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Ciprofibrate diminishes non-HDL-c and improves HDL-c in patients with Frederickson type IV dyslipidemia phenotype

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 indispensability. The combination of hypertriglyceridemia (HTG) with abnormally low concentrations of High Density Lipoprotein Cholesterol (HDLc) is one of the most common and atherogenic profiles of lipid metabolism. This is a highly frequent form of dyslipidemia in the metabolic syndrome and it is also found in subjects affected by primary dyslipidemias (e.g. familial combined hyperlipidemia). Data from the Prospective Cardiovascular Munster (PROCAM) study indicate that triglyceride and HDLc levels are important determinants of risk irrespective of Low Density Lipoprotein cholesterol level (LDLc). This study also demonstrates that elevated triglycerides (TG) are an independent risk factor for an early myocardial infarction or cardiac death. The prevalence of this abnormality varies among gender, age and ethnic groups. For example, it is found in 13% of the Mexican adults living in urban areas; it is more common in men than in women (20.9% vs. 7.2%) and in men aged 30 to 39 years, its prevalence is as high as 30%.

Although ATP III does not specify a target goal for HDLc levels, the panel does acknowledge that raising HDLc will likely reduce the risk of coronary heart disease (CHD). The guidelines place greater emphasis on triglyceride levels as both a component of the metabolic syndrome and a predictor of higher CHD risk. In addition, they introduce the Non-High Density cholesterol (Non-HDLc) parameter as a secondary target of therapy when triglycerides are elevated.
(≥200 mg/dL). Non-HDLc comprises LDLc and Very Low Density Lipoprotein cholesterol (VLDLc) and is added to CHD risk assessment because it is considered an accessible and reliable measure of atherogenic VLDLc remnant lipoproteins, which are elevated in the presence of high triglycerides\(^6\). The goal for Non-HDLc is 30 mg/dL higher than the goal for LDLc or <130 mg/dL for the highest-risk patients. The simple Non-HDLc measurement can be conducted in the non-fasting state and can be determined regardless of TG concentrations.

Fibrates, including Bezafibrate, Ciprofibrate, Fenofibrate, and Gemfibrozil are class of hypolipidemic drugs widely used to treat hypertriglyceridemia, mixed hyperlipidemia and hypertriglyceridemia with low HDLc\(^7\). The TG-lowering effect of fibrates has been attributed to both inhibition of hepatic fatty acid synthesis and increased catabolism of TG-rich lipoproteins\(^8\). This increase in VLDLc catabolism results from up-regulation of lipoprotein lipase (LPL) expression\(^10\) and increased LPL activity due to a reduction in apolipoprotein C-III (ApoC-III) levels\(^11,12\). The elevation in HDLc seen with fibrates correlates with increased expression of apoA-I and apoA-II\(^13,14\). Fibrates are generally indicated for the treatment of HTG\(^15-17\); however, these compounds have variable effects on HDLc apolipoprotein and cholesterol elevation.

The fibrates exert its effect on plasma lipids by altering the expression of genes involved in lipid metabolism through activation of peroxisome proliferator activated receptor (PPAR)\(^18\). Upon activation by ligands, such as fatty acids, eicosanoids, and hypolipidemic drugs (these compounds may mimic the natural ligands), PPAR forms a heterodimer with RXR, which binds to the peroxisome proliferator response element (PPRE) and modulates gene transcription\(^19\). Three PPAR isoforms, \(\alpha\), \(\beta\) and \(\gamma\) have been identified. Human PPAR expression is greatest in skeletal muscle, followed by liver, kidney, and adrenal. In the liver, PPAR-\(\alpha\) is the predominant form and plays a pivotal role in regulation of lipid metabolism\(^20\). In the present study, the efficacy of Ciprofibrate in the treatment of hypertriglyceridemia with low HDLc was evaluated as well as, the effect of this drug on Non-HDLc concentration.

**Lipidic Profile**

**Total Cholesterol and LDLc:** A statistically significant reduction was observed in Total cholesterol in both groups after the treatment (Group A: 223,2 ± 6 mg/dl vs. 208,07 ± 5,2 mg/dl; \(p<0,01\); Group B: 220,0 ± 7,8 mg/dl vs. 185,8 ± 7,2 mg/dl; \(p<0,01\)) (Figure 1-2). However, drug therapy group registered a significantly blood cholesterol level reduction of 14,2 % vs. a smaller reduction of 4,8 % in group A \((p<0,02)\) (Table 1, Figure 3). No difference was found in inter-group and intra-group comparisons for LDLc.

