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Effects of fenofibrate therapy on circulating adipocytokines in patients with primary hypertriglyceridemia

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Effects of Fenofibrate Therapy on Circulating Adipocytokines in Patients with Primary Hypertriglyceridemia

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Triglyceride and CHD Risk

Adjusted odds ratio, **1.72** (95% CI, 1.56 to 1.90) in an updated **meta-analysis** involving a total of 10158 CHD cases from **262525** participants in 29 studies

*Sarwar N, et al. Circulation 2007;115;450*
Effects of Fibrates on CV Outcomes: Meta-analysis with 18 Trials (1950-2010)

Fibrates may reduce the risk of major CV events in individuals at high risk and with combined dyslipidaemia. 

*Lancet 2010;375:1875*
Potential Pleiotropic Effects of Fibrates (PPARα agonist)

1. Endothelium-dependent vasodilation
2. Anti-inflammatory effects
3. Plaque stabilization
4. Reduction of thrombogenic response
   Fibrinogen, Tissue factor, PAI-1
5. Inhibition of platelet thrombus formation

Koh KK. Atherosclerosis 2004;174:379
Hypertension 2005;46:1086,
Int J Cardiol 2008;124:149
Coronary heart disease is characterized by endothelial dysfunction (ED) & frequently clusters with disorders of metabolic homeostasis.

These co-morbidities may be explained, in part, by reciprocal relationships between ED and insulin resistance (IR).

Han SH, Quon MJ, Koh KK. Curr Op Lipidol. 2007;18:58
Koh KK. ParkSM, Quon MJ. Circulation 2008;117:3238
Effects of Fenofibrate on Vasomotor Function

P<0.001

Effects of Fenofibrate on Inflammation in 46 Hypertriglyceridemic Patients

Fibrinogen (mg/dl)

- Placebo: 281
- Fenofibrate: 230
- P<0.001

hsCRP (mg/l)

- Placebo: 0.80 (0.50-2.50)
- Fenofibrate: 0.70 (0.40-1.20)
- P=0.001

### Adiponectin and CVD

#### I. Anti-atherogenic Properties

| ↑Endothelial vasodilation | ↓Oxidized LDL effects on EC |
| ↑Nitric oxide | ↓Function of mature macrophages |
| ↓Adhesion molecules | ↓Growth factor in EC |
| ↓Cytokines production | ↓Macrophage-to-foam cell transformation |
| ↑IL-10 and -1 receptor antagonists | ↓Scavenger receptor class A-1 |
| ↓Endothelial cell apoptosis | ↓Neointimal thickening |
| ↑Tissue inhibitor of MMP-1 | ↓SMC proliferation |

#### II. Anti-insulin-resistant Properties

| ↑Insulin sensitivity and ↑fatty acid oxidation | ↓Hepatic glucose production |

SMC = smooth muscle cells  
EC = endothelial cell

PCVD 2009;52:126 (review)
Effects of Fenofibrate on Insulin Sensitivity

**Adiponectin (µg/ml)**

- Placebo: 3.21 (2.62-4.92)
- Fenofibrate: 3.54 (2.64-5.13)

*P*=0.008

14% increase

**QUICKI**

- Placebo: 0.430
- Fenofibrate: 0.449

*P*=0.048

*QUICKI=Quantitative Insulin-Sensitivity Check Index, a surrogate index of insulin sensitivity, QUICKI = 1/[log(insulin)+log(glucose)]

Leptin and CVD

I. Atherogenic Properties

- ↓Endothelial vasodilation
- ↑cholesterol ester in foam cells
- ↑Cytokines production
- ↑IL-2, TNF, MCP-1, and CRP
- ↑SMC proliferation and MMP
- ↑Angiotensinogen, Ang II, AT1 Receptor, SNS activity
- ↑ROS formation
- ↑Scavenger receptor type B1
- ↓Paraoxonase 1 activity
- ↑P-selectin, Platelet aggregation
- ↑PAI-1, VWF
- ↓t-PA, protein kinase C, TFPIs

II. Insulin-resistant Properties

- ↓insulin signaling and insulin action
- ↓glycogen synthesis

Koh KK, et al.
Circulation 2008;117:3238 (review)

SMC = smooth muscle cells
EC = endothelial cell
Hypothesis

• We hypothesized fenofibrate therapy may improve endothelial dysfunction, adipocytokines levels, and insulin sensitivity in patients with primary hypertriglyceridemia.
Study Design

- We administered placebo or fenofibrate 160mg daily to 53 patients with hypertriglyceridemia (>150 mg/dL) during 8 weeks.
- Baseline TC 195, TG 308, LDL-C 93, HDL-C 40, non-HDL-C 155, Apo B 102, Apo A-I 137 mg/dL
- Randomized, single-blind, cross-over design
- Mean age 54 years, M:F=31:22, BMI= 25.4 Kg/m²
Laboratory Assays

