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Original Article

Heart failure is associated with non-adherence to pharmacotherapy in elderly with type 2 diabetes mellitus in public health system Brazilians

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ABSTRACT

The rising prevalence of T2DM poses a serious threat to human health and the viability of many health care systems around the world. Non-adherence to therapeutic in the T2DM is high, and Brazilian studies of public heath for to identify new variables are scares. The present study explored cardiovascular consequences associated with compliance and non-adherence among T2DM in Brazilian patients seeking medical care in Brazilian basic health unit clinics.

Methods: This is a cross-sectional study carried out in a city the interior of Sao Paulo state, with patients with T2DM, being municipal PHS users. Data were collected from the computerized system of the municipality for a one single researcher and patient records, and analyzed using the IBM SPSS v.18 statistical package. The response variables was categorized in adherent MGT (>80) and non-adherent MGT (≤80).

Results: The mean age of patients was 63.6 ± 9.5 with predominance for the sex male 66.4% and 42% of patients with T2DM do not adherence to treatment. We found an associated odds ratio (OR) = 2.3 (1.1 −5.1) between heart failure and non-adherence in patients with T2DM.

Conclusion: Heart failure is a factor associated with non-adherence to treatment in patients with T2DM and in the practice clinical, the screening for heart failure and interventions may improve adherence to pharmacotherapy.

1. Introduction

Currently, chronic diseases such as type 2 Diabetes Mellitus (T2DM) are a heavy burden in the public health milieu worldwide due to its macrovascular and microvascular complications; increasing direct medical costs such medications, medical exams, hospitalizations and medical fees [1]. Hyperglycemia, when blood glucose levels are not well controlled produce either macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and/or microvascular complications (diabetic nephropathy, neuropathy, and retinopathy). It is important for physicians to understand the relationship between diabetes and vascular disease because the prevalence of diabetes continues to increase [2]. Additionally, more than 415 million people have Diabetes Mellitus (DM) in the world and the tendency is increasing and the number is estimated to reach 642 million by 2040. T2DM represent 90% of cases in Brazil and currently, there are 12 million of people with diabetes (DM) in the country [3].

Although several prescription medications can play a vital role in controlling symptoms and preventing complications, non-adherence to these therapies is highly prevalent and has been linked to increases in morbidity, mortality, and health care costs [4]. Mirroring this worldwide trend, many Brazilian patients do not

Abbreviations: T2DM, diabetes mellitus type 2; PHS, public heath system; MGT, Morisky-Green Test modified,; MT, MedTake; DC, Diabetes Complications; CP, Complexity of Pharmacotherapy,; ACT, Auto-Compliance Test.

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continue following the agreed-upon medical treatment recommendations; when under limited supervision, or, when faced with conflicting demands. Thus, non-adherence to therapeutic recommendations among T2DM in Brazilian patients is high. Compounding the problem, individuals with T2DM have a twofold increased risk for cardiovascular disease (CVD) (myocardial infarction, stroke, peripheral vascular disease), and CVD is the principal cause of death in T2DM patients [5]. Moreover, another problem is a paucity of Brazilian public health medical studies that identify contributing variables and implications on the consequences of not following diabetes therapeutic recommendations.

The management cornerstones of T2DM include non-pharmacological therapies; such as medical nutrition therapy; regular physical activity and adherence to therapeutic. Following treatment recommendations, adherence to therapeutic is crucial for achieving healthy glycemic levels, which would decrease the complications of diabetes, lowering public health expenses [6]. Non-adherence to prescribed therapeutic is a worldwide challenge for health professional and in formulation public health policies. Some factors negatively effecting adherence such as: gender, age, disease duration, polypharmacy, comorbidities, family issues, complex regime and financial constraints are described in existing literature [7,8]. However, knowledge about therapeutic recommendations, regime complexity, drug load, time spent on medical consultations, and number of insulin injections missed in the previous months in patients with T2DM is missing in medical literature. This vacuum in the literature is an opportunity to explore the consequences of different comorbidities effecting patients not following treatment recommendations. Especially, exploring depression and congestive heart failure in T2DM patients attended primary care not adhering to treatment recommendations.

Despite the significant impact of DM has on public health, there are few studies in the Brazilian public health system exploring new factors linked non-adherence in T2DM. This research paucity and the financial burden that DM presents to Brazilian public health resources, we propose it is essential to investigate new variables that may be influencing T2DM patients attending primary care clinics that do not to follow treatment recommendations; a trend, that unfortunately, in Brazil, is becoming more prevalent.

