Original Article

Patient's lack of understanding producing insulin drug-interactions in Southeast Brazilian primary care clinics

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ABSTRACT

Detrimental drug-drug interactions (DDIs) in Diabetic patients could be from the simultaneous use of multiple drugs, polypharmacy. Brazilian public health studies evaluating the practical knowledge about drug interactions are scarce. This study's objective is to identify drug interactions and prevalence of detrimental DDIs in diabetic patients attending Brazilian basic health system clinics.

Methods: Patients using insulin between the age of 18—90 years were selected to complete the MedTake questionnaire, to evaluate the indication, dosage, regimen and drug interaction. The MedTake test was employed. For each medicine, the test was scored as the percentage of correct actions and compared with printed instructions one single researcher downloaded all the data was from the municipality's computerized system.

Results: The median age of recruits was 60.2 ± 14.3 and MedTake test scores were low 60.3 ± 20. One hundred patients missed the correct dose question, 40 missed why they were prescribed the drug, indication and 65 missed the therapeutic regimen. These diabetes patients did not know the DDIs between insulin combined with other medicines. Drugs that had more interaction with insulin were: acetylsalicylic acid (40%), enalapril (18%), losartan (32%) and hydrochlorothiazide (23%).

Conclusions: Diabetes patients without practical knowledge about insulin interacting with other pharmaceutical drugs that can produce DDIs with other medicines illustrates a need to develop education programs for diabetics.

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1. Introduction

Typically, as an essential tool of modern health care for the treatment of chronic diseases, multiples prescribed drugs may cause iatrogenesis, medicinal cause of death and illness. Within the current public health scenario, iatrogenic complications are a substantial economic burden [1]. Noteworthy, concurrent prescription of multiple drugs may increase therapeutic effectiveness; however, some combinations are detrimental, through increased risk of DDIs [2]. Polypharmacy, the prescription of multiple drugs is

standard of care in therapeutic recommendations with diabetic individuals [3], due to intersecting drug action pathways and shared metabolism pathways [4]. In fact, potential interactions are present in the day-to day patient clinical management [5] and given the wide varied complex combinations of drugs prescribed [6] the safety of medications and knowledge about DDIs in primary care is a topic of considerable importance.

DDIs are more serious with elevated risk diseases such as Diabetes, a chronic metabolic disorder characterized by an increase in blood glucose level, hyperglycemia. An elevated level specifically of the sugar glucose in the blood requires, to prevent undesirable events, a vigilant pharmacotherapy workup. Among Brazilian diabetics, the prevalence of T1DM is 5%, caused by impaired production of insulin, and euglycemia (normoglycemia), normal blood glucose levels is clinically managed only with insulin aspart injections and recommended lifestyle changes. 95% of Brazilian diabetics are T2DM, rising hyperglycemia reflecting the inability of

cell's insulin receptor to respond to insulin (insulin resistance) and requiring the use of oral hypoglycemic agents, and recommended lifestyle changes.

A tremendous equalizer is the practical, working knowledge of a disease and the correct application of treatment recommendations, which, surpasses cutting edge technology or a new drug. Recently, our research group reported an association where younger diabetics had both a lower regimen complexity and polypharmacy than those with more education. In contrast, diabetics with less attained education levels have a poor knowledge of therapeutic. This lack of working knowledge contributes to higher comorbidities, increasing the number a prescribed medicine and increasing possible DDIs [7]. Data mining primary care studies report prevalence value for clinically relevant DDIs ranging from 2 to 28% [8,9]. In Brazil, studies involving people living in a community-dwelling environment report prevalence rates ranging 4.5—17.5% [10,11]. Currently, studies examined in the literature report that healthcare professionals do not know enough about community-dwelling people [12,13] and there is a deficiency of knowledge of diabetics in primary care, suffering from the effects of DDIs. So, our study fills this medical research gap. We believe this paper is the first study done in primary care providing information on DDIs among diabetics.

The objective of this study was to evaluate knowledge level about drug interactions and the prevalence of DDIs among diabetic patients being treated in the basic health system in the Franca-SP municipality, in the southeastern region of Brazil. The lack of appreciation of DDIs and the deficiency of studies addressing this topic, makes this present study timely. These results can be the foundation to develop diabetes education programs that amplify and improve therapeutic standards and procedures.

