Assessing the adherence to and the therapeutic effectiveness of hypolipidemic agents in a population of patients in Brazil: a retrospective cohort study

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INTRODUCTION

Dyslipidemia is a metabolic disorder of high prevalence worldwide. It is one of the major risk factors related to cardiovascular disease, whose incidence is increasing in developing countries such as Brazil.1,2

The clinical approach to primary prevention to reduce cardiovascular disease risk is founded on life style changes, including reduced intakes of saturated fat, trans fatty acids, cholesterol and carbohydrate; increased physical activity and weight control.2-5 Drug therapy is applied to reduce plasma lipids levels when these modifications fail to control the dyslipidemia.6

Numerous studies have shown the benefit of statins in reducing the mortality and morbidity associated with cardiovascular disease.5,9

The success of drug therapy for the control, prevention or cure of any disease, especially the chronic ones, depends on the patient’s adherence to the treatment.10-12 Non-adherence to drug therapy is a principal cause of treatment failure13 and is considered a high priority public health issue.12

Adherence to treatment is an active, intentional and responsible process of care in which patient’s degree of compliance with the health professionals’ recommendations.13-15 It implies two different behaviors. First means the duration of dosing before patient’s premature interruption of treatment. On the other hand, good quality of execution, which describes the daily patterns of patient adherence behavior.13

Medication adherence can be characterized either by direct or indirect methods. Direct methods are designed to detect the therapeutic drug or its metabolites in the patients’ biological fluids. On other hand, indirect methods mainly include interviews, pill counting, medication electronic monitoring systems and Medication Possession Ratio (MPR) evaluation.11,15 MPR considers the amount of times the patient takes out medicines from the health service pharmacy. This procedure to assess patient adherence applies particularly to the public healthcare service, considering that patients must always take their medicines in the same healthcare center. It represents the patient’s willingness to comply with his treatment and has been associated with the treatment success.15-20

The absence of a gold standard to measure

ABSTRACT

Objective: to evaluate the relation between patient adherence and therapeutic effectiveness of hypolipidemic agents in clinical practice.

Methods: A retrospective cohort study of 417 patients using hypolipidemic drugs (simvastatin, atorvastatin) between 2003 and 2010 was performed. The population studied consists of patients assisted by the Public Health Service in the far-west region of the State of Santa Catarina, Brazil. The Medication Possession Ratio obtained from pharmacy refill data was used to measure patient adherence. Therapeutic effectiveness was evaluated based on the difference obtained in the serum levels of total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides, before and after taking the drug, in an average time of 8.3 months.

Results: Following the treatment with hypolipidemic agents, it has been observed a reduction of 14.3% for total cholesterol, 19.6% for LDL-cholesterol, and 14.4% for triglycerides. HDL-cholesterol increased by an 8.0% average. The major changes in lipid profile were promoted by atorvastatin 20 mg daily. The medication adherence rate decreased over the monitoring period. Adherence rates below 60% were associated with therapeutic failure, while rates equal to 80% or higher were associated with the best response to the lipid-lowering drugs.

Conclusion: Adherence to hypolipidemic agents is higher at the beginning of the treatment, but it decreases over time, affecting the achievement of therapeutic goals.

Keywords: Medication Adherence; Hypolipidemic Agents; Outcome and Process Assessment (Health Care); Primary Health Care; Brazil
adherence and the use of self-report methods hamper adherence research and the assessment of interventions provided. However, electronic monitoring and pill count have shown the best validity to assess adherence.

Adherence is influenced by many demographic factors, such as gender, age, race, socioeconomic status and pre-existing cardiovascular disease. Others including lack of adequate knowledge about medication and treatment goals, beliefs about the medication, complex regimens that are difficult to manage and side effects can play important roles in predicting adherence.