Based on the points presented, this study proposes to investigate the impact of known variables affecting compliance to therapeutic recommendations, or not, in T2DM patients. Specifically, we aim to explore which factors are associated with adherence or non-adherence T2DM patients.

2. Methods

2.1. Setting and design

From August to December 2017, a cross sectional study was conducted in the Sao Paulo, Franca, Brazilian municipality. This study followed the recommendations outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE Statement) and we included all adult T2DM patient's data found in the basic health unit medical histories. In Brazil, PHS, also called basic care (BC), is the best access to medical treatment for citizens within Unified Health Services [Sistema Único de Saúde (SUS)] that manages public health organization and mangement of Brazilian healthcare networks.

2.2. Inclusion criteria

All patients who attended the Basic Health Unit Clinics between August to December 2017 and who fulfilled the following inclusion criteria were selected: T2DM diagnosis, age equal to or greater than 18 years, both genders, using oral hypoglycemic agents and isophane insulin(NPH) or Regular insulin. Collected from medical records were the last six months results of clinical parameters, the variables for factual data, including: fasting, non-fasting, and postprandial blood glucose levels; glycemic control; and glycated hemoglobin (A1c).

2.3. Exclusion criteria

Individuals with no A1c score, or with duplicate and/or incomplete data in the integrated Health System (system used in municipality) during the collection period, Illiterate patients; pregnant women; cognitive deficit individuals and/or mental disorders; chronic diseases of greater complexity (kidney disease for example) were excluded.

2.4. Patients and data collection

All patients were given an open-ended questionnaire and data collected by one researcher. Before administration, the questionnaire was evaluated and standardized by twenty patients to correct regional Brazilian Portuguese language differences of usage and interpretation. These volunteers were excluded from being included in the data.

Before their medical consultation, patients were selected, and interviewed in a room separated from the doctor's office. The average time of each interview was 20 min. The variables collected through the questionnaire included: age, gender, marital status, per capita income, school level attained, comorbidities, time since diabetes diagnosis, number of pharmaceuticals used, drug load, average consultation duration, waist circumference (WC), body mass index (BMI), levels of fasting blood glucose, postprandial glucose, and (A1c).

To evaluate patient's compliance to using recommended pharmaceutical medications, pharmacotherapy, the complications from diabetes; number of insulin injections missed; the patient's knowledge of the drugs scripted and the complexity of pharmacotherapy; the following tests were applied: Morisky-Green modified (MGT), Diabetes Complication (DC), Complexity of Pharmacotherapy (CP), MedTake (MT), and Auto- Compliance Test (ACT).

The Self-Reports Scale for Measuring Adherence to Medication, the Morisky-Green modified (MGT) modified was utilized to evaluate the level of compliance to therapeutic recommendations. Six questions with Yes/No answers were included in the MGT: (1) Have you ever forgotten to take your medicine for diabetes? (2) At times, are you not careful about taking your medicine for diabetes? (3) When you feel better, do you sometimes stop taking your medicine? (4) At times, if you feel worse when you take your medicine, do you stop taking it? (5) Do you know the long-term benefits of taking your medicine? (6) At times do you forget to replace your medicines before it finishes? The patient only answers questions five (long-term benefits) and six (forget to replace) if they answer 'yes' to all questions one to four. The patients with MGT scores greater than eighty percent ($\geq$80%) were considered as being 'compliant [9].

Complications associated with diabetes were evaluated using Diabetes Complications (DC). The DC is a questionnaire composed of 17 questions. In this questionnaire: five questions evaluate coronary heart disease, three questions stroke, two questions are on peripheral vascular disease, two questions cover neuropathy, three questions are related to foot problems, and two questions uncover diabetic retinopathy. Each complication is determined by two or more questions, for example, coronary heart disease is present if the patient reported having a myocardial infarction, symptoms of

angina pectoris, or have a prior diagnosis. The DC calculates the sum of any complications present and is scored from 0 to 6 [10].

To evaluate patient's ability to manage their medication, the MedTake (MT) questionnaire was utilized to evaluated dosage, indication, food or water co-ingestion, regimen, and knowledge about prescribed medications. The MT evaluates dosage (units), indication, regime, and knowledge about the drug-interaction or food-drug interaction of medications being taken. Scored between 0 and 100% and the individual mean of all test scores is calculated for each patient; thus, assessing patient's ability utilize their drugs safely. Subjects who answered correctly the four questions have a score of 100% and subjects who answered only three questions receive a score of 75% [11].