2. Methods

2.1. Study setting, design and outcome variable

This was a cross-sectional study conducted in a basic health unit in the municipality in the Brazilian, state of Sao Paulo, Franca, Brazil. The city of Franca has 347 thousand inhabitants, being served by five family health programs, fourteen public health systems, as well as outpatient and specialty care units (Diabetic Care Home, Assistance Management Center, Ophthalmology Center, Adult and Infantile Mental Health Outpatient Clinic). Our study was done in the basic health unit, known as Diabetic Care Home and had a mean monthly attendance of 350 people insulin users.

It was a prospective, descriptive and observational study, conducted from August to December 2017, designed according to the study objectives. The outcome indicators, specific, observable, and measurable characteristic or change will represent achievement of the are related with patient's therapeutic knowledge.

2.2. Study inclusion/exclusion criteria

Individuals selected in our study are all patients attending the basic health system during the period of study, from August to December 2017; insulin users; between the age of 18—90 years. Excluded from the data were patients with cognitive deficits and/or mental disorders, pre-literacy, pregnant women, and chronic diseases of greater complexity (chronic renal disease for example).

2.3. Data collection

In this study, all the guidelines to strengthen the reporting of observational studies in epidemiology, the STROBE statement were followed, and data were collected during a four month period. A questionnaire was conducted by a trained pharmacist and asked of all patients. This questionnaire was composed of open questions to collect clinical data and the demographics of all patients. The variables collected from the questionnaire were: age, gender, marital status, per capita income, schooling, co morbidities, time since diabetes diagnosis, number of drugs taken, drug load, consultation duration, WC, and, BMI. Before the medical consultation, patients were selected, and the interviews were performed in a room separate from the doctor's office. The average time of each interview was 20 min. All data were collected by one research. To correct differences of language interpretation twenty patients evaluated and standardized the questionnaire. These volunteers were excluded from the study.

2.4. Measurements

To evaluate the patient's diabetic complications, working knowledge of the drugs they use and the complexity of pharmacotherapy, the following tests were applied: DC, CP, and MT.

The diabetes complications were evaluated by the DC. DC is a questionnaire containing 17 questions: 5 questions evaluate coronary heart disease; 3 questions are related to stroke; 2 questions cover peripheral vascular disease; 2 questions cover neuropathy; 3 questions relate to feet problems; and 2 questions question diabetic retinopathy. Each complication is verified by 2 or more questions. For example, coronary heart disease is listed if: the patient reported having a myocardial infarction, symptoms of angina pectoris, or having been diagnosed by a doctor. The DC the total results, of any complications that were presented, were calculated, that resulting in scores from 0 to 6 [14].

To determine patient's familiarity with the medications that she or he are taking, understanding was evaluated by the MT instrument. The MT instrument evaluates: dosage (units), indication, regime, and knowledge about the drug-drug interaction or food-drug interaction of medications being taken. Patient's scores are from 0 to 100% and each patient's mean test scores is calculated, assessing the ability of patients to take their drugs safety. Subjects who correctly answered the 4 questions have a score of 100% and subjects who answered only three questions receive a score of 75% [15].

To evaluate patient's knowledge of the complexity of their medications was evaluated by the CP instrument. CP is divided into three sections: A, B and C. Results are obtained by the total of scores of all three sections. High section scores are defined as greater complexity and possible side effects to patient [16].

The anatomical therapeutic chemical/defined daily dose (ATC/DDD) system is as a World Health Organization tool for presenting drug utilization statistics whose aim is to improving drug use. The ATC Classification System is used for the classification of active ingredients of drugs according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. The DDD assumes the average maintenance dose per day for a drug used for its main indication in adults. We used the drug load to calculated patient's medicine overload using the ATC/DDD system. The drug load was calculated by taking the dose of drugs that the patient was taking, divided by defining the daily dose according to international drug utilization research. When the subject takes more than recommended of a drug, the ATC/DDD ratio values are increased. Subjects with high ATC/DDD ratio values of drug load have an overload in treatment and a high probability of developing adverse effects [17].

3. Statistical analysis and analyses of potential drug-drug interactions

Descriptive statistics using the Statistical Package for the Social Sciences (SPSS) software, version 17.0 was used to characterize the

sociodemographic, clinical pharmacotherapeutic profile of the patients in the present study. The categorical variables were displayed using numbers and proportions (%) and continue variables were presented using mean and standard deviation values.

All DDIs were identified in the Medscape [18] and Micromedex database [19] according to the degree of severity (minor, moderate, major) and data was cataloged in Microsoft Excel 2010. We analyzed all DDIs in pairs and all were analyzed for potential risk.