In addition to these patient factors, health care system factors, such as access to care, may influence a patient’s likelihood to take their medications to improve adherence. Pharmacists are one of the most utilized members of the health care team due to their ease of accessibility to the general patient population. There are many opportunities for the pharmacists to become involved in lipid management, such as patient education, lipid levels rechecked, decreasing cardiovascular disease risk factors, along with counseling on adverse effects, administration times and drug interactions. Pharmacists can promote medication adherence and take part in enhancing continuity of care among healthcare professionals in the community.

This study aims to evaluate the relationship between adherence rate to hypolipidemic agents assessed by MPR and therapeutic effectiveness, for patients whose treatment has been delivered at the primary care level in Brazilian Public Health System.

METHODS

A retrospective analysis of medical records of 417 active patients of Brazilian Health System was carried out. All of them were registered in the state health program for access to hypolipidemic medication. The study was conducted in twenty-two cities in the far-west region of the State of Santa Catarina, Brazil.

Data collection was carried out by the indirect method using a form developed by the authors. This form consists of structured interview based on standardized information by the Brazilian Health System, which are required to ensure that patients have access to medication. The data from the structured interview form were obtained from standardized information registered on medical records and pharmacy records. Patients with incomplete medical records were excluded, as well as those who had left the hypolipidemic agents therapy before the first follow-up evaluation, and those with monitoring tests dated earlier than 30 days or later than 46 months from the treatment beginning.

The Information data collected in the form were age, gender, weight, height, date of treatment beginning, type of hypolipidemic agent, dosage regimen and changes made in the treatment during the study period. The body mass index (BMI) was calculated and expressed in kg/m². The presence / absence of comorbidities such as high blood pressure, type 2 diabetes mellitus, chronic kidney disease, liver disease, hypothyroidism and obesity was identified according to the clinical notes in each patient’s medical file.

The serum laboratory tests for total cholesterol, triglycerides, HDL-cholesterol, alanine aminotransferase and fasting plasma glucose were performed in the automated system Cobas mira (Roche Diagnostic) with reagents, calibrators and controls purchased from Labtest Diagnostics SA (Brazil). The LDL-cholesterol was estimated by the Friedewald equation. Thyroid-stimulating hormone was measured by automated chemiluminescence with all reagents and equipment provide by Abbott Diagnostics (Architect Cib8200, Abbott Diagnostic Laboratory, Brazil).

The lipid profile results were evaluated according to the treatment goals established by the Brazilian Society of Cardiology (2001)²⁹, that is similar to the American Heart Association, and its recommendations for preventive therapy. To calculate the amount of time the treatment had been taken, it was considered the time between the first and last medication dispensing. The lipid-lowering therapeutic effectiveness was evaluated for the time elapsing between the beginning of the treatment and the first monitoring assessment for simvastatin 10 mg, 20 mg, 40 mg and atorvastatin 10 mg and 20 mg daily. The difference seen in the serum concentration of the lipid profile elements during that period was calculated in percentage. The rate of adherence to the treatment was evaluated based on the patient’s medication possession ratio of the hypolipidemic agents, according the following formula:

\[
\text{Adherence rate (\%) = \frac{\text{Tablets dispensed} \times 100}{\text{Tablets to be dispensed}}}
\]

Patients with adherence rate 80% or above were considered to have good adherence to the treatment.²⁰

Kolmogorov-Smirnov Test was used for normality test, before selecting the statistical tests. Continuous variables have been shown as mean and standard deviation or median (interquartile range), as appropriate. For variables with normal distribution, Student t-test (independent) was applied to compare means between two groups and ANOVA was used for three or more groups. Wilcoxon test was applied to compare means of dependent groups for non-parametric variables, and Mann-Whitney U test was applied to compare non-parametric variables between two independent groups. For three or more groups, Kruskal-Wallis test was used. For the comparison of categorical variables, Fisher Exact test (two-tailed) or chi-square was employed as appropriated. Results were considered significant with a probability less than 5% (p<0.05). Statistical analyses were performed with SPSS software v.17.0 (Statistical Package of Social Science).
This study was approved by the Ethics Committee on Human Research of the Health Science Department, from Federal University of Paraná (CEP / SD: 962.087.10.07 and CAE: 3083.0.000.091-10).

