japhac.wix.com/japhac
ISSN 2358-3495

Journal of Applied Pharmaceutical Sciences

Submitted:
04/08/2019
Revised version:
04/11/2019
Accepted:
18/11/2019
REVIEW ARTICLE

Effectiveness on diabetes mellitus treatment through a pharmaceutical care in a government program for access to medicine: a randomised controlled trial

Ana Elisa Prado Coradi[1*], Francisco Winter dos Santos Figueiredo[2], Fernando Adami[2,1], Fernando Luiz Affonso Fonseca[3], Ricardo Peres do Souto[4]

1- Professor of Pharmacy, Faculdade de Medicina do ABC, Santo André, SP, Brasil; 2- Department of Public Health, Faculdade de Medicina ABC, Santo André, SP, Brasil; 3- Department of Oncology, Faculdade de Medicina ABC, Santo André, SP, Brasil; 4- Department of Morphology and Physiology, Faculdade de Medicina ABC, Santo André, SP, Brasil .
*Corresponding author: ana.coradi@fmabc.br

Abstract: Benefits from pharmaceutical care in type 2 diabetes mellitus (DM2) among patients from the government program for access to medicine *Programa da Farmácia Popular do Brasil* (PFPB) were assessed, through a randomized controlled trial. Fifty DM2 patients from a community pharmacy participating in PFPB were divided into two groups: control group (n = 25) and intervention group (n = 25). Both groups were analyzed during the period of four months. All subjects received the same initial instructions and underwent the same final assessment, whereas the intervention group took part in two additional intermediate interviews with emphasis on health education. Procedures followed principles established by the Dader method. At the end of study, control and intervention groups had respectively 9 and 20 patients. The dropout rate was higher for members of the control group (64% *vs* 20%), mostly due to lack of interest. More Drug Related Problems (DRPs) per patient were solved in the intervention group ($p<0.014$). There was an average rate of 0.50% of reduction in glycated hemoglobin in the intervention group and an average increase of 0.07% in the control group ($p=0.09$). The Student test was used analyzing variables with normal distribution (Shapiro-Wilk, $p\geq0.05$) and the Mann-Whitney test for variables with asymmetric distribution (Shapiro-Wilk, $p<0.05$). Pharmaceutical care provided to patients in a government-funded program for medicine distribution may be an efficient tool to improve treatment and help control DM2.
Keywords: Pharmaceutical care, diabetes, pharmacy practice, access to drugs, Dader Method

INTRODUCTION

According to the International Diabetes Federation there are in the world 425 million adults with diabetes mellitus (DM), and the disease is projected to reach 629 million people in 2045. In Brazil, there are 12.5 million people with DM [1]. Epidemiological survey of patients from nine countries in Latin America reveals that DM control assessed by blood glucose levels and hemoglobin glycation is unsatisfactory, and high frequency of comorbidities is observed [2]. Deficiencies of the disease treatment in the countries of the region result in large consumption of resources of health services, among other economic impacts [3]. With the advance of DM and insufficient treatment, the programs for more intensive and efficient control of the disease are needed in the region.

An important strategy to improve the treatment of DM is the pharmacotherapeutic follow-up. This is a clinical practice of pharmaceutical care involving monitoring and continuous evaluation of the patient's drug therapy. The follow-up is based on the detection of drug-related problems (DRPs), situations that cause or may cause the appearance of negative results in pharmacotherapy, to educate patients and propose corrective interventions [4, 5]. DM treatments that incorporate pharmacotherapeutic follow-up practices have improved results, as compiled in recent revisions [6-10]. Regarding the control of glycated hemoglobin (HbA1c), one of the main goals in diabetes treatment [11], three meta-analyses covering this type of intervention found differences in the reduction of this metabolic parameter between 0.6 and 0.76% compared to control groups [6, 8, 9].

The benefits of this type of pharmaceutical intervention in DM are not restricted to favorable outcomes for therapeutic goals, but also include in reducing the occurrence of adverse drug reactions and increase the quality of life [9-11].

The role of the pharmacist as a member of the diabetes health care team can be seen in several scenarios [7]. In Brazil, recent studies have evaluated the pharmacotherapeutic follow-up in the treatment of type 2 DM (DM2) provided by basic health units, academic services and community pharmacies, and documented many positive aspects including reduction of HbA1c, gain in quality of life, identification and resolution of DRPs and optimization of financial resources utilization [12-21].