3.1. Ethical considerations

This study was approved by Research Ethics Committee of the Faculdade de Medicina de Ribeirão Preto (FMRP), Universidade de São Paulo (USP), protocol no.7724/2015 and release no. 2941 CEP/FMRP; ruling no.049698/2015; CA EE45668815.9.0000.5440. All individuals who met the inclusion criteria were asked to sign the "Free and Informed Consent Terms".

4. Results

Table 1 shows, of 301 patients recruited, the male gender predominated 58% (174/301), schooling 69% (210/301), age (60.2 ± 14.3) and, $BMI = 30 \pm 5.93$. The number of comorbidities was 4 ± 29 and chronic complications of Diabetes were 2.29 ± 1.42. Additionally, overweight patients with a BMI between 25 and $29.9 \, kg/m^2$ took more than five drugs, while patients with BMI $>30 \, kg/m^2$ took more than six drugs.

Variables used that pertain to medicines being taken were: the number of medicines in use 5.94 ± 2.59; the drug load was $1.94 \pm$ and the CP scores was 18.77 ± 6. The scores of MT test were low 60.3 ± 20, because 100 patients missed the question about the correct dose, 40 missed the indication rationale, 65 missed the regimen therapeutic and all patients did not know the DDIs of insulin with other medicines.

As seen in Table 2, the main DDIs found with insulin were acetylsalicylic acid 40% (119/301), enalapril 18% (55/301), losartan 32% (96/301) and hydrochlorothiazide 23% (70/301). In Table 3, the range age (61–80) have the most DDIs compared with the others range age.

5. Discussion

Our study is one of few studies found in medical literature demonstrating patients with diabetes do not have sufficient knowledge of DDIs between insulin and other medicines. This topic contributes to the understanding why there are increasing medicinal side effects burdening diabetic patients. Our work should serve as advanced warning, an alert for clinicians and managers to develop relevant patient diabetes education programs. Patients need a clear understanding of their treatment recommendations and medicines. According to the Agency for Healthcare Research and Quality (AHRQ), patients being discharged from the hospital are 30% less likely to be readmitted or visit the emergency department when they have a clear understanding of their after-hospital care instructions, including how to take their medications and when to make follow-up appointments.

The age of patients presents as an important variable to consider with medicinal prescription. The mean age of our sample (60 years) was like that reported in other studies conducted on primary care (60–62 years) [20,21]. The mean number of prescription drugs was more than other studies conducted in similar settings (5.9–4.4) [22]. Approximately 41% of patients were prescribed more than seven drugs, results that were different than others similar studies (4.4–6.6) [22,23]. The value of drug load (1.94 ± 0.8) and CP scores (18.7 ± 6) were high due to high number of prescription added.

Similarly, high comorbidities (4 ± 2) and complication of diabetes (2.2 ± 1.4) scores reflect the increased number of medications. This data reflects what is found in the literature [3,7].

Noteworthy in the present study in insulin users (26.2 and 41%) is the high prevalence of polypharmacy (five or more drugs). The greater number of drugs used is associated with an increased risk for potential DDIs in similar studies and research worldwide [22,25]. Interestingly, our data demonstrated that insulin users with a BMI between 25 and $29.9 \, kg/m^2$ took more than five drugs (mean 5.6 ± 2.4), while patients with BMI $> 30 \, kg/m^2$ took more than six drugs (mean 6.6 ± 2.5). In similar reports, obesity more than doubles medicines prescribed in primary care [26]. An explanation to why more medicines are prescribed in increasing BMI could be that as BMI increases the comorbidities of diabetes increase.

Our research group demonstrated that only increasing insulin dosage without lifestyle changes in primary care does not ameliorate hyperglycemic levels nor treatment overload the public medical system [27]. In the study of the utilization and effects of drugs in large numbers of people, pharmacoepidemiological studies, the number of prescribed drugs is a significant predictor of potential DDIs and illuminates the crucial need to promote rational primary care therapy.

The prevalence for the DDIs among insulin users being treated in the primary care setting was 80%. DDIs rates ranging from 63 to 78.8 have been described for all potential drugs in patients receiving ambulatory care [22,24]. This high prevalence may be partially explained due variables such as: population characteristics, study design, definitions, methodology, number of medications prescribed, complexity of medication regimen, compendium of drug interaction or software checking DDIs [22,24]. All DDIs found in the present study were classified as moderate, but it's is considered clinically important and should be avoided by pharmacists, physicians and others healthcare professionals. Local pharmacists are crucial and should avoid the dispensing combinations of medicines that may have DDIs. Unfortunately, data dictates that prescription medications are being dispensed to patient without checking for DDIs.