RESULTS

The characteristics of the patients included in the study group are shown in Table 1. The sample consisted of 417 patients, most of them were women (62.1%). The median Body Mass Index was 27.7 kg/m². The most frequent comorbidities for both genders were hypertension (83%) and type 2 Diabetes mellitus (29%), followed by obesity (13.7%), hypothyroidism (6.7%), kidney disease (1.4%) and hepatic disease (0.7%). The statins were the most used hypolipidemic class (92.8%), and simvastatin 20 mg daily was the most frequent treatment prescribed. Ciprofibrate 100 mg daily was the most prescribed fibrate (3.4%).

Serum levels at baseline and the first monitoring laboratory tests of the studied group are shown in Table 2.

Serum level of total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol were significantly lower (p<0.05) in the follow-up evaluation, when compared to the serum dosages at the beginning of the treatment. Serum levels of alanine aminotransferase, thyroid-stimulating hormone and fasting plasma glucose were not significantly different (p>0.05) in the same period.

Our study shown that until the first follow-up evaluation, in average eight months after the start of the treatment, it was verified that 92.6% of patients achieved an adherence rate of 80% or above. At the first monitoring time the number of patients with treatment adherence rate of 80% or above was significantly higher (p<0.001) in patients aged more than 65 (94.7%) when compared to those <65 years old (91.0%). The adherence rate 80% or above was not different when the overall time was considered (84.9%). As to the evaluation of the full-length treatment period (19.7 months in average), the number of patients who got adherence 80% or above decreased to 82.6%.

The therapeutic effectiveness of hypolipidemic agents in the population of the study is shown in Figure 1. The evaluation of hypolipidemic therapeutic effectiveness in the studied population showed a decrease in lipid profile serum concentration by daily using the drug simvastatin 10 mg, 20 mg, 40 mg and atorvastatin 10 mg and 20 mg. The greatest reduction of total cholesterol (17%), LDL-cholesterol (27%) and triglycerides (12%) was obtained with the use of atorvastatin 20 mg / day. For HDL-cholesterol, the best result was achieved with simvastatin 20 mg / day (an increasing of 8%).

### Table 1. Baseline anthropometric, clinical, pharmacotherapy, and adherence to treatment characteristics of the studied subjects.

| Variables | All patients (n=417) | Male group (n=158) | Female group (n=259) | P-value |
|-----------|----------------------|-------------------|----------------------|---------|
| Age in years (SD) | 61.0 (11.5) | 58 (11.9) | 62 (10.9) | 0.001 |
| BMI in kg/m² | 28.1 (4.6) | 28.0 (4.0) | 28.1 (4.9) | 0.920 |
| Ethnicity, n (%) | Euro-Brazilians | 354 (84.8) | 134 (84.8) | 220 (84.9) | 0.756* |
| | Afro-Brazilians | 63 (15.2) | 24 (15.2) | 39 (15.1) | 0.438* |
| Comorbidities *, n (%) | High Blood Pressure | 346 (83.0) | 130 (82.3) | 216 (83.4) | 0.789* |
| | Diabetes mellitus type 2 | 121 (29.0) | 42 (26.6) | 79 (30.5) | 0.437* |
| | Obesity | 57 (13.7) | 18 (11.4) | 39 (15.1) | 0.308* |
| | Hypothyroidism | 28 (6.7) | 4 (2.5) | 24 (9.3) | 0.008* |
| | Kidney disease | 6 (1.4) | 3 (1.2) | 3 (1.2) | 0.677* |
| | Hepatic disease | 3 (0.7) | 2 (1.3) | 1 (0.4) | 0.560* |
| Hypolipidemic agent, n (%) | Simvastatin | 310 (74.3) | 111 (70.3) | 199 (76.8) | 0.165* |
| | Atorvastatin | 75 (18.0) | 29 (18.4) | 46 (17.8) | 0.896* |
| | Others | 32 (7.7) | 18 (11.3) | 14 (5.4) | 0.372* |
| Adherence rate to the treatment ≥80%, n (%) | 386 (92.6) | 147 (93.0) | 239 (92.2) | 0.774* |

The values were mean ± 1-standard deviation or n (%).