**Materials and methods**

**Patient selection:** Both sexes 75 (41 women and 34 men) middle-aged patients that attended the Research Center for Endocrine and Metabolic Disease “Dr. Félix Gómez” (School of Medicine, University of Zulia, Maracaibo, Venezuela) with type IV dyslipidemia and low HDLc were selected to participate in this study. Previous informed consent form, a complete clinical history was carried out to each patient. After, they were assigned at random to one of the two therapeutic intervention groups:

- **Group A:** This group was encouraged to follow a Step 2 diet according to the American Heart Association recommendations plus physical activity (walk 60 minutes/day) during 8 weeks.
- **Group B:** This group received 100 mg/day Ciprofibrate. In addition they followed Step 2 diet according to the American Heart Association and physical activity (walk 60 minutes/day) for 8 weeks.

**Lipidic profile determination**

Blood samples were obtained by venipuncture of the brachial vein after an overnight fast at the time of inclusion into the study and after 8 weeks of pharmacologic and dietary treatments. Total Cholesterol, TG and HDLc were quantified by enzymatic-colorimetric method (Human Gesellschaft für Biochemica und Diagnoses Mbh). VLDLc and LDLc were calculated using the Friedewald’s formulas (21). Non-HDLc was calculated by adding VLDLc and LDLc.

**Statistical analysis:** All data was presented as mean ± EE and treatment effectiveness was calculated as percentage increment or decrease in the lipidic variables. The student t test for paired observations was used to compare each group after intervention and the unpaired student t test to compare percentage changes between intervention groups. All the statistical procedures were carried out by SPSS version 12.0 and a \(p\) value < 0,05 was considered statistically significant.

**Figure 1. Lipidic profile changes in Ciprofibrate treated group**
Triglycerides and VLDL Cholesterol: there was a statistically significant reduction in triglycerides after treatment for both groups (Group A: 226.1 ± 10.1 mg/dl vs. 170.1 ± 6.6 mg/dl; p<0.001; Group B: 333.5 ± 20.7 mg/dl vs. 198.1 ± 18.4 mg/dl; p<0.001) (Figure 1-2). Inter-group comparisons showed statistically significant differences, with a market triglyceride reduction of 38.0 % in group B vs. only 21.6 % reduction in group A, p<0.007. (Table 1, Figure 3). VLDLc closely imitate triglycerides behaviour with a higher drop percent in Ciprofibrate group (38 %) vs. only 21.6 % reduction in diet and physical activity treated group; p<0.007 (Table 1, Figure 3).

HDLc and Non-HDLc: A statistically significant increase was observed in HDLc before and after treatment in both groups (Group A: 38.6 ± 1.5 mg/dl vs. 41.2 ± 1.4 mg/dl; p<0.04. Group B: 34.2 ± 1.6 mg/dl vs. 40.7 ± 1.6 mg/dl; p<0.001) (Figure 1-2). When inter-group comparisons was performed, a statistically significant difference was also observed: a strong 25.0% HDLc increase in group B vs. only a 9.6% in group A; p<0.02. (Table 1, Figure). On the other hand Non-HDLc showed intra-group differences as much as for group A: 184.6 ± 5.8 mg/dl vs. 167.5 ± 5.2 mg/dl; p<0.004 and group B: 185.8 ± 7.5 mg/dl vs. 145.1 ± 7.4 mg/dl; p<0.001. When inter-group contrast was made, Ciprofibrate treated group exhibited a higher percent diminution of 20.5 % vs. only 7.1 % in diet group; p<0.007. (Table 1, Figure 3).