The aforementioned studies cover a wide range of pharmaceutical professional practice scenarios, but only one research group evaluated the effect of this type of intervention in the context of the Programa Farmácia Popular do Brasil (PFPB) [19, 20, 22]. The PFPB aims to promote population access to basic and essential drugs, thus minimizing expenditure on medicines in the family budget [23, 24].

Under this perspective, it is expected that the follow-up of pharmacotherapy of DM2 patients receiving medicine from the Brazilian public program PFPB may improve disease control despite the complexities of the program. Therefore, the objective of this study was to evaluate the efficiency of the pharmaceutic intervention in DM2 patients participating in the PFPB program.

METHODS

Patients

A randomized controlled study was carried out with a convenience sample of 50 patients suffering from DM2. The randomization process was been done by manual drawing. All of them got their medicine from a pharmacy of the PFPB system in Santo André, São Paulo, Brazil, from October 2012 to February 2013. The study followed the guidelines of the Declaration of Helsinki and was approved by the Institutional Research Ethics Committee, Process No. 51033/2012.

The subjects included in the study were at least 18 years old, took at least one antidiabetic agent orally and voluntarily agree to participate by signing the informed consent form and attending the interviews. The subjects who did not meet these criteria were excluded.

Recruitment occurred with customers who visited the pharmacy to acquire antidiabetic drugs and who declared a condition of medical treatment for Type 2 diabetes from June to September 2012. Initially, 115 individuals were invited and 50 were included in the study. Reasons for refusing to participate were no time to attend the pharmaceutical consultation, declined to participate or not meeting inclusion criteria.

Pharmacotherapeutic follow-up

An adaptation of the Dader method was used [5]. Patients attended a series of interviews with the same pharmacist (Figure 1). The initial interview (Day 1) took an average duration of 60 minutes for collecting information about personal and medical history, medication used, system review, identification of DRPs, initial orientation. The variables considered were gender, marital status, private health service, family history, hypertension, dyslipidemia, sedentary lifestyle, age and information about weight and height was collected to calculate the body mass index (BMI). The drug list was investigated by prescription review and patient self-report.

This stage corresponds to the first interview in the Dader method. Severe DRPs identified in the initial interview were immediately presented and discussed with the patient, according to the interviewer's decision. When the 50 initial interviews were completed, patients were randomly, by manual drawing, divided into two groups: the intervention group (IG) and the control group (CG). Information on all patients were used by a pharmacist to elaborate individual assessment forms and action plans, which is the following stage of the Dader method.

The final stage, corresponding to Dader´s intervention, was different for both groups. Intervention group had 2 intermediate interviews (Day 40 and Day 80) with emphasis on education in diabetes regarding risk factors for complications, the management of signs and symptoms, changes in lifestyle, selfmonitoring glycaemic control, physical activity, diet and medication adherence. And one final interview (Day 120) consisting of DRP solution and concluding orientations. Control group had only the final interview. Blood was collected for determination of glucose in all interviews and for determination of glycated hemoglobin (HbA1c) in the initial interview and about ten days (Day 110) before the final interview.

Data collection

The determination of HbA1c was carried out by ion exchange chromatography Diafast device (Prime Diagnostics). The variation in the final HbA1c (at the fourth interview) was calculated based on the initial (at the first interview). The capillary blood glucose test was performed using Accu-Check Active (Roche).

Statistical analysis

The Shapiro-Wilk test was used for assessing normality of variable distribution. Description of the data was made by measures of central tendency and dispersion, as well as through absolute and relative frequency. The Student test was used analyzing variables with normal distribution (Shapiro-Wilk, $p \geq 0.05$) and the Mann-Whitney test for variables with asymmetric distribution (Shapiro-Wilk, $p < 0.05$). For both types of variables, 95% confidence intervals were estimated. The association between group and baseline variables was estimated using the chi-square test. The statistical software used was Stata 11.0.

RESULTS AND DISCUSSION

A total of 50 patients with DM2 were included in the study, divided into two groups: the intervention group receiving follow-up (n = 25) and the control group (n = 25). At the starting point, intervention and control groups were homogeneous in relation to most of the study variables (gender, marital status, private health servisse, hypertension, sedentary lifestyle, age, BMI and HbA1c initial) except for dyslipidemia and family history (Table 1). The intervention group reported higher prevalence of family history and dyslipidemia than the

control group respectively: 76% vs 48% (p = 0.041), and 64% vs 28% (p = 0.011).