P-value: Mann-Whitney U test or (*) Fisher Exact test (two-tailed).

(*) Comorbidities were identified according to the registration in each patient’s medical record (presence / absence).

(1) Others hypolipidemic agent were Ciprofibrate (3.4%), Gemfibrozil (2.6%), Bezafibrate (1.2%) and Lovastatin (0.5%).

Adherence rate to the treatment (%) = (Number of tablets dispensed in the period X 100)/Quantity of tablets which should have been dispensed.

### Table 2. Serum levels at baseline and the first monitoring of laboratory tests of the studied group.

| Variables | Baseline | First monitoring | P-value |
|-----------|----------|-----------------|---------|
| Total Cholesterol (mg/dL) | 232.0 (83.0 - 415.0) | 196.0 (87.0 - 386.0) | <0.001 |
| LDL-cholesterol (mg/dL) | 142.0 (20.0 - 327.6) | 115.1 (14.2 - 281.0) | <0.001 |
| HDL-cholesterol (mg/dL) | 47.0 (15.0 - 103.0) | 49.0 (16.0 - 113.0) | <0.001 |
| Triglycerides (mg/dL) | 170.0 (56.0 - 1564.0) | 143.0 (48.0 - 1630.0) | <0.001 |
| Fasting Plasma Glucose (mg/dL) | 94.0 (60.0 - 420.0) | 94 (42.0 - 325.0) | 0.175 |
| Serum Creatinine (mg/dL) | 1.0 (0.5 - 9.7) | 1.0 (0.4 - 3.9) | 0.587 |
| Alanine Aminotransferase (U/L) | 20.0 (5.0 - 148.0) | 21.0 (7.0 - 66.0) | 0.087 |
| Thyroid-stimulating Hormone (µU/mL) | 3.7 (0 - 52.5) | 1.9 (0.2 - 16.4) | 0.886 |

The values were median (interquartile range).

Sample size 417 subjects; first monitoring 8.3 months (average)

P-value: Mann-Whitney U test.
The relation between the adherence rate to hypolipidemic therapy and the reduction obtained for total cholesterol and LDL-cholesterol, in the period between the start of the treatment and the first clinical monitoring examinations, is shown in Figure 2.

Patients who had adherence rate to hypolipidemic therapy lower than 55% did not present any reduction in total cholesterol. For the patients who had adherence rate from 55 to 80%, the reduction for total cholesterol was 0-7%; while the greatest reduction, of about 11%, was observed for the ones with an adherence rate higher than 80%. For LDL-cholesterol, adherence rates to the treatment lower than 60% had no therapeutic effectiveness. A significant reduction (14%) of LDL-cholesterol was only obtained with adherence rates higher than 80%.

**DISCUSSION**

This was a retrospective cohort study that shown that lipid profile serum concentration was significantly reduced after the use of hypolipidemic therapy by patients with good to optimal medication adherence. To our best knowledge, this is the first study regarding the evaluation of the adherence rate for hypolipidemic agents in a Brazilian population assisted by the Public Health Service.

