Research Article ISSN 2639-9326

Diabetes & its Complications

Impact of Adverse Events Related to Oral Antidiabetics Agents on Adherence and Quality of Life on Type 2 Diabetic Patients

Carina Almeida[1], Clara Rocha[2] and Rui Cruz[1,3*]

[1]*Polytechnic Institute of Coimbra, ESTESC-Coimbra Health School, Pharmacy, Portugal.*

[2]*Polytechnic Institute of Coimbra, ESTESC-Coimbra Health School, Complementary Sciences, Portugal.*

[3]*Centre for Health Studies & Research, University of Coimbra, Coimbra, Portugal.*

***Correspondence:**
Rui Santos Cruz, Polytechnic Institute of Coimbra, Coimbra Health School, Pharmacy, Portugal, Escola Superior de Tecnologia da Saúde de Coimbra-Coimbra Health School Rua 5 de Outubro – S. Martinho do Bispo – Apartado 7006 - 3046-854 Coimbra, Tel. +351 239 802430, Fax: +351 239 813395.

Received: 17 November 2020; **Accepted:** 13 December 2020

Citation: Almeida C, Rocha C, Cruz R. Impact of Adverse Events Related to Oral Antidiabetics Agents on Adherence and Quality of Life on Type 2 Diabetic Patients. Diabetes Complications. 2020; 4(5); 1-6.

ABSTRACT

Introduction: *Diabetes is a metabolic disorder with many comorbidities, microvascular and macrovascular complications. In Portugal the prevalence was 13,3% which corresponds to 1 million portuguese diagnosed, but the forecasts are for a big increase. The various therapeutic options currently available have been shown to be effective in controlling glycaemia and HbA1 levels. Adherence with this therapeutic is essential for optimization and control of chronic conditions. However, they present side effects that may compromise adherence to therapy and the quality of life of the patients.*

Objectives: *The objective of this study is to evaluate the impact of the adverse effects of oral antidiabetic agents on adherence and quality of life in patients with type 2 diabetes.*

Methodology: *We developed a cross-sectional study in a sample of 65 patients with type 2 diabetes recruited in several portuguese pharmacies. Data collected through a questionnaire previously validated with 3 parts: Inventory of Adverse Events, Measure of Adherence to Therapy and EQ-5D-3L questionnaire.*

Results: *In total, 36 men (55,4%) and 29 women (44,6%) participated in the study, the mean age was 65 years. 73,8 % take oral medication and 92,30% of people have high adherence. The adverse events with more impact in the patients' perception are "Discomfort in the genital area", "Peripheral edemas", "Paresthesias" and gastrointestinal events such as "Abdominal distention", "Flatulence" and "Constipation". The number of adverse events have a negative impact on patients' quality of life (r_s=-0,479; p≤0,01). The satisfaction with the therapeutic regime is significantly associated with adherence (r = 0,348; p<0,01) and their quality of life (r = 0,316; p<0,01).*

Conclusion: *We concluded that the adverse events have a negative impact on adherence and quality of life. The presence of adverse events, the type of medication and the therapeutic regimen are factors that negatively influence the patients' quality of life, especially in the polymedicated elderly people.*

Keywords

Type 2 Diabetes Mellitus, Adverse events, Adherence to therapy, Quality of life.

Introduction

In a society where advances in medicine, technology and development of new drugs have led to an increase in average life

expectancy, the main concern is now centred on the paradigm of chronic disease, among which is Diabetes Mellitus. This condition is characterized by a complex metabolic disorder that causes the onset of hypoglycaemia state. In addition to being a chronic condition that has a major impact on mortality and morbidity of the population, diabetes brings with it an increase in risk factors for other diseases such as hypertension, dyslipidemia, among others [1].

The major cause for diabetes morbidity is related to vascular complications. Long-term diabetic patients have the potential for vision loss, nephropathy that can progressively lead to kidney failure, peripheral neuropathy with increased risk of ulcers and also autonomic neuropathy responsible for gastrointestinal, genitourinary, cardiovascular and sexual dysfunction problems [2-4].

Type 2 Diabetes Mellitus (T2DM) is the most prevalent, and the mechanisms that lead to the onset of DM2 are not yet clearly defined but were thought to be related to metabolic stress and an inflammatory state that lead to loss of pancreatic β cell function and tissue resistance to insulin action [5,6]. Lifestyle and increased consumption of processed foods, the epidemiological impact of diabetes has increased.