The comorbidities reported by the studied patients, both in the control and intervention groups, are related to metabolic syndrome: 40% DM2 associated with systemic arterial hypertension, 12% DM2 associated with dyslipidemia, 34% DM2 associated with systemic arterial hypertension and dyslipidemia and only 14% had isolated DM2. Most patients (76%) were overweight or obese, and 62% of the total did not practice any physical activity. Of all patients included in the study, 30% mentioned signs or symptoms related to chronic complications of diabetes, including: diabetic neuropathy (60%), diabetic retinopathy (20%), macroangiopathy (13%) and nephropathy (7%).

In both groups, predominance of private health service users was observed (84% and 88% control intervention). Regarding the number of medicines, 18% of patients used 1 to 2 drugs, 32% used 3 to 4 drugs and 50% of the patients used 5 different drugs. The pharmacotherapy for the latter group was considered polypharmacy. Table 2 shows the medications used by patients when the initial interview was conducted. Among the oral hypoglycemic agents, metformin was noticed as the most common product (96%), followed by glibenclamide (18%), glimepiride (14%), sitagliptin (4%) and gliclazide (6%). Four patients used insulin.

Until the completion of the final interviews, 20 of 25 patients in the intervention group and 9 of 25 patients in the control group remained in the study, totaling 42% dropout, 20% in IG and 64% in the CG. The reasons for dropout were lack of interest (n = 6), limited mobility and/or displacement (n = 5), loss of contact (n = 5), removal (n = 4) and incompatibility with job time (n = 1). Lack of interest, the most alleged reason, was more common in the control group (n = 5) compared to IG (n = 1).

Regarding the follow-up approach in pharmacotherapy during the interviews of the two groups, 173 DRPs were detected in 46 of 50 patients, totaling an average of 3.76 DRPs per person. These DRPs were distributed between the three major classifications: need (23%), effectiveness (45%), and safety (32%), as described in Table 3. The intervention group had 108 DRPs and the control group, 65 DRPs.

From the total amount of DRPs, 63 were solved at the end of the study, 51 in the intervention group (13.7% were related to need DRPs, 62.8% of effectiveness and 23.5% of safety). In the control group, only effectiveness and safety DRPs (respectively 58.3% and 41.7%) were solved. All interventions were documented and reported to the physician in charge whenever necessary. The main interventions included explanation about the importance of adherence to treatment (42.9%), discontinuation or dose adjustment due to adverse drug reaction or drug interaction (23.8%), change in pharmacotherapy due to an untreated health condition (6.3%), and orientation on the risks of self-medication (4.8%). For the number of DRP resolutions, which had an uneven distribution ($p < 0.001$), the Mann-Whitney test was used. Figure 2 shows that the pharmacist orientation in the intervention group was effective in solving DRPs of patients with DM2 ($p < 0.014$). The average amount of DRPs resolved in the intervention group was 2.8, ranging in terms of population between 1.9 and 3.7, compared to an average resolution of DRPs for the unsupervised group of 1.3 and population variation from 0.7 to 1.9.

There were no differences in values from variables in Table 1 (except for HbA1c) among those who completed the study (n = 29) and those who did not (n = 21), with p values> 0.23 denoting homogeneity among variables that may interfere in the quality of the orientation process.

Changes in HbA1c during the study were normally distributed (p = 0.557) and the Student t test was used. In both groups it was found that the average HbA1c of subjects who finished the study was lower: 6.2% ± 1.5% in CG and 6.9% ± 1.0% in IG (p = 0.177). As shown in Figure 3, there was a trend towards better disease control in the intervention group (p = 0.09), when considering average levels of glycated hemoglobin reduced 0.50% (population variation from -1.01 to -0.11%) compared to 0.07% increase in control group (population variation from -0.53 to 0.67%).

Apart from the HbA1c test, blood glucose testing was also performed. In the first interview with all patients, 72% were examined fasting and 28% were in the postprandial period. Blood glucose was above normal in 72% and 76% of patients in the intervention and control groups, respectively. In the last interview with patients who completed the study, the proportion of patients who showed high blood glucose was 76% in the intervention group and 67% in the control group.