**Total Cholesterol to HDLc and LDLc to HDLc ratio:** a statistically significant reduction was observed in Total cholesterol to HDLc ratio by comparing each group individually before and after the treatment (Group A: 6.1 ± 0.3 vs. 5.3 ± 0.2; p<0.004; Group B: 6.8 ± 0.3 vs. 4.8 ± 0.3; p<0.001) (Figure 1-2). Also, a statistically significant difference was found by comparing total cholesterol to HDLc ratio before and after treatment among the groups. Consequently, group B registered a significantly reduction of 25.6 % vs. a smaller reduction of 9.4 % in TC to HDLc ratio for group A (p<0.01) (Table 1, Figure 3). A statistically significant difference was found in Ciprofibrate group before and after treatment for LDLc to HDLc ratio (3.7 ± 0.3 vs. 2.8 ± 0.3; p<0.01) (Table 1, Figures 1-3).

### Table 1: Effect of Ciprofibrate (Group B) and AHA diet (Group A) on plasma lipids in type IV Frederickson’s dyslipidemia phenotype patients.

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=44)</th>
<th>Group B (n=31)</th>
<th>Overall Reduction after treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>p</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>223.2 ± 6.0</td>
<td>208.7 ± 5.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>226.1 ± 10.1</td>
<td>170.1 ± 6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-HDLc (mg/dl)</td>
<td>184.6 ± 5.8</td>
<td>167.5 ± 5.2</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>HDLc (mg/dl)</td>
<td>38.6 ± 1.5</td>
<td>41.2 ± 1.4</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>LDLc (mg/dl)</td>
<td>139.3 ± 6.1</td>
<td>133.5 ± 5.0</td>
<td>NS</td>
</tr>
<tr>
<td>VLDLc (mg/dl)</td>
<td>45.3 ± 2.0</td>
<td>34.0 ± 2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHOL/HDL</td>
<td>6.1 ± 0.3</td>
<td>5.3 ± 0.2</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>LDL/HDL</td>
<td>3.8 ± 0.2</td>
<td>3.5 ± 0.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are presented as mean ± EE; n=75.
NS: No significant

Coronary artery disease (CAD) is the major cause of death in western countries, including Venezuela. In CAD, the primary pathologic process implicated -in most cases- is atherosclerosis and the main mechanisms involved are the endothelial cell injury and lipidic deposition with subsequent immune-inflammatory process leading by monocytes-macrophages and T lymphocytes.22
Since Framingham study developed the risk factor concept most of research has been focused on those that directly promote atherosclerosis development (causal risk factors). They include elevated LDLc, low HDLC, and elevated Non-HDLc, high TG levels, hypertension and diabetes mellitus\textsuperscript{23,24}.

The past decade afforded new insight into the mechanism of action of fibrates on lipid and lipoprotein metabolism. Fibrates are agonists of peroxisome proliferator-activated receptor (PPAR-\(\alpha\)), specific transcription factors belonging to the nuclear hormone receptor superfamily. Activation of PPAR-\(\alpha\) by fibrates in tissues corresponding to major sites of fatty acid metabolism, such as the liver, adipose tissue, and macrophage, modulate the expression of several key genes encoding proteins involved in lipid metabolism\textsuperscript{17,20}.

The clinical usefulness of fibrates in managing the condition characterized by high triglycerides, low HDLC and small-dense LDLc is well established, but the extraordinary results of the statins trials and the focus in the most recent guidelines on LDLc control appear to support a simplified approach to lipid-based reduction relying exclusively on LDLc lowering\textsuperscript{15}. A statin based approach is unlikely to correct problems related to TG and HDLC, whereas the use of fibrates will have stronger effect in small and dense LDL and remnant particles\textsuperscript{26}. Thus, Clinicians dealing with this common phenotype encounter a practical problem: The use of statins to lower LDLc and subendothelial inflammation (evidenced by C reactive protein), or the use of fibrates to control TG, increase low HDLC and to transform lipoprotein patterns.

The present study was focused in the effect of a second generation fibric acid derivative, Ciprofibrate (do not available in USA) on lipidic parameters in patients with Frederickson’s class IV dyslipidemia with low HDLC and mild elevation of Non-HDLc. This drug is widely used in the treatment of atherogenic dyslipidemias exerting a marked lowering effect (up to 35% less) on plasma TG and TG-rich lipoprotein levels but display lesser effects (up to 15% less) on plasma cholesterol concentrations\textsuperscript{27}.