Epidemiology

Worldwide the numbers have reaching more than 382 million people in the world and diabetes has responsible for the deaths of 5.1 million people in 2013 [7,8].

But the most recent projections of International Diabetes Federation pointed to reach 578 million adults with diabetes by 2030, and 700 million by 2045 [9].

Portugal is among the european countries with the highest prevalence rate. The latest data estimate a prevalence of diabetes in the portuguese population aged between 20 and 79 years old was 13.3%, that is, more than 1 million portuguese in this age group have Diabetes [10].

The trend of prevalence of DM2 is changing. Traditionally the pathology was characterized by affecting the older population. Nowadays there is a higher incidence of prediabetes in younger populations [8].

Treatment

The main therapeutic strategy involves nutritional education and lifestyle change and the use of drugs to control blood glucose levels. The principal oral antidiabetic agents include biguanides, sulphonylureas, thiazolidinediones, alfa-Glucosidase Inhibitors, glinides and the new antidiabetic classes such as Dipeptidylpeptidase-4 inhibitors (DPP-4) and sodium-glucose cotransporter 2 (SGLT2) inhibitors that have new mechanisms of action [11-13].

The new class of GLP-1 receptor agonists (subcutaneous injections) is an incretin hormone responsible for inducing insulin release and reducing glucagon levels. It also plays a role in the proliferation of β cells and in reducing their apoptosis. However, the action of these hormones is rapidly inactivated through degradation by the DPP-4 enzyme. Glyptins (DPP-4 inhibitors) are a class of drugs responsible for inhibiting this enzyme and increasing the amount of circulating available GLP-1 and promoting control of blood glucose levels. This class of medicines promote metabolic control without causing severe hypoglycaemia [14-16].

The kidney plays an important role in regulating blood glucose levels by mediating glucose reabsorption back into the plasma in the proximal renal tubule after its excretion. The SGLT1 and SGLT2 transporters are responsible for 90% glucose reabsorption back into the plasma. Inhibition of SGLT2 will greatly reduce glucose resorption capacity in the proximal tubule by increasing its excretion through the kidney [17,18]. Like other oral antidiabetics, SGLT2 inhibitors have the ability to reduce toxicity caused by excess blood glucose and to promote increased insulin sensitivity of cells. This class of medicines further has some pharmacological advantages such as: a lower risk of hypoglycemia and an independent mechanism of insulin being unaffected by its poor production or cell resistance to it [17,19].

Despite the therapeutic benefits of these drugs, it is also known that the various existing oral antidiabetic agents may trigger a large number of adverse events, either alone or in combination.

In the specific case of DPP-4 inhibitors and SGLT2, some side effects have been reported for this classes that may in some way compromise adherence to therapy. Increased incidence of nasopharyngitis, respiratory tract infections, pancreatitis, vaginal candidiasis, and increased incidence of urinary tract infections are just a few examples of adverse events caused by this medication, in addition to compromising adherence to the therapeutic, also have a negative impact on quality of life [20,21].

Despite the importance of adherence to pharmacological therapy especially in chronic diseases, it is precisely in this field that strategies fail. Adherence to therapy is a problem in the diabetic patient, who naturally causes treatment failure, increasing the risk of complications related to this condition. One of the main barriers to adherence to therapy are related to polymedication, complex therapeutic regimens, adverse effects caused by medication [22,23].

Promoting adherence to therapy in chronic conditions is an extremely important factor for preventing the complications of the disease. Is important to increase patient education with the disease, have better medical and primary care follow-up and implementation of simpler treatment regimens, effective and comfortable for the user. These measures are important to increase adherence to therapy, reduce discomfort with therapy and therefore improving quality of life of patients [24,25].

The purpose of this study was to understand the impact of adverse events of oral antidiabetics agents on treatment adherence and quality of life in patients with type 2 diabetes.

Methods

This cross-sectional study [26], included a sample of 65 patients with T2DM attending in community pharmacies of the central region of Portugal.

The selection criteria for participation in the study were: patients older than 18 years old, diagnosed with type 2 diabetes, taking oral antidiabetic agents such as DPP-4 inhibitors and SGLT- 2 inhibitors, alone or in association with other antidiabetics agents and accepting to voluntarily participate in the study.