The follow-up approach in pharmacotherapy has a very favorable outcome in the clinical treatment of DM2 patients [6, 7, 9, 10]. In this study, the effect of follow-up based on the Dader method as a pharmaceutical care strategy provided to DM2 patients users of the Brazilian medicine access program was assessed, and a higher resolution of DRPs was observed (Figure 2), as well as the reduction of HbA1c (Figure 3).

The average level of HbA1c pre-intervention found among patients was 7.3% in the control group and 6.9% in IG (Table 1). These values are lower than in other studies in Brazilian populations where the initial averages ranged from 7.7 to 12.1% [12-21]. Such a difference in the level of hemoglobin glycation in the beginning of the intervention could explain at least in part why the reduction of HbA1c in this study nearly met but did not reach statistical significance of 5% (Figure 3). Choe *et al.* [25] showed that patients with HbA1c levels higher at baseline have greater reductions after pharmacotherapeutic follow-up than those with mild elevations. In addition, the pharmaceutical intervention period in this study was quite brief (120 days) when compared to other investigations, which took from 6 to 36 months [12-21]. Nevertheless, the average HbA1c reductions found (0.5%) approached the range of 0.6 to 0.76% calculated as meta-analyzes [6, 8, 9].

The PFPB system for drug access aims to serve people, depending or not of public health services, but particularly those using private health services with difficulties in purchasing their medicines in normal drugstore [23]. This predominance of private system users was confirmed in this study population (Table 1). In fact, the frequency of comorbidities (dyslipidemia, hypertension and obesity) and incidence of signs and symptoms of clinical complications are consistent with the profile observed in DM2 patients served by private health care system in Latin America [2].

The polypathology of DM patients favors polypharmacy and thus justified the large amount of DRPs found. In this study, 25 subjects were taking 5 or more drugs. A recent population study showed that patients taking 5 or more medications had an 88% higher risk of adverse effects associated with the use of medications [26]. Several other problems are associated with polypharmacy, including non-adherence to treatment, high costs and reduced

quality of life of the patient [27]. On the other hand, the current guidelines for the treatment pharmacotherapeutic follow-up service is justified to assess the adequacy of the drugs used, to ensure adherence to treatment, and to improve patient quality of life in treatment and knowledge about the disease.

The dropout rate in the study was high (42%), similar to the study conducted in community pharmacies [14, 20, 21]. Other studies found abandonment ranging from 3 to 22% [12, 15, 17, 18]. Dropouts in both groups were markedly different, with 16% in IG and 64% by CG. It is possible to conjecture that the more extensive care provided to the intervention group contributed to establishing a more stable relationship with the participating pharmacy, closer to that observed between patients and public services.

of diabetes recommend the simultaneous use of several drugs [27]. In this way need for

