Efficacy, Safety and Protective Effects of Lipid Lowering Drugs in Patients with Diabetes

Y. Hitira, M. Dridi, Z. Hadj Ali, N. Trabelsi, F. Ben Mami

ABSTRACT

Aim: The aim of the study was to assess the effects of statins and fibrates on the lipid profile of patients with diabetes and to determine their side effects.

Methods: It was a transversal study. We included patients with type 1 or 2 diabetes that are followed in an outpatient department, treated for at least 3 months by statins or fibrates. We performed an interrogation, a medical examination, dietary survey and biological tests for all patients.

Results: The mean age was 59.5 ± 9.2 years. Women were 65% of patients. The mean duration of treatment with statins and fibrates was 2.2 ± 2.6 years and 4.9 ± 4.2 years, respectively. Under statin therapy, total cholesterol and LDL cholesterol decreased significantly by 1.02±1.25 mmol/l and 0.32±0.47 mmol/l, respectively, triglycerides and HDL cholesterol decreased insignificantly. Fibrates caused a significant decrease in total cholesterol and triglycerides by 1.15± 2.24 mmol/l and 1.73 ±2.96 mmol/l, respectively and a non-significant decrease in LDL cholesterol and a non-significant increase in HDL cholesterol. No case of significant hepatic cytolysis was noted. Muscle pain was reported by 10.4% and 11.6% of patients on statins and fibrate, respectively. Under statins, the incidence of gastrointestinal symptoms increased significantly.

Conclusion: The efficacy of lipid lowering drugs is widely proven. Although side effects are possible, the prescription of lipid lowering drugs should be largely encouraged for better health care of patients with diabetes.

Keywords: Diabetes, Fenofibrate, lipids, statin.

I. INTRODUCTION

During diabetes mellitus, lipid abnormalities are very frequent and constitute added cardiovascular risk factors, in particular in type 2 diabetes.

The therapeutic arsenal for dyslipidemia is currently relatively expanded with molecules like having demonstrated their effectiveness not only on lipid parameters but also, for many of them, on the prevention of cardiovascular diseases. This is how some statins currently have marketing authorizations for primary and secondary cardiovascular prevention, even in patients without lipid abnormalities.

Fibrates, known for their indisputable hypotriglyceridemic effect, are beginning to gain interest in other indications, in the context of microangiopathic complications of diabetes such as diabetic nephropathy, but especially diabetic retinopathy, effects also called “pleiotropic”.

However, the tolerance of lipid-lowering drugs, statins and fibrates, can be hampered by some side effects, mainly hepatic and muscular but also other rarer effects, little sought in routine medical practice and which it is important to detect, such as digestive, cutaneous or haematological side effects.

In this work, we set out to evaluate the effects of statins and fibrates on lipid parameters in patients with diabetes and to detect the adverse effects of these molecules.

II. METHODS

We carried out a cross sectional study which focused on patients with diabetes (type 2 and type 1) followed on an outpatient basis, treated with statin or fibrate for at least 3 months. No patient was on the statin-fibrate combination. We excludes from the study subjects with hypothyroidism, Cushing’s syndrome, patients on corticosteroid therapy, patient with chronic non-steatotic liver disease and alcoholic patients.

All patients had a physical examination, an interrogation specifying the general characteristics, personal and history, any symptoms that may suggest poor tolerance of the lipid-lowering treatment, a food survey using the eating habits method, blood tests (glycemia, glycated hemoglobin, liver enzymes and muscle enzymes). Lipid goals are those of the American Diabetes Association (ADA) 2020 [1].

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The comparison of the percentages on independent series was carried out by Pearson’s chi-square test, and in case of non-validity of this test, by Fisher’s two-tailed exact test.

III. RESULTS

We included 150 patients. The majority (72%) were between 50 and 70 years old. Women represented 65.3% of the patients. Almost all of the patients (97.3%) had type 2 diabetes. The mean duration of diabetes was 14.39±7 years. The mean glycated hemoglobin (HbA1c) was 9.62±2.16%. The distribution of patients by diabetes treatment is shown in Fig. 1.

The distribution of patients according to lipid-lowering treatment is shown in Table I.

The mean duration of treatment with statins and fenofibrate were 2.2 ± 1.3 years and 4.9 ±2.3 years, respectively.

Only 12.7% of patients have no dyslipidemia. They were on statins, as part of cardiovascular prevention.

Lipid abnormalities before starting lipid-lowering treatment are shown in Table II.

On lipid lowering therapy, hypertriglyceridemia, hyperLDLcholesterolemia and high levels of both triglyceride and LDL were present in 20.7, 36.6 and 30% of patients respectively.