The data collection instrument consisted of two parts. The first part was composed of sociodemographic variables (age, gender, level of education, marital status, and professional situation) and clinical variables (Diagnostic time of diabetes, type of medication, clinical situations, and physical activity).

The second part consisted in three different questionnaires: Adverse Events Inventory, the Therapeutic Adherence Measure and the HRQoL questionnaire-EQ-5D-3L. Each of the composite parts of the questionnaire previously validated for the Portuguese population [27-29].

The Adverse Events Inventory consists of a list of adverse events associated with oral antidiabetic agentes with a Likert scale with four levels (1-Never/None; 2-Rarely/Low intensity; 3-Often/ Strong intensity; 4-Always/Severe) to assess the frequency and intensity of adverse events self-perceived by patients [27].

Therapeutic Adherence Measure questionnaire is an instrument makes it possible to assess the users' behavior towards compliance with the prescribed therapy and is composed of 7 questions and a six-point Likert scale for each question: 1- Always, 2- Almost always, 3- Often, 4- Sometimes, 5- Rarely, 6- Never. This Likert scale can also be converted into a dichotomous scale (Adherent / Non-Adherent). The therapeutic adherence index was obtained through the sum of each question, thus transforming the variable into a scalar numerical variable. From the analysis of the treatment adherence questionnaire, it is important to mention that only the first 7 questions are considered for the adherence sum, since the 8th question was added to the one after the original questionnaire and for that reason it will be treated individually [28].

The EQ-5D-3L is a descriptive system of the HRQoL that includes five dimensions: Mobility (MO), Self-Care (SC), usual activities (UA), Pain/discomfort (PD) and Anxiety/depression (AD). The answers predict three levels of severity: no problems, some problems, and extreme problems. It also comprises a visual analogue scale (VAS) in which respondents classify their general health status from 0 (worst health state imaginable) to 100 (best health state imaginable). The global index is generated by an algorithm, based on the preferences of the answers obtained for the five dimensions. The EQ-5D uses a scale from 1 (perfect health) to 0 (death) [29].

Data were collected between september 2018 and february 2019, used the instrument previously described was delivered to community pharmacies with prior knowledge and authorization of all Technical Directors of the respective establishments.

Participants were asked to participate on a voluntary basis. They were informed about the study objectives, procedures, risks, benefits, alternatives, their rights, and data anonymity and confidentiality.

Statistical analysis consisted of descriptive tests and inferential statistics techniques were also used. The normality of the distribution of the differents variables was assessed using the Kolmogorov-Smirnov- Lilliefors test and the variables present in the study did not present a normal distribution ($p<0.05$). The significance level was set at 0.05 for a confidence interval of 95%. Data were analyzed using Statistical Package for the Social Sciences (SPSS), version 25.0 for Windows.

Results & Discussion

In this study, the sample was composed of 65 individuals with T2DM were completed the diferents questionnaires.

Table 1 shows the sociodemographic and clinical characteristics of the sample. Most participants were male (55.4%). The mean age was 64.80 ± 9.95 years, ranging from a minimum of 43 years to a maximum of 87 years.

Variable		n (%)
Gender	Male	36 (55.4%)
	Female	29 (44.6%)
Age (years)	Min: 43; Max: 87 | Mean= 64.80 ± 9.95	
Level of education	Not read or write	1 (1.5%)
	Primary School	25 (38.5%)
	Basic Education	14 (21.5%)
	High school	13 (20%)
	Higher Education	12 (18.5%)
Professional situation	Employee	18 (27.7%)
	Self-employed	7 (10.8%)
	Domestic	6 (9.2%)
	Retired	34 (52.3%)
Marital status	Married/Cohabiting	54 (83.1%)
	Single	1 (1.5%)
	Widower	9 (13.8%)
	Divorced/separated	1 (1.5%)
Time of Diagnosis DM	Min: 2; Max: 50; | Mean= 12.66 ± 9.01	
Type of Medication	Oral	48 (73.8%)
	Oral + Injectable	17 (26.2%)
Clinical Situations	Hypertension	44 (67.7%)
	Renal Insufficiency	2 (3.1%)
	Dyslipidemia	41 (63.1%)
	Obesity	24 (36.9%)
	Retinopathy	13 (20.0%)
	Diabetic Foot	4 (6.2%)
	Other Situations	2 (3.1%)
Physical Activity	No Once a week Twice a week Three or more times a week	41 (63.1%) 5 (7.7%) 10 (15.4) 9 (13.8%)

Table 1: Sociodemographic and clinical characteristics of the sample.