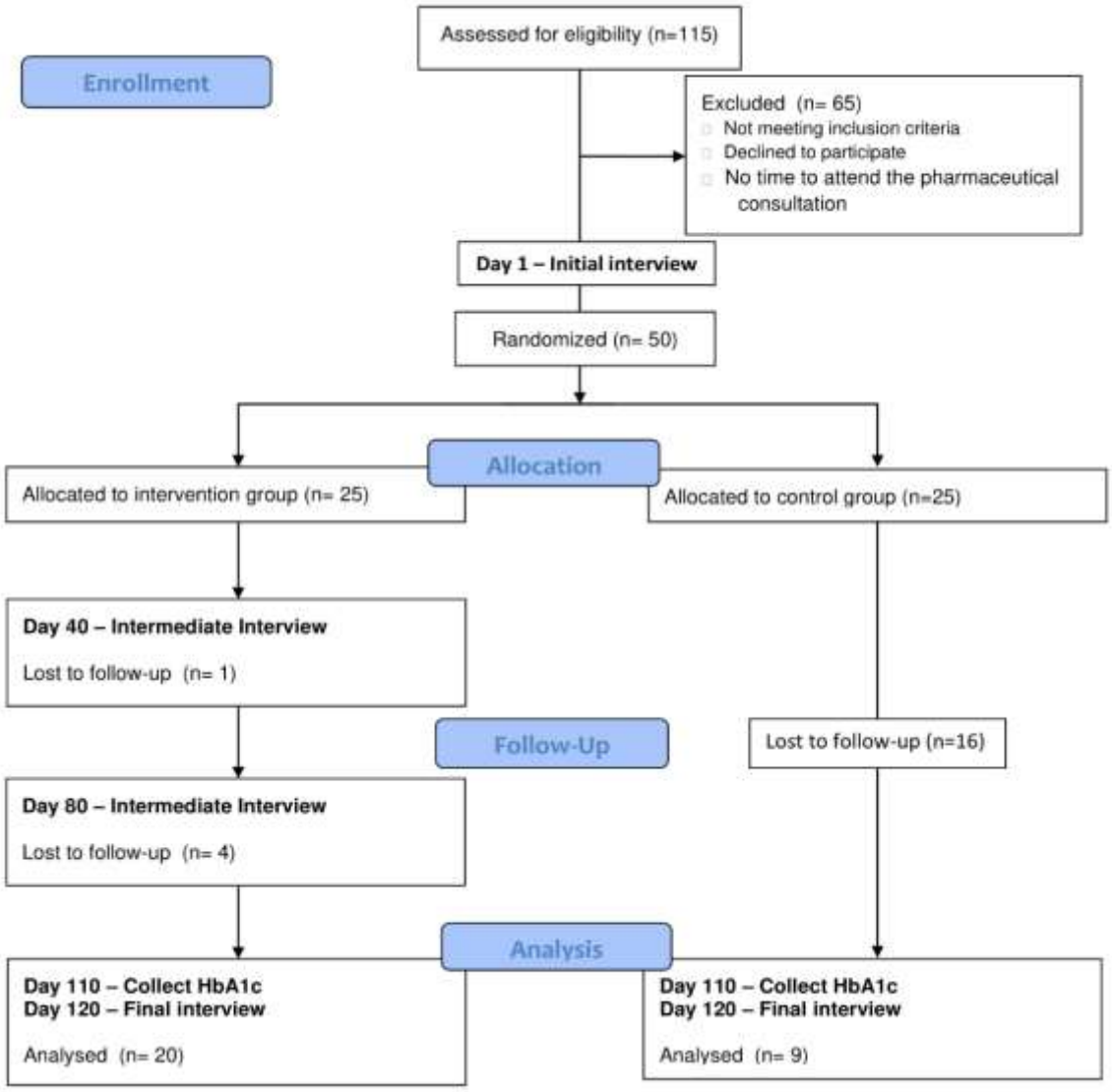

Figure 1: Patient flowchart

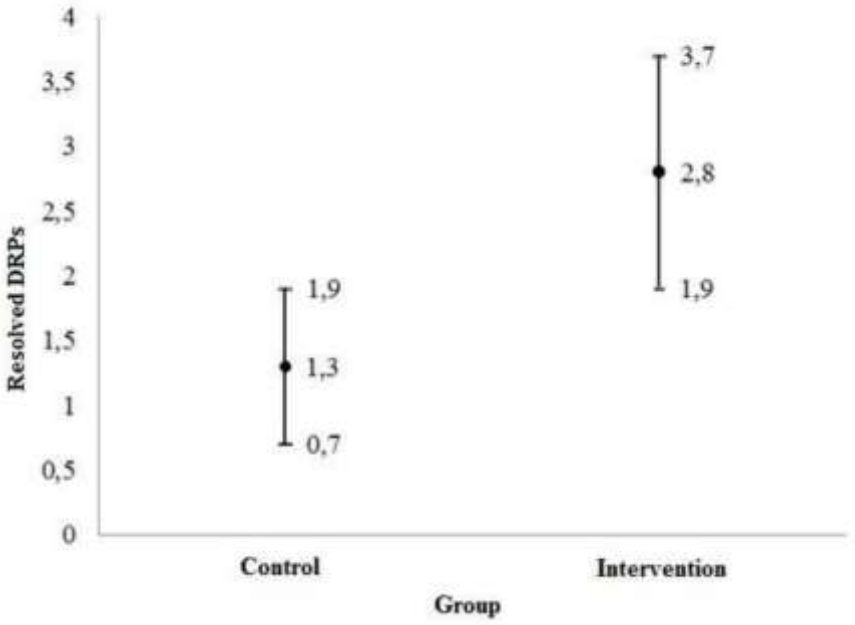

Figure 2: Mean and confidence interval of 95% of the number of Drug Related Problems (DRPs) resolved in DM2 patients accordingly to study group. p <0.014 (Mann-Whitney test); n = 36 (intervention group = 18, control group = 8)