The change in lipid parameters on statins is shown in Table III. The change in lipid parameters on fenofibrate is shown in Table IV.

As for the adverse effects of lipid-lowering treatment, in our patients we noted no cases of cholestasis or significant elevation of liver enzymes (greater than 3 times the upper limit) or muscle enzymes (greater than 5 times the upper limit).

As far as the muscle tolerance is concerned, 10.4% of patients had muscle pain on statins compared to 11.6% on fenofibrate. Muscle tenderness on palpation was found in 12.3% of subjects on statins and 20.9% in those on fibrates. Muscle enzymes increased insignificantly on statin while it did not change on fibrate.

IV. DISCUSSION

In our study, we noticed a significant decrease of 1.02±1.25 mmol/l in total cholesterol (CT) level, 0.32±0.47 mmol/l in LDL cholesterol level and a non-significant decrease of 0.1 ±0.73 mmol/l in Triglyceride (TG) level on statins. HDL levels fell insignificantly by0.035 ±0.27mmol/l.

Fenofibrate allowed a significant decrease in total cholesterol level of 1.15±2.24 mmol/l, TG of 1.73±2.96 mmol/l and a non-significant decrease in LDL levels of 0.09 ±0.37 mmol/l. A non-significant increase of 0.1 ±0.35 mmol/l in HDL levels was observed.

In a meta-analysis of 181 controlled studies including 256,827 patients, all statins reduced CT levels in a dose-dependent way [2]. The decrease in CT in large statin intervention studies ranged from 17.9 % to 25 % [3]-[8]. Different studies have proven the effectiveness of statins in lowering LDL cholesterol. This effectiveness is depending on the statin prescribed as well as the dosage administered. In the ASPEN study [9], atorvastatin reduced LDL cholesterol levels by 29%. This reduction reached 40% in the CARDS study[10]. As for simvastatin, it reduced LDL

### Table I: Distribution of 150 Tunisian Diabetics According to Lipid-Lowering Treatment.

<table>
<thead>
<tr>
<th>Patients on statins</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>108</td>
<td>72</td>
</tr>
<tr>
<td>42</td>
<td>28</td>
</tr>
<tr>
<td>49</td>
<td>45,3</td>
</tr>
<tr>
<td>26</td>
<td>24,1</td>
</tr>
</tbody>
</table>

### Table II: Frequencies of Lipid Abnormalities Before Starting Lipid-Lowering Treatment.

<table>
<thead>
<tr>
<th>Lipid Abnormality</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolemia</td>
<td>17,6</td>
</tr>
<tr>
<td>HyperLDLcholesterolemia</td>
<td>66,2</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>36,7</td>
</tr>
<tr>
<td>HypoHDLcholesterolemia</td>
<td>72,3</td>
</tr>
</tbody>
</table>

### Table III: Changes in Lipid Parameters on Statins.

<table>
<thead>
<tr>
<th>Before statins</th>
<th>On statins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean cholesterol (mmol/l)</td>
<td>5,25 ± 1,31</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Mean LDLcholesterolemia (g/l)</td>
<td>1,32 ± 0,38</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Mean HDL-cholesterolemia (mmol/l)</td>
<td>1,08 ± 0,3</td>
</tr>
<tr>
<td>P</td>
<td>0,225</td>
</tr>
<tr>
<td>Mean Triglyceridemia (mmol/l)</td>
<td>1,6 ±0,74</td>
</tr>
<tr>
<td>P</td>
<td>0,15</td>
</tr>
</tbody>
</table>

### Table IV: Changes in Lipid Parameters on Fenofibrate.

<table>
<thead>
<tr>
<th>Before statins</th>
<th>On statins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean cholesterol (mmol/l)</td>
<td>6,04 ±2,44</td>
</tr>
<tr>
<td>P</td>
<td>0,003</td>
</tr>
<tr>
<td>Mean LDLcholesterolemia (g/l)</td>
<td>1,23 ± 0,36</td>
</tr>
<tr>
<td>P</td>
<td>0,31</td>
</tr>
<tr>
<td>Mean HDL-cholesterolemia (mmol/l)</td>
<td>0,93 ±0,32</td>
</tr>
<tr>
<td>P</td>
<td>0,126</td>
</tr>
<tr>
<td>Mean Triglyceridemia (mmol/l)</td>
<td>3,63 ±3,28</td>
</tr>
<tr>
<td>P</td>
<td>0,001</td>
</tr>
</tbody>
</table>
cholesterol by 30% in the HPS study [6] and by 35% in the 4S study [3].

