antiatherogenic subspecies of total HDL (3,6,32).

The effect of raloxifene on serum triglycerides has generally been found to be neutral. Most studies have shown no significant changes in triglyceride levels with raloxifene, but nearly all of the studies excluded individuals who had type 2 diabetes and/or were taking lipid-lowering medications, thereby excluding women who may be susceptible to hypertriglyceridemia (1,3,26,28–31). The Multiple Outcomes of Raloxifene Evaluation (MORE) study, a large ($n = 7,705$), randomized, 4-year, placebo-controlled osteoporosis treatment trial did include women with type 2 diabetes, lipid-lowering drugs, and coronary artery disease. The authors of that study found a very small ($0.01$ mmol/l [0.89 mg/dl]) but significant 1% increase in serum triglycerides in postmenopausal women treated with raloxifene (7). Further analyses of the MORE data revealed that women with elevated baseline triglyceride levels ($>500$ mg/dl) or women with diabetes did not have significant increases in serum triglycerides with raloxifene (8,33).

Of the 12 patients who were enrolled in our study, 9 (75%) completed the 8-week trial and experienced a nonsignificant increase in mean fasting triglyceride levels from off-patch baseline to end.

![Figure 1](image-url)
hypertriglyceridemia on raloxifene

Among the other markers of cardiovascular risk measured in this open-label study, HL activity and HDL2 cholesterol levels changed significantly with raloxifene treatment. The effect of raloxifene in lowering HL activity is similar to the effect of estrogen, and raloxifene may have beneficial effects on cardiovascular outcomes (34,35). Although total HDL cholesterol was not increased with raloxifene, there was a significant increase in HDL2 cholesterol after raloxifene treatment. HL activity contributes to plasma HDL levels, as it promotes the conversion of large buoyant HDL2 to small dense HDL3 (36). Elevated HL activity is associated with reduced plasma HDL levels and reduced large, buoyant HDL3 particles, thought to be the more antiatherogenic subspecies of total HDL (37). Raloxifene’s effect in lowering HL activity may have beneficial effects on cardiovascular outcomes, as it most likely accounted for the decreased HDL3 levels. The reduction in the susceptibility of LDL cholesterol to oxidation with raloxifene is consistent with results of previous studies demonstrating antioxidant properties of raloxifene in vitro (38). The effect of raloxifene on major cardiovascular events is currently being tested in the Raloxifene Use for the Heart cardiovascular/breast cancer outcomes trial (n = 10,101 patients) (39,40).

The current study was limited by its small sample size and the lack of a placebo control. The rise in triglycerides with raloxifene could be due to chance, but the stability of the triglyceride levels between the two baseline visits (on and off estrogen patch) argues against this. It is also important to remember that these susceptible women do not represent the general population. Although it is well documented that oral estrogen therapy can cause severe hypertriglyceridemia in some women, these women always have an underlying familial (primary) cause of hypertriglyceridemia (13,15,41). Severe hypertriglyceridemia (>2,000 mg/dl) almost always results from the coexistence of familial (primary) and secondary forms of hypertriglyceridemia (42). Severe exacerbation of familial forms of hypertriglyceridemia can be caused by untreated diabetes; hypothyroidism; alcohol or drugs; hormones, including oral (but not transdermal) estrogen (16,17), tamoxifen (another selective estrogen receptor modulator), and clomiphene; β-blockers; thi- azide diuretics; cyclosporine; isoretinoin (Accutane); protease inhibitors; atypical antipsychotics; and glucocorticoids (43,44). The ability of these drugs to induce hypertriglyceridemia in susceptible individuals is not well recognized by clinicians, as Goldenberg et al. (45) recently found that 53% of women referred to a lipid clinic with triglyceride-induced pancreatitis were still receiving oral estrogen therapy and only 25% were being treated with fibrate medications.

We have shown that susceptible women (i.e., those with a history of severe hypertriglyceridemia on oral estrogen) may develop clinically relevant hypertriglyceridemia when treated with raloxifene. The three women who developed marked hypertriglyceridemia on raloxifene had higher baseline triglyceride and glucose levels, were not being treated with lipid-lowering agents, and were more likely to have diabetes. Patients with a history of hypertriglyceridemia in response to oral estrogen therapy should have their serum triglyceride levels monitored closely after beginning raloxifene therapy and may even require fibrate therapy before beginning raloxifene.

Data are means ± SD (median, where given). Worsened hypertriglyceridemia was defined as triglyceride levels ≥11.3 mmol/l (≥1,000 mg/dl). *Triglyceride and Lp(a) levels were log-transformed. LDL levels were determined by direct enzymatic method, and LDL-2 levels were calculated by the Friedewald equation. P values were determined by an unpaired t test.
ney Basson, PhD, for contributions to the study design and protocol, Carey Carr for study implementation and data collection, and David A. Cox, PhD, for review and input on the manuscript.

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