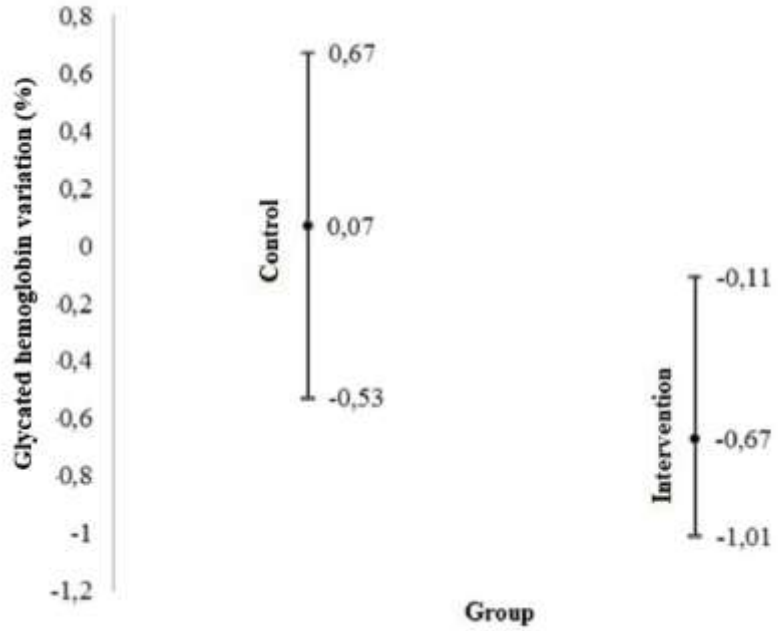

Figure 3: Average and 95% confidence interval of glycated hemoglobin level variation (final minus initial) in DM2 patients being treated according type of orientation. p = 0.09 (Student's t test) n = 29 (IG = 20, CG = 9)

Table 1: Characteristics of the patients allocated to control and intervention groups at baseline.

Variables	Control Group (n-25)	Intervention Group (n=25)	P*
	n (%)	n (%)	
Gender			
Male	14 (56)	11 (44)	0.396
Female	11 (44)	14 (56)	
Marital Status			
Married	19 (76	18 (72)	0.827
Divorced	1 (4)	1 (4)	
Widower	2 (8)	4 (16)	
Single	3 (12)	2 (8)	
Private health service			
Yes	21 (84)	22 (88)	0.684
No	4 (16)	3 (12)	
Family History			
Yes	12 (48)	19 (76)	0.041
No	13 (52)	6 (24)	
Hypertension			
Yes	20 (80)	17 (68)	0.333
No	5 (20)	8 (32)	
Dyslipidemia			
Yes	7 (28)	16 (64)	0.011
No	18 (72)	9 (36)	
	Mean (standard deviation)		
Age (years)	64.4 (12.7)	63.6 (11.1)	0.804
BMI (Kg/m2)	26.7 (4.2)	27.1 (3.4)	0.360
HbAlc initial (%)	6.9 (2.1)	7.3 (1.4)	0.421

*Chi-square test for qualitative variable; and test for quantitative

Table 2: Medication used by patients.

Pharmacological group	N	%
Oral hypoglycemic	50	100
Anti hypertensive	37	74
Anti dyslipidemic	26	52
Anti dyspeptic	19	38
Platelet antiaggregant and Antithrombotic	15	30
Thyroid hormones	14	28
Antidepressants	8	16
Vitamins	7	14
Painkillers	5	10
Female Hormones	5	10
Anti osteoporosis	5	10
Anxiolytics	4	8
Anti inflammatory	4	8
Drugs for sexual dysfunction	2	4
Bronchodilators	1	2
Anticonvulsants	1	2
Antifungals	1	2
Anti gouty	1	2

Table 3: Classification of negative outcomes associated with medication (NOM) identified and resolved, according to Third Consensus of Granada, Dader[5].