In this study, the greatest reduction of total cholesterol, LDL-cholesterol and triglycerides was obtained with the use of atorvastatin 20 mg / day. Similarly, a study by Jones et al. with 534 hypercholesterolemic patients, revealed that atorvastatin 20 mg daily, produced greater (p <0.01) reductions in total cholesterol and in LDL-cholesterol (46%), than other hypolipidemic agents like simvastatin. On the other hand, Brown et al., in a study that compared the efficacy of atorvastatin, fluvastatin, lovastatin, and simvastatin with 318 patients with atherosclerosis, verified that atorvastatin 10 mg daily produced significantly greater decreases (p<0.05) in plasma LDL-cholesterol than the other treatments. Consistent results about atorvastatin 10 mg were reported by Andrews et al. They demonstrated that atorvastatin 10 mg daily achieved the greatest
mean reduction in LDL cholesterol (36%, SD=11% at 6 weeks) than pravastatin 10 mg, simvastatin 10 mg, fluvastatin 20 mg and lovastatin 20 mg, in the same period.

According to Brazilian Society of Cardiology, statins may reduce LDL-cholesterol from 15% to 55% and triglycerides from 7% to 28%. They also may increase HDL-cholesterol from 2% to 10%. The expected reduction depends upon the drug and the dosage regimen used. Therefore, the expected reduction of LDL-cholesterol, for simvastatin 20 mg to 80 mg, is from 27% to 42%; whereas for atorvastatin 10 to 80 mg, the expected reduction for the same parameter is from 37% to 55%. Considering the results of simvastatin 20 mg for the population under study, the reductions obtained for LDL-cholesterol and triglycerides were lower than the theoretical effectiveness described in the literature. For HDL-cholesterol the obtained results are consistent with the expectations.

Cardiovascular medications adherence is often low. For hypolipidemic therapy, the limit value (cut off value) for adherence rate is 80%. It is considered good adherence when the adherence rate to the treatment 80% or above and poor adherence when its <80%. In our study, a good adherence was observed in about 90% of the patients at the first 8 months of therapy and reduced to about 80% after 20 months. The observed reduction in patient adherence over the time can be a result of several interacting factors, like side effects, patient misunderstanding about treatment and lack of appropriate patient monitoring.

A study by Andrade et al. with users of hypolipidemic therapy, revealed that the rate of adherence reduces 4-15% in the first year of treatment and approximately 11 to 30% when the clinical monitoring lasts five years or more. Similarly, Applegate 37 in his study with elderly patients, verified that adherence to statin therapy declined more than 25% in the first 6 months after the original prescription, with further declines in adherence the longer the cohort was followed. Benner et al. also reported a reduction of medication adherence in the long-term therapy. Their study reported that 39% of their patients shown adherence rate above 80% after 12 months of treatment with statins. These authors have also verified that patients with comorbidities, such as hypertension, diabetes or a past history with cardiovascular disease, have a better persistence for hypolipidemic therapy. Catalan et al. shown that a higher index of chronic morbidity and pre-existing cardiovascular disease were predictive of longer persistence on statin medication. Consistent results were reported by Jackevicius et al. The results of their study shown that elderly patients’ adherence to statin therapy continually reduced from initiation of therapy through 2 years follow-up and shown that patients at higher risk for cardiovascular disease were more adherent to therapy than those patients treated for primary prevention. Ruokoniemi et al. have verified therapeutic adherence rates to statins over 80% in more than 50% of their studied population, and also that older patients with comorbidities have a higher adherence to the treatment. Avorn et al. have not identified any therapeutic adherence difference between genders, which is consistent with our results.

In a study to implement pharmaceutical care program to improve medication adherence in new users of statin, the authors verified that pharmacist has an important role to play in ensuring that drug therapy is appropriate and effective. They compared discontinuation of statin therapy over time between patients in the pharmaceutical care and usual care groups. They found that patients in the pharmaceutical care group were more likely to persist with treatment compared to patients in the usual care group.