In primary care, we urgently need to improve patient's knowledge about their therapy because low MT test scores were 60.3 ± 20. The results show that 100 of patients missed the question about dose, 40 missed why the indication, 65 missed the therapeutic regimen and all patients do not know the DDIs of insulin with other medicines. Highlights in our findings are: first, the mistakes about insulin dosage may lead to hypoglycemia, increasing medical expenses; and, second, complex therapeutic regime, too many medicines reflect in the high CP scores (18.7 ± 6) and drug load (1.94 ± 0.8). Both of these problems make it more difficult for patient to adhere to treatment recommendations. Comparable results for MT test (61 ± 19), CP (22.5 ± 5) and drug load (2.1 ± 0.8) was reported by our research group in diabetes patients in primary care with polypharmacy use [7]. Knowledge of potential DDIs among health professional in primary care is also limited. A search of medical literature illuminates a knowledge gap about potential DDIs [28,29] reflecting a necessity to develop and implement training and education courses for all health professionals.

Five most active substances involved in potentially clinically significant interaction were: acetylsalicylic acid, enalapril, losartan, propranolol and hydrochlorothiazide (Table 2). Acetylsalicylic acid and enalapril may enhance the insulin effects by pharmacodynamic synergism. Enalapril in combination with potassium-sparing drugs may increase the risk of hyperkalemia [30]. Losartan increases insulin effects by an unspecified, poorly understood interaction mechanism and concomitant use may

Table 1
General patients characteristics of the study population.

Variable	Frequency (%)
Gender	
Male	174 (57.2)
Female	127 (42.8)
Ethnicity	
White	141 (46.8)
Black	38 (12.6)
Mixed	122 (40.6)
Marital status	
Married	160 (53.3)
Single	33 (10.9)
Divorced	57 (18.9)
Widowed	51 (16.9)
Education	
Till 8 years	210 (69.7)
9–12 years	61 (20.2)
>12 years	30 (10.1)
Age (mean ± standard deviation)	60.24 ± 14.38
18-30	15 (0.07)
31-60	114 (37.9)
61-80	161 (53.5)
>80	11 (0.03)
Drugs (mean ± standard deviation)	5.9 ± 2.59
1-2	31 (10.2)
3-4	69 (22.9)
5-6	79 (26.2)
7-14	122 (40.7)
Body mass index (mean ± standard deviation)	30.1 ± 5.93
18.5–24.9	56 (19)
25–29.9	103 (34)
>30	142 (47)
Body mass index and number of drugs (mean ± standard deviation)	
18.5–24.9	4.7 ± 2.6
25–29.9	5.6 ± 2.4
>30	6.6 ± 2.5
Number of drug-drug interactions per patient (mean ± standard deviation)	1.24 ± 0.14
1	81 (21.7)
2	253 (67.2)
3	37 (9.8)
4	5 (1.3)
MedTake scores (mean ± standard deviation)	60.3 ± 20
Drug load	1.94 ± 0.8
CP scores	18.7 ± 6
Comorbidities	4 ± 2
Complications of diabetes	2.2 ± 1.4

Table 2
Frequency of pair of moderate potential drug-drug interaction (DDIs) of insulin with the prescription dispensed (n = 376).

Drug	Potential risk	Frequency (%)	Confidence interval	Intervention
Acetylsalicylic acid	Increases effects of insulin by pharmacodynamic synergism. (combined action is greater)	119 (31.8)	0.40 (0.33 −0.44)	Modify therapy or monitoring closely
Enalapril	Increases effects of insulin by pharmacodynamic synergism.	5514.6%	0.18 (0.13 −0.22)	Use caution/Monitor
Fluoxetine	Increases effects of insulin by unspecified interaction mechanism.	5 (1.3)	0.01 (0.00 −0.02)	Concomitant use may require insulin dosage and increase glucose monitoring
Losartan	Increases effects of insulin by unspecified interaction mechanism.	96 (25.5)	0.31 (0.25 −0.36)	Concomitant use may require insulin dosage and increase glucose monitoring.
Propranolol	Pharmacodynamic antagonism. Non-selective beta blockers delay recovery of normoglycemia after insulin induced hypoglycemia	17 (4.5)	0.05 (0.02 −0.07)	Use caution/Monitor
Hydrochlorothiazide	Increases effects of Novolin insulin (Neutral Protamine Hagedorn, NPH) by pharmacodynamic synergism	70 (18.6)	0.23 (0.18 −0.27)	Use caution/Monitor
Amitriptyline		14 (3.7%)	0.04 (0.01 −0.06)	Use caution/Monitor

require insulin dosage adjustment and increase glucose monitoring. Propranolol a selective beta blocker pharmacodynamically antagonistically delays the recovery of normoglycemia after insulin induced hypoglycemia and if used with insulin requires careful monitoring. Hydrochlorothiazide is on diuretic that decreases effects of Neutral Protamine Hagedorn (NPH) insulin by pharmacodynamic antagonism and requires monitoring. In 2017, our research group demonstrated that fasting blood glucose levels

Table 3
Number (%) of potential drug-drug interactions (DDIs) of accord with age of patients exposed.