Classification of NOM	Type of DRP	Identified DRP			Resolved DRP		
		CG	IG	Total	GC	IG	Total
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Need	Untreated health problem	9 (13.8)	20 (18.5)	26 (15.0)	0 (0.0)	4 (7.8)	4 (6.3)
	Effects of an unnecessary drug	3 (4.6)	9 (8.4)	14 (8.1)	0 (0.0)	3 (5.9)	3 (4.8)
Effectiveness	Non-quantitative lack of efficacy	8 (12.3)	12 (11.1)	21 (12.1)	4 (33.3)	8 (15.7)	12 (19.0)
	Quantitative lack of efficacy	28 (43.2)	29 (26.9)	56 (32.4)	3 (25.0)	24 (47.1)	27 (42.9)
Safety	Non-quantitative insecurity	16 (24.6)	35 (32.4)	49 (28.3)	5 (41.7)	10 (19.6)	15 (23.8)
	Quantitative insecurity	1 (1.5)	3 (2.7)	7 (4.1)	0 (0.0)	2 (3.9)	2 (3.2)
TOTAL		65 (100.0)	108 (100.0)	173 (100.0)	12 (100.0)	51 (100.0)	63 (100.0)

ADVANTAGES AND LIMITATIONS

The main limitations of the research are related to the decision that all participants would be seen by same investigator, for homogeneous procedure. The number of patients had to be limited (and quite reduced during the final interviews, because of the high dropout rates), the intervention had to be short (4 months), and the analysis had to be restricted to a single pharmacy. Nevertheless, this approach shows that positive outcomes from the follow up approach of DM2 pharmacotherapy may be achievable by a single pharmacist in an ordinary community pharmacy. If replicated in other units from this nationwide program to medicine access, the positive impact over DM2 control in the country may be quite relevant.

CONCLUSIONS

In conclusion, this study suggests that a pharmacotherapeutic follow-up may provide important contributions to reduce HbA1c levels in type 2 diabetes patients and to develop the self-management of diabetes in some patients. Moreover, the promotion of the rational use of drugs may be better achieved in the context of the Brazilian program for access and distribution of drugs.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Leandro Carlos Leite and Marcelo Polacow Bisson.

CONFLICTS OF INTEREST

The authors have no conflict of interest with regard to this study.

FINANCING

The study was supported by Faculdade de Medicina do ABC.

REFERENCES

1.International Diabetes Federation. *IDF Diabetes Atlas, 8th edn.* Brussels, Belgium: International Diabetes Federation, 2017. http://www.diabetesatlas.org

2. Lopez Stewart G, Tambascia M, Rosas Guzmán J, Etchegoyen F, Ortega Carrión J, Artemenko S. Control of type 2 diabetes mellitus among general practitioners in private practice in nine countries of Latin America. Rev Panam Salud Publica. 2007;22(1):12-20.

3. Ringborg A, Cropet C, Jönsson B, Gagliardino JJ, Ramachandran A, Lindgren P. Resource use associated with type 2 diabetes in Asia, Latin America, the Middle East and Africa: results from the International Diabetes Management Practices Study (IDMPS). Int J Clin Pract. 2009;63(7):997-1007.

4. Strand LM, Cipolle RJ, Morley PC, Frakes MJ. The impact of pharmaceutical care practice on the practitioner and the patient in the ambulatory practice setting: twenty-five years of experience. Curr Pharm Des. 2004;10(31):3987-4001.

5. Pharmaceutical Care Research Group, University of Granada (Spain). Pharmacotherapy follow-up: The Dader method (3rd revision: 2005). Pharm Pract. 2006; 4(1):44-53.

6. Machado M, Bajcar J, Guzzo GC, Einarson TR. Sensitivity of patient outcomes to pharmacist interventions. Part I: systematic review and meta-analysis in diabetes management. Ann Pharmacother. 2007;41(10):1569-82.

7. Armor BL, Britton ML, Dennis VC, Letassy NA. A review of pharmacist contributions to diabetes care in the United States. J Pharm Pract. 2010;23(3):250-64.

8. Chisholm-Burns MA, Kim Lee J, Spivey CA, Slack M, Herrier RN, Hall-Lipsy E, Graff Zivin J, Abraham I, Palmer J, Martin JR, Kramer SS, Wunz T. US pharmacists' effect as team members on patient care: systematic review and meta-analyses. Med Care. 2010;48(10):923-33.

9. Collins C, Limone BL, Scholle JM, Coleman CI. Effect of pharmacist intervention on glycemic control in diabetes. Diabetes Res Clin Pract. 2011;92(2):145-52.

10. Krass I, Dhippayom T. Pharmaceutical care – impact on quality of life in patients with type 2 diabetes: a review. Clin Audit. 2013;5:17-32.