In this research was founded an impressive 38 % reduction in TG concentration without concomitant LDLc increase when Ciprofibrate was combined with AHA step 2 diet, a more remarkable achievement than previous reports on statins or any other fibric acid derivative. This fact represents an invaluable alternative for patients with genetic forms of HTG (i.e. Familial hyperchylomicronemia) or such in high CAD risk with combined hyperlipidemia.

Another point of interest of this research is low HDLC syndrome. This abnormality is a very common lipidic alteration defined as HDLC level < 35 mg/dl with LDLc <160 mg/dl and TAG near to normal levels. However, low HDLC may be present with other dyslipidemias like HTG and hyperchylomicronemia\textsuperscript{28}. In this perspective, VA-HIT study concluded convincingly that an HDLC increase in patient with CAD reduce major coronary events by 24 %, supporting an aggressive intervention when HDLC is low and another risk factor exists\textsuperscript{29}. In recent studies, Ciprofibrate has shown important effects on HDLC concentrations (up to 2-fold), with concomitant increase in plasma levels of apolipoprotein apoAI and apoAl\textsuperscript{14}. Indeed, activation of PPAR-\(\alpha\) by fibrates induces hepatic expression of LPL and thus enhances intravascular lipolysis of TG-rich lipoprotein particles improving HDLC particles maturation and a simultaneous reduction in cholesteryl esters transfers from HDL to atherogenic VLDL, IDL, and LDL as a consequence of reduction in apoB-containing lipoprotein acceptors\textsuperscript{15}. This reduction thereby results in the normalization of intravascular CETP-mediated remodeling of triglyceride-rich lipoprotein particles and enhancing their removal from plasma\textsuperscript{30}. More recently, it has been demonstrated that the expression of the CLA1 gene in human monocyte-macrophages can be induced by fibrate-activated PPAR-\(\alpha\). Because the scavenger receptor class B, type I (SR-BI)/CLA-1, is involved not only in HDL-mediated removal of cholesterol from peripheral cells but also in hepatic cholesterol uptake from HDL, fibrates may enhance both cellular cholesterol efflux and the reverse cholesterol transport pathway. In this study was founded that Ciprofibrate was able to improve HDLC by 25 % in opposition with only 9.6 % by AHA step 2 diet alone. Again, this increase was superior to those reported previously and may be due to combined effects of AHA diet, physical activity and PPAR-\(\alpha\) agonism, making this drug a first line alternative to treat low HDLc syndrome.

Non-HDLc is an emerging CAD risk factor calculated by subtracting HDLC level from total cholesterol. It thus included Lp(a) cholesterol, LDLc, IDLC and other pro-atherogenic triglyceride rich particles such as lipoprotein remnants\textsuperscript{22,33}. Data among prospective cohort studies in middle-age men in Europe showed that Non-HDLc levels are related to CAD morbidity and mortality\textsuperscript{24,35}. Cross sectional data from Framingham Offspring Study suggested that Non-HDLc was also a risk factor for coronary heart disease in middle-aged women\textsuperscript{36}. In a large cohort study whom participated in the lipid research clinics program follow-up study, both LDLc and Non-HDLc levels predicted cardiovascular death over 19 years follow-up, being a stronger predictor than LDLc level in both sexes, because 30 mg/dl over normal limits confer a 19 % (men) and 11 % (women) excess in risk of CAD\textsuperscript{37}.

Statins, fibrates, nicotinic acid and ezetimibe lower LDLc and triglycerides levels and would be expected to diminish Non-HDLc in most persons with dyslipidemia. Few studies have specifically reported changes in Non-HDLc with pharmacological therapy. However, all statins high doses studies reported reductions in Non-HDLc levels between 23,6-39,2
% independent of baseline TG levels but only the Helsinky study showed reductions in Non-HDLc by 14 % with Gemfibrozil\(^1\). Actually, small amount data about Ciprofibrate on Non-HDLc is available. Our study has shown a significantly Non-HDLc reduction in Ciprofibrate treated group from 20,5% Vs. 7,1% in step 2 AHA diet patients, p<0,007 and that represent one of the first reports about this topic. More studies must be performed in order to know Ciprofibrate's influence on lipoprotein remnants structure and its long term reduction on CAD mortality and acute coronary events risk reduction.

References

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