In addition, it is possible that part of the pleiotropic effects of statins, in this case the increase in HDL levels, is through stimulation of PPAR-alpha. In the STELLAR study [11], HDL cholesterol increased by 5 to 9% on atorvastatin and by 8 to 10% on simvastatin. In the TNT study [12], low HDL levels hardly changed on atorvastatin 80 mg. In the STELLAR study [11], the reduction in TG was 23-33% with atorvastatin and 15-23% with simvastatin.

The FIELD study [13], carried out over 5 years and including 9,795 type 2 diabetics, showed a decrease in CT by 0.311 g/l and in LDL by 0.247 g/l on fibrate. The increase in HDL levels with fenofibrate was only 0.011 g/l according to the same study.

In a review of the literature on double-blind, randomized controlled studies examining the effects of fibrates on lipid parameters [14], the reduction in TG level was 0.208 to 3.213 g/l. It was 0.235 g/l in the FIELD study [13].

The results of our study, relating to the efficacy of lipid-lowering drugs on lipid parameters appear to be in agreement with those of the literature.

As for the adverse effects of lipid-lowering drugs, we noted no case of cholestasis or significant elevation of liver enzymes. Muscle tolerance was however less good than that described in the literature. In fact, clinically, 10.4% of patients reported muscle pain under statins compared to 11.6% under fenofibrate. Muscle tenderness on palpation was found in 12.3% of subjects on statins and 20.9% in those on fibrate. There was no significant difference between the two drugs.

The prevalence of elevated muscle enzymes level increased insignificantly on statins while it did not change on fibrate.

The most frequent hepatic adverse reaction reported with statins is elevated liver enzymes without histopathological changes. The underlying mechanism is unknown. According to some authors, this cytolysis is related to the alteration of the lipid components of the hepatocyte membrane leading to an increase in membrane permeability and the release of hepatic enzymes [15]. This effect is therefore secondary to the lipid lowering process and is not specific to statins. Very often, this elevation in liver enzymes subsides even with continued drug administration [16]. It is generally asymptomatic, reversible, dose-dependent, and similar for all statins. Its incidence was 1.8% with atorvastatin 10 mg / day in the ARIANE study [17]. In the TNT study [12] significant hepatic cytolysis was observed in 1.2% of patients treated with high-dose atorvastatin compared with 0.2% in the low-dose group. In the 4S study [3], it was found that an increase in liver enzymes greater than 3 times normal was significantly more frequent in the group of patients treated with simvastatin compared to the placebo group. Accordingly to Mallat and Larrey, fenofibrate is sometimes implicated in the occurrence of cytolytic liver disease [18],[19] while, according to [20], the hepatotoxicity of fenofibrates is poorly characterized and remains exceptional. According to these same authors, atorvastatin is sometimes responsible for cholestatic or mixed hepatitis (cholestasis and cytolysis). According to [18] and [19], acute cholestatic hepatitis can be seen with fenofibrate and often produces a pseudo-angiocholitic syndrome.

The muscular side effects of statins are rare, occurring in less than 1 case per 1000. They are dose-dependent, ranging from asymptomatic biological myolysis to a deficit myalgia reversible on discontinuation of treatment but sometimes performing rhabdomyolysis. According to [21], myalgia generally appears during the first 6 months of treatment. More rarely, the onset can be seen after several years and this myalgia typically resolves after two months of stopping treatment. In a review of 20 clinical trials, the prevalence of mild muscle pain on statins was 195 per 100,000 patients and that of rhabdomyolysis 1.6 per 100,000 patients years [22]. According to [23], myopathy with CPK levels of more than 10 times the upper limit is observed in 0.1% of patients on statins. In the ARIANE study [17], the incidence of myalgia was 5.4 and elevation of CPKs was observed in 3.9% of patients after 12 weeks of treatment with atorvastatin. Regarding fibrates, the rhabdomyolysis observed was mainly been reported in the presence of renal failure, hypothyroidism or drug interaction, in particular with statins. In the FIELD study [13], three patients experienced rhabdomyolysis on fenofibrate compared to a single patient on placebo. In a meta-analysis including 15,313 patients on fibrates, no significant increase in the risk of rhabdomyolysis was noted [24],[25].

V. CONCLUSION

The results of our study confirm the efficacy and good tolerance of statins and fibrates, which should encourage the optimization of the doses of statins or, if necessary, the use of the combination of these two molecules for a better control of dyslipidemia in people with diabetes.

CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

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[17] Danschin N, Chadarevian R, Gayet JL, Licour M, Valensi P. Compared with atorvastatin at the dose of 10mg per day rosuvastatin was more effective to reach an LDL goal of <1.00 g/l in high cardiovascular risk patients (ARIANE study). *Ann Cardiol Angiol*. 2007;56(2):82-7.