11. American Diabetes Association. Standards of medical care in diabetes--2014. Diabetes Care. 2014;37 Suppl 1:S14-80.

12. Andrade RCG, Pelá IR. Seguimento farmacêutico e o seu impacto sobre os resultados glicêmicos no tratamento de pacientes diabéticos tipo 2. Seguimiento Farmacoterapéutico. 2005;3(2):112-122.

13. Correr CJ, Pontarolo R, Souza RAP, Venson R, Melchiors AC, Wiens A. Effect of a Pharmaceutical Care Program on quality of life and satisfaction with pharmacy services in patients with type 2 diabetes mellitus. Braz J Pharm Sci. 2009;45(4):809-817.

14. Correr CJ, Pontarolo R, Wiens A, Rossignoli P, Melchiors AC, Radominski R, Fernandez-Llimós F. Economic evaluation of pharmacotherapeutic follow-up in type 2 diabetes mellitus patients in community pharmacies. Arq Bras Endocrinol Metabol. 2009;53(7):825-33.

15. Correr CJ, Melchiors AC, Fernandez-Llimos F, Pontarolo R. Effects of a pharmacotherapy follow-up in community pharmacies on type 2 diabetes patients in Brazil. Int J Clin Pharm. 2011;33(2):273-80.

16. Borges AP, Guidoni CM, Freitas Od, Pereira LR. Economic evaluation of outpatients with type 2 diabetes mellitus assisted by a pharmaceutical care service. Arq Bras Endocrinol Metabol. 2011;55(9):686-91.

17. Obreli-Neto PR, Guidoni CM, de Oliveira Baldoni A, Pilger D, Cruciol-Souza JM, Gaeti-Franco WP, Cuman RK. Effect of a 36-month pharmaceutical care program on pharmacotherapy adherence in elderly diabetic and hypertensive patients. Int J Clin Pharm. 2011;33(4):642-9.

18. Mourão AO, Ferreira WR, Martins MA, Reis AM, Carrillo MR, Guimarães AG, Ev LS. Pharmaceutical care program for type 2 diabetes patients in Brazil: a randomised controlled trial. Int J Clin Pharm. 2013;35(1):79-86.

19. Zubioli A, Silva M, Tasca RS, Curi R, Bazotte RB. Pharmaceutical consultation as a tool to improve health outcomes for patients with type 2 diabetes. Braz J Pharm Sci. 2013;49(1):85-94.

20. Balisa-Rocha BJ, Guimaraes VG, Mesquita AR, Aguiar PM, Krass I, de Lyra Jr DP. Enhancing health care for type 2 diabetes in Northern Brazil: A pilot study of pharmaceutical care in community pharmacy. African J Pharm Pharmacol. 2012;6(35):2584-91.

21. Balisa-Rocha BJ, Aguiar PM, Cerqueira KS, Novaes MB, Alcântara TS, Lyra Jr DP. Evaluation of the effects of long-term of pharmacotherapeutic intervention on clinical and humanistic outcomes in diabetes mellitus patients. Afr J Pharm Pharmacol. 2014;8(14):372-8.

22. Machado CV, Baptista TW, Nogueira C de O. Health policies in Brazil in the 2000s: the national priority agenda. Cad Saude Publica. 2011;27(3):521-32.

23. Pinto C du B, Miranda ES, Emmerick IC, Costa N do R, Castro CG. Medicine prices and availability in the Brazilian Popular Pharmacy Program. Rev Saude Publica. 2010;44(4):611-9.
24. Santos-Pinto C du B, Costa N do R, Osorio-de-Castro CG. The "Farmácia Popular do Brasil" Program and aspects of public provision of medicines in Brazil. Cien Saude Colet. 2011;16(6):2963-73.
25. Choe HM, Mitrovich S, Dubay D, Hayward RA, Krein SL, Vijan S. Proactive case management of high-risk patients with type 2 diabetes mellitus by a clinical pharmacist: a randomized controlled trial. Am J Manag Care. 2005;11(4):253-60.
26. Bourgeois FT, Shannon MW, Valim C, Mandl KD. Adverse drug events in the outpatient setting: an 11-year national analysis. Pharmacoepidemiol Drug Saf. 2010;19(9):901-10.
27. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf. 2014;13(1):57-65.
28. Bauer S, Nauck MA. Polypharmacy in people with Type 1 and Type 2 diabetes is justified by current guidelines--a comprehensive assessment of drug prescriptions in patients needing inpatient treatment for diabetes-associated problems. Diabet Med. 2014;31(9):1078-85.