• Blood samples were obtained following overnight fasting before and at end of each treatment period.
• Lipids, glucose and adiponectin, leptin, resistin in duplicate by ELISA (R & D Systems), hsCRP by latex agglutination, insulin by immunoradiometric assay

• Quantitative Insulin-Sensitivity Check Index (QUICKI) = \(1/\[\log (\text{insulin}) + \log (\text{glucose})]\), a surrogate index of insulin sensitivity  
  
  Quon MJ. JCEM. 2000;85:2402

• Imaging studies: right brachial artery for flow-mediated dilation, ATL HDI 3000 ultrasound machine
• All laboratory assays were performed blinded to subject identity or study sequence.
**Effects of Fenofibrate on Body Mass Index and Lipids**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo</th>
<th>Fenofibrate</th>
<th>% Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>25.62 ± 0.40</td>
<td>25.61 ± 0.40</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>195 ± 3 (25)</td>
<td>186 ± 4* (29)</td>
<td>-3 ± 2 (15)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>267 ± 12 (89)</td>
<td>153 ± 9‡ (65)</td>
<td>-39 ± 4 (26)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>101 ± 4 (26)</td>
<td>105 ± 4 (26)</td>
<td>9 ± 5 (35)</td>
</tr>
<tr>
<td>Apo B</td>
<td>100 ± 2 (16)</td>
<td>86 ± 3‡ (20)</td>
<td>-14 ± 2 (17)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>41 ± 1 (10)</td>
<td>50 ± 1‡ (10)</td>
<td>28 ± 4 (31)</td>
</tr>
<tr>
<td>Apo A-I</td>
<td>138 ± 4 (27)</td>
<td>150 ± 3‡ (24)</td>
<td>10 ± 2 (18)</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>154 ± 3 (23)</td>
<td>136 ± 4‡ (28)</td>
<td>-11 ± 2 (17)</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SEM (SD) or median (25th percentile-75th percentile).

*P<0.05, ‡P<0.001 vs. placebo.
Non-HDL cholesterol=total cholesterol-HDL cholesterol.
Effects of Fenofibrate on Lipoproteins

**Triglycerides (mg/dl)**

- Placebo: 300 mg/dl (P<0.001)
- Fenofibrate: 160 mg/dl (39%) (P<0.001)

**HDL-C (mg/dl)**

- Placebo: 40 mg/dl (28%)
- Fenofibrate: 56 mg/dl (P<0.001)
Effects of Fenofibrate on Apolipoproteins

Apo B (mg/dl)

- Placebo
- Fenofibrate

Apo A-I (mg/dl)

- Placebo
- Fenofibrate

14% P<0.001

10% P<0.001
Effects of Fenofibrate on FMD, Cytokines, Adipocytokines, QUICK

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo</th>
<th>Fenofibrate</th>
<th>% Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMD (%)</td>
<td>4.82±0.26</td>
<td>6.89±0.25‡</td>
<td>55±7</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>2.80±0.44</td>
<td>2.58±0.40*</td>
<td>-6±3</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>1.1 (0.6-2.8)</td>
<td>0.9 (0.5-1.9)+</td>
<td>-10±9</td>
</tr>
<tr>
<td>ADP (µg/mL)</td>
<td>1.8 (1.3-3.2)</td>
<td>2.4 (1.5-3.2)+</td>
<td>17±4</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>7.12±0.53</td>
<td>6.38±0.68</td>
<td>-7±6</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>102±2</td>
<td>102±3</td>
<td>1±4</td>
</tr>
<tr>
<td>QUICKI</td>
<td>0.36±0.01</td>
<td>0.37±0.01+</td>
<td>4±1</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>4.6 (1.7-10.7)</td>
<td>4.2 (1.4-8.7)*</td>
<td>-4±7</td>
</tr>
<tr>
<td>Resistin (ng/mL)</td>
<td>7.3 (4.8-11.1)</td>
<td>6.3 (4.0-8.5)+</td>
<td>-10±3</td>
</tr>
</tbody>
</table>

Data are expressed as means ±SEM or median (25th%-75th%).

*P<0.05, ‡P<0.001 vs. placebo.