With regard to level of education is distributed across different levels although prevails primary school (38.5%). Most respondents are retired (52.3%) and marital status, 83.1% of the participants were married or cohabiting.

The time of diagnosis to diabetes ranging from a minimum of 2 years to a maximum of 50 years with a mean 12.66 ± 9.01 years. The type of medication, 73.8% of patients had only oral antidiabetic and 26.2% had the combination of oral and injectable medication.

Diabetes is a multidimensional pathology that carries with it other types of comorbidities. From the sample analysis we can verify that the most prevalent pathologies were hypertension present in 67.7% of cases, dyslipidemia in 63.1%, followed by obesity in 36.9%, retinopathy in 20% of the sample and diabetic foot in 6.2%.

Concerning the practice of physical activity, 63.1% of our sample did not practice any physical activity, only 15.4% e 13.8%, respectively, practiced physical activity on a regular basis.

Treatment Adherence Measure

Regarding the analysis of adherence to treatment, the data are summarized in table 2. The majority of patients comply with the therapy, but patients showed to be most careless was with the time of taking the medicines where 27.7% of the respondents answered that almost always did not take the medicines at the right time.

No significant correlation could be obtained between the sociodemographic variables, and adherence to therapy. However, previous studies have shown that patients diagnosed longer show better adherence [30]. In previous studies, it was verified that a better knowledge of the user regarding diabetes was an indicator of better adherence [31,32].

General Health Status: EQ-5D-3L

The results of the survey EQ-5D-3L showed total mean scores for the population of T2DM patients of 0.693±0.296 in the EQ-5D-3L and 71.18±17.860 in the EQ-VAS (Table 3).

As expected, in our sample the scores of the EQ-5D-3L (0.693) and the EQ-VAS (71.18), they are lower than the values for the portuguese population norms (EQ-5D-3L=0.758 and the EQ-VAS=74.9). [33]

Considering the collection of adverse event inventory data we can see that the adverse event that was more reported by patients were in table 4. This adverse events had a negative significant relation on the quality of life mainly "Paresthesias" (r = -0,421, p<0.05);

	Never n (%)	Rarely n (%)	Sometimes n (%)	Frequently n (%)	Almost Always n (%)	Always n (%)
Question 1	19 (29.2%)	37 (56.9%)	6 (9.2%)	3 (4.6%)		
Question 2	16 (24.6%)	31 (47.7%)	11 (16.9%)	4 (6.2%)	1 (1.5%)	2 (3.1%)
Question 3	57 (87.7%)	2 (3.1%)	4 (6.2%)	1 (1.5%)		1 (1.5%)
Question 4	59 (90.8%)	4 (6.2%)	2 (3.1%)			
Question 5	60 (92.3%)	3 (4.6%)	2 (3.1%)			
Question 6	42 (64.6%)	18 (27.7%)	4 (6.2%)		1 (1.5%)	
Question 7	54 (83.1%)	8 (12.3%)	3 (4.6%)			
Question 8	49 (75.4%)	13 (20%)	3 (4.6%)			

Table 2: Distribution of adherence to therapy.

HRQL	N	Min	Max	Mean	Std. Deviat.
EQ-VAS	65	30	100	71.18	17.860
EQ-5D-3L	65	0.000	1.000	0.693	0.296

Table 3: Distribution of adherence of the EQ-5D-3L and the EQ-VAS.

Adverse Events	% Patients reported AE	EQ- 5D-3D (r)	P Value
Dry Mouth	41.6	-0.28	0.024
Flatulence	27.7	-0.348	0.005
Peripheral Edemas	23.1	-0.34	0.006
Constipation	20	-0.429	0
Abdominal Distension	20	-0.362	0.003
Drowsiness	17	-0.315	0.01
Paresthesias	13.9	-0.421	0
Headache	12.3	-0.282	0.023
Wheith Gain	12.3	-0.272	0.029
Genital Discomfort	10.7	-0.328	0.008
Allergic Reactions	7.7	-0.258	0.038
Dizziness	6.1	-0.267	0.032
Dyspnea	4.6	-0.271	0.029

Table 4: Relation of the adverse events reported and the EQ-5D-3L.