A recent survey that sought to determine views of pharmacist effectiveness and impact on health care delivery found that 96% of respondents reported...
benefits, including improved disease management outcomes, increased return on investment, and increased access to patient care.\textsuperscript{41}

Another study about adverse drug events suggests that pharmacist intervention decreases 34\% the risk of adverse drug events and medication errors in patients with cardiovascular disease.\textsuperscript{42}

A review of several studies to quantify the impact of pharmacist interventions in hyperlipidemia management\textsuperscript{43} and in cardiovascular and renal disease\textsuperscript{44}, evidenced that total cholesterol is sensitive to pharmacist interventions\textsuperscript{43}, and there are improvements in cardiovascular and renal outcomes.\textsuperscript{44} Furthermore, patient-specific recommendations made by pharmacist can positively affect prescribing habits and make steps to improve patient safety.\textsuperscript{45}

Nevertheless, there are limitations in this study. First, a potential limitation was the impossibility to determine if the patients effectively used the hypolipidemic drugs that were dispensed from the Brazilian Public Health System. Second, we did not consider those patients who might have been taken a statin and a fibrate simultaneously. Third, we did not compare the therapy adherence between patients without any history of cardiovascular event with those who had any previous cardiovascular events.

CONCLUSIONS

Lipid profile presented a significant reduction in serum total cholesterol, LDL-cholesterol and triglycerides, as well as an increase in HDL-cholesterol in patients with good to optimal medication adherence. A medication possession ratio above 80\% was related to the best health outcomes.

The adherence rate assessment by recording the pills that a patient received shows to be a simple, low cost and effective process to assess therapeutic effectiveness for hypolipidemic drugs and a potential predictor of the treatment effectiveness.

The access to the medicines, which are supplied free of charge by the Brazilian Health System, as an isolated action in the treatment of dyslipidemia, does not ensure a successful drug therapy outcome in the long-term. On the contrary, patients’ adherence and clinical outcomes monitoring can go together with drug dispensing all over the treatment in order to ensure its therapeutic success. The pharmacists have the opportunity to promote health and disease prevention through improved treatment adherence.

CONFLICT OF INTEREST

The authors declare not having any conflict of interest.

EVALUANDO LA ADHERENCIA Y LA EFECTIVIDAD TERAPÉUTICA DE LOS HIPOLIPÉMIANTES EN UNA POBLACIÓN DE PACIENTES EN BRASIL: ESTUDIO DE COHORTE RETROSPECTIVA

RESUMEN

Objetivo: Evaluar la relación entre la adherencia del paciente y la efectividad terapéutica de los hipolipémiantes en la práctica clínica.

Métodos: Se realizó un estudio retrospectivo de 417 pacientes que usaban hipolipémiantes (simvastatina, atorvastatina) entre 2003 y 2010. La población estudiada estaba compuesta de pacientes atendidos en el Servicio Público de Salud de la región del oeste lejano del estado de Santa Catarina, Brasil. Se usó como medida de adherencia el ratio de posesión de medicación obtenido de los datos de consumo en la farmacia. La efectividad terapéutica se evaluó en base a la diferencia obtenida en los niveles séricos de colesterol total, colesterol-LDL, colesterol-HDL y triglicéridos antes y después de tomar el medicamento en una media de tiempo de 8,3 meses.

Resultados: Después del tratamiento con hipolipémiantes, se observó una reducción del 14,3\% para el colesterol total, 19,6\% para el LDL, y 14,4\% para los triglicéridos. El HDL aumentó en una media del 8,0\%. Los mayores cambios del perfil lípido fueron promovidos por la atorvastatina 20 mg diáriamente. La tasa de adherencia a la medicación disminuyó durante el periodo seguido. Las tasas de adherencia por debajo del 60\% estaban asociadas con fracaso terapéutico, mientras que las tasas del 80\% o superiores estaban asociadas a la mejor respuesta a los hipolipémiantes.

Conclusión: La adherencia a los hipolipémiantes fue mayor al principio del tratamiento, pero disminuye a lo largo de éste, afectando a la consecución de los objetivos terapéuticos. Los procedimientos sistemáticos de monitorización de la tasa de adherencia y la evaluación del perfil lípido por el farmacéutico

Palabras clave: Cumplimiento de la Medicación; Hipolipémiantes; Evaluación de Procesos y Resultados (Atención de Salud); Atención Primaria de Salud; Brasil

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