Quantitative Insulin-Sensitivity Check Index (QUICKI)= 1/[log (insulin) + log (glucose)]
Effects of Fenofibrate on FMD and TNF-α Levels

FMD (%)

- Placebo: 55%
- Fenofibrate: 6%

P<0.001

TNF-α (pg/ml)

- Placebo: 6%
- Fenofibrate: 6%

P=0.014
Effects of Fenofibrate on Inflammatory Biomarkers Levels

hsCRP (mg/l)

- Placebo
- Fenofibrate

P=0.004

10%

TNF-α (pg/ml)

- Placebo
- Fenofibrate

P=0.014

6%
Effects of Fenofibrate on Insulin Sensitivity

Adiponectin (μg/ml)

Placebo  Fenofibrate

P=0.001

17%

QUICKI

Placebo  Fenofibrate

P=0.009

4%

**QUICKI**=Quantitative Insulin-Sensitivity Check Index, a surrogate index of insulin sensitivity, \( \text{QUICKI} = 1/([\log(\text{insulin})+\log(\text{glucose})]) \)
Effects of Fenofibrate on Plasma Leptin and Resistin Levels

Leptin (ng/ml)

- Placebo
- Fenofibrate

P = 0.022

4%

Resistin (ng/ml)

- Placebo
- Fenofibrate

P = 0.001

10%
Correlations (I)

- No significant correlations between % changes in FMD to hyperemia, insulin, adiponectin, leptin, resistin levels, or insulin resistance and % changes in lipoprotein levels

- Correlations between % changes in QUICKI and % changes in adiponectin ($r=0.279$, $P=0.043$) or leptin levels ($r=-0.280$, $P=0.042$)
• PPAR$\alpha$ decreases inflammation and stimulates increased expression of adiponectin receptors AdipoR-1 and R-2 in mice$^1$, and reduces expression of TNF-$\alpha$ mRNA, an inhibitor of adiponectin in mice$^2$.

Therefore, we investigated whether changes in plasma levels of adiponectin and changes in plasma levels of hsCRP or TNF-$\alpha$ were correlated. We did not observe any significant correlations between changes in these parameters following fenofibrate therapy.

Conclusions

• Fenofibrate therapy significantly improved % flow-mediated dilator response to hyperemia, reduced pro-inflammatory biomarkers, and improved adipocytokines levels and insulin sensitivity in hypertriglyceridermic patients.

• Thus, actions of fenofibrate to regulate adipocytokine levels may be linked to beneficial effects on pro-inflammatory status that simultaneously improve both endothelial and metabolic function in patients with primary hypertriglyceridemia.
1. These findings are not unexpected given that the patient population was not ideal. At baseline median triglycerides were 162 mg/dL.

2. In a pre-defined subgroup analysis in patients with baseline triglycerides $\geq 204$ mg/dL and high-density lipoprotein cholesterol levels $< 34$ mg/dL (17% of the total population), there was suggestion of benefit.

3. Adding fenofibrate resulted in a further 31% reduction versus simvastatin treatment alone.
### Table 2. Effects of Intensive Glycemic Control, Fenofibrate, and Intensive Blood-Pressure Control on Progression of Diabetic Retinopathy and Moderate Vision Loss.*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Progression of Diabetic Retinopathy</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P Value</th>
<th>Moderate Vision Loss</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemia therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive</td>
<td>104/1429 (7.3)</td>
<td>0.67 (0.51–0.87)</td>
<td>0.003</td>
<td>266/1629 (16.3)</td>
<td>0.95 (0.80–1.13)</td>
<td>0.56</td>
</tr>
<tr>
<td>Standard</td>
<td>149/1427 (10.4)</td>
<td></td>
<td></td>
<td>273/1634 (16.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia therapy†</td>
<td></td>
<td>0.60 (0.42–0.87)</td>
<td>0.006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive</td>
<td>67/647 (10.4)</td>
<td>1.23 (0.84–1.79)</td>
<td>0.29</td>
<td>145/749 (19.4)</td>
<td>1.27 (0.99–1.62)</td>
<td>0.06</td>
</tr>
<tr>
<td>Standard</td>
<td>54/616 (8.8)</td>
<td></td>
<td></td>
<td>113/713 (15.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Moderate vision loss was defined as loss of visual acuity by three or more lines in either eye.
† Dyslipidemia therapy consisted of simvastatin plus either fenofibrate or placebo.
1. Fibrate + statin therapy is safe for patients like those involved in the study. However, intensive blood sugar control to near normal glucose levels increased the risk of death and severe low blood sugar, so patients and their doctors must take these potential risks into account.

2. Intensive blood pressure control did not reduce diabetic eye disease progression.
The risk associated with low HDL-C and elevated TG is **not abolished in HPS**

Lipid values are in mmol/l

HPS Collaborative Group, Lancet 2002;306:7-22
Statins, TG, and HDL-Cholesterol: TG and HDL-C remains an independent RF

- Statins successfully treat the LDL-C risk
- However, risk of low HDL-C and high TG is not altered by statin therapy.
- HDL-C were predictive of major CV events in patients treated with statins. This relationship was also observed among patients with LDL-C levels < 70 mg/dl. (TNT study. NEJM 2007;357:1301)
- Low on-treatment TG<150 mg/dl was associated with reduced CHD risk in univariate analysis (HR 0.73; p < 0.001) and in adjusted analysis; LDL-C and others (HR 0.80; p=0.025). (PROVE-it study. JACC 2008;51:724)