"Constipation" (r = -0,429, p<0.05); "Abdominal Distension" (r = -0.362, p<0.05); "Flatulence" (r = -0.348, p<0.05), Peripheral Edemas (r=-0.340, p<0.05); "Genital Discomfort" (r = -0.328, p<0.05) and "Drowsiness" (r = -0,315, p<0.05).

In our sample it appears that the quality of life and the treatment adherence is influence by the adverse events (Table 5). There is a negative significant association (p <0.05) between the quality of life and treatment adherence and the adverse events reported by the patients. The higher the number of adverse events reported, the lower the perception of quality of life in health.

The lower the side effects of medication, the higher the rate of adherence and success of therapy, which is verified by similar studies carried out in this subject [25].

When asked the patients about their therapy and whether they were uncomfortable with their diabetes treatment plan, patients who showed greater dissatisfaction with the therapy implemented also had a lower perception of quality of life (r = 0.316; p = 0.01) (Table 6).

The same we can conclude with regard to the number of symptoms (adverse events) as shown in table 9. Patients reporting greater dissatisfaction with the treatment plan implemented also had a greater perception of adverse drug events (r = -0.327; p< 0.05) (Table 6).

Regarding adherence to treatment, there was a statistically significant association with the discomfort felt by patients with the treatment plan for diabetes (r=0.327; p<0.05), and this association was moderate and positive (r = 0.348; p<0.05). It means that patients that aren't very comfortable with the treatment and its demands where, therefore, more likely not to adhere to it (Table 6).

Conclusion

The aim defined for this work was to study the impact of adverse events of oral antidiabetic have on the adherence to therapy and on the quality of life in health. A data collection tool was delivered to community pharmacies in Portugal to 65 type 2 diabetic users.

From the analysis of the data collected we have a population mainly composed of men with the average age of 64 years old. The analysis of the clinical profile reveals that the average time of diagnosis of diabetes was about 13 years and that the majority of patients had oral therapy.

From the inventory of adverse events we concluded that the events that most impacted had on quality of life were paraesthesias, constipation, abdominal distension, flatulence, peripheral edemas and genital discomfort.

Regarding adherence to therapy, the adherence factor in which patients failed most was the time of taking the medicines, and in this subject, men showed to be more careless than women.

There is a correlation between adverse events to oral anti diabetics agents and adherence rate, the lower the number of events, the greater the rate of adherence to therapy.

From the analysis of the general state of health we can conclude that the mean score of the EQ- 5D-3L and the EQ-VAS was 0.693 and 71.18, respectively, are lower than that presented for the Portuguese population (0.758; 74.9).

Patients who showed greater dissatisfaction with the treatment plan also had a lower rate of adherence to therapy and a lower perception of quality of life. The number of adverse events reported has also been found to have a negative impact on patients' satisfaction with their treatment.

Acknowledgments

The authors want to thank all participants in the study for their availability and time.

We would like to thank the directors of pharmacies for all their collaboration.

Variable	Adverse Events		
	n	**rô Spearman**	**P**
Quality of Life	65	-0.479	**0.000**
Treatment Adherence Measure	65	-0.334	**0,007**

Table 5: Relation between the adverse events and the adherence and general quality of life of patients.

Variable	Number of Symptoms AE			Quality of Life			Treatment Adherence		
	n	**Rô Spearman**	**p**	**n**	**Rô Spearman**	**p**	**n**	**Rô Spearman**	**p**
Have you ever felt uncomfortable about your diabetes control treatment plan?	65	0.327	**0.008**	65	0.316	**0.01**	65	0.348	0.005

Table 6: Correlation between number of symptoms, quality of life, adherence and diabetes' treatment plan.

Question 1: Have you ever forgotten to take your diabetes medicines? ***Question 2:*** Have you ever been careless about the time you take your diabetes medicines? ***Question 3:*** Have you ever reduced or stopped taking diabetes medicines because you felt better? ***Question 4:*** Have you ever reduced or stopped taking your diabetes medicines after feeling worse? ***Question 5:*** Have you ever taken one or more Diabetes pills on your own after feeling worse? ***Question 6:*** Have you ever stopped your diabetes therapy for letting your medicines run out? ***Question 7:*** Have you ever stopped taking diabetes medicines for any reason other than a medical indication? ***Question 8:*** Have you ever felt uncomfortable about your diabetes control treatment plan?

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