Age	One DDIs	Two DDIs	Three DDIs	Four DDIs	Total
18−30	2 (0.8)	0 (0)	0 (0)	0 (0)	2 (0.5)
31−60	36 (13.6)	26 (39.4)	11 (28.2)	2 (33.3)	75 (20)
61−80	223 (84.1)	38 (57.6)	28 (71.8)	4 (66.7)	293 (77.9)
>80	4 (1.5)	2 (3)	0 (0)	0 (0)	6 (1.6)
All	265 (70.5)	66 (17.5)	39 (10.4)	6 (1.6)	376 (100.0)

of elderly hypertensive diabetics taking propranolol and hydrochlorothiazide in primary care were affected by age, number of medicines being taken and the amount of comorbidities [31]. In a less, severe reaction fluoxetine and amitriptyline increases insulin effects through an unspecified interaction mechanism and concomitant use may require adjusting insulin dosage and increase glucose monitoring. Amitriptyline is drug with strong anticholinergic properties in the elderly and should be avoided according to the updated Beers Criteria [32]. The risk/benefit ratio for these drugs in combinations with the insulin should always carefully analyzed [22].

The principals DDIs found in the present study were cardiovascular system medication such as: angiotensin-converting-enzyme (ACE) inhibitions, diuretics, angiotensin II receptor blockers, beta-blockers and substances that act on the central nervous system. These drug interactions are similar in studies carried out in different setting [8,30−33]. An Italian study reported that acetylsalicylic acid and enalapril were the most prescribed [34]. Consistent with previous studies, in adult and older individuals it would be expected there would be higher amount of cardiovascular and central nervous system medication prescribed [35]. We recommend public health services should have a standard list of substances that most interact with other drugs dealing with the most common diseases and medical conditions in each health service. Prescribers should have access to a list of potential DDIs available at the service desk, so physicians could be avoiding potential DDIs and side effects.

All primary care health professionals are responsible for the prevention of clinically relevant negative interactions. Especially, pharmacists dispensing pharmaceutical drugs are in a key position to prevent pharmacotherapy-related problems. Pharmacists can develop the most accurate list possible of all medications a patient is taking, drug reconciliation, prepare guidelines and pharmacotherapy educational materials for patients and education teams. Most of DDIs are predictable and prevention is the primary prescriber responsibility, rather than the patient, Therefore, if pharmacists could participate in clinical team discussion it should prevent potential DDIs. The challenge for all health professionals is to develop reliable prescribing standards and procedures, continuously revised and monitored as a methodology for analyzing potential DDIs. These standards and procedures can be used in the education and training of primary care clinical teams to reduce to impact of DDIs.

Our study has design limitations that should be addressed. First, the analyses of DDIs pairs were based on only two databases. Second, the study was done in a single health unit, so the generalization of data should be performed with caution to others setting or patients with different age groups. Despite these limitation, our study offers important insight in prescribing medication with potential DDIs in primary care to insulin users.

6. Conclusion

Our findings show the estimated prevalence of potential DDIs is higher in diabetes patients in Brazilian primary care units. Undeniably, prescribing more medicines (three or more) increases drug load and CP and is a significant predictor of DDIs. Additionally, overweight patients with a BMI between 25 and 29.9 kg/m^2 took more than five drugs, while patients with BMI >30 kg/m^2 took more than six drugs. Explaining increased risk for DDIs in obese patients due to higher number of drugs used because of increased comorbidities can be ameliorated by teaching relevant lifestyle changes.

We have tested diabetes patients and shown participants do not have with have a satisfactory working knowledge about the insulin DDIs with other medicines. This lack of knowledge increases the need for more medical consultations and a greater medical cost burden. There is an established need to develop educational programs for diabetics whose aim is to enhance therapeutic knowledge. Future studies done in primary care should focused on increasing patient pharmacotherapy knowledge, especially about the greatest DDIs.

Conflicts of interest

No conflict of interest.

Source of finding

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