Medication regimen attributes, such as the number of drugs, dosage frequency, administration instructions, and the prescribed dosage forms, have been shown to influence patient outcomes. To quantify the complexity of prescribed medication regimens we employed the complexity of pharmacotherapy (CP) questionnaire. Divided into three sections: A, B, and C, the CP is determined by the sum of scores of all sections. High section scores are defined as greater complexity and possible side effects to patient [12].

The Auto- Compliance Test (ACT) was used for the evaluated the number of insulin injections missed in the previous months. This instrument assesses the patient's self-reporting of the difficulty of applying the insulin by asking two open questions: (1) “Did you have any difficulties in insulin injection?” and (2)” How many times did you skip insulin injection in the last month?” Individual ACT results were calculated through the following formula: Total number of insulin injections, divided by the Total number of prescribed insulin injections x 100. Individuals who affirmed taking more than 80% of the total of number of prescribed insulin injections were compliant [13].

The main purpose of the ATC/DDD system is as a tool for presenting drug utilization statistics with the aim of improving drug use. We used the drug load for the calculated the overload of medicines by patients. The basis of this system is the presentation and comparison of drug consumption statistics at international and local levels. The dose of drugs that the patient was taking was divided by defining the daily dose according to international drug utilization research. When the subject takes more of one drug, the ATC/DDD ratio values are increased. Subjects with high values of drug load have a medication overload and a high probability of developing adverse effects [14].

2.5. Statistics analysis

For statistics analysis, patient data was initially divided into two groups: one group with scores in the Self-Reports Scale for Measuring Adherence to Medication, the Morisky-Green modified (MGT) scoring less than eighty (MGT<80) and the other group with scores more than eighty (MGT>80). To follow the correct presentation of statistical results, the continuous variables were reported as median and standard deviation and categories variables as frequency and percentage. Statistical analyses were performed using The Statistical Package for the Social Sciences (SPSS 18).

A logistic regression model was performed to evaluate the effect of variables in the adherence and non-adherence to pharmacotherapy recommendations. Thus, we used the Morisky-Green modified (MGT) results as the dependent variable vis-a-vis the independent variables: clinical data, demographics, and relating to medication, Complexity of Pharmacotherapy (CP) and the Auto-Compliance Test (ACT).

To associate observance to treatment recommendations, with the independent variables, we used a logistic regression model. This model produces odds ratios (OR) as association measures, with respective 95% confidence intervals (95%IC). Confidence intervals not including 1 was statistically significant (analogous to $p < 0.05$). To control for the possible confounding effects of gender, age and time of diagnosis, a multiple logistic regression model produced adjusted odds ratios (OR) measures. The Statistical Analysis System (SAS) software version 9 was used for all statistic procedures.

This study was approved by the ‘Research Ethics Committee’ in the School of Medicine of Ribeirão Preto, University of São Paulo, 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 invited to sign the Free and Informed Consent Terms, available for inspection.

3. Results

A total of 400 primary care center patients were initially identified, of which 200 (50%) were not eligible because they are diagnosed as having, insulin deficient Diabetes Mellitus type 1 or patient data with no glycated hemoglobin results (HbA1c). Thus 200 patients (50%) were potentially eligible. Processed through the analysis exclusion criteria, 143 (71.5%) were selected. After recruitment, the subjects were classified according to the Self-Reports Scale for Measuring Adherence to Medication, the Morisky-Green modified (MGT) modified scores, with 83 patients adherents (58%) and 60 patients non-adherents (42%). Fig. 1 shows the patient recruitment flowchart.

Table 1 show, of the 143 patients recruited, the male gender predominated 66.4% (95/143), schooling 79% (113/143), age (63.6 ± 9.5), married 54.5% (78/143), white 46.1% (66/143) and body mass index, BMI = 31.2 ± 5.8. The number of comorbidities was 4.2 ± 1.8 and chronic complications of Diabetes were 2.4 ± 1.3.

For the glycemic control, the levels of fasting blood glucose was 166 ± 72.9, postprandial glucose 229 ± 94.5 and HbA1c 8.9 ± 1.8. For the variables related to medicines, the drug load was 2.3 ± 0.7, MT scores 62.8 ± 17, ACT 97.6 ± 6 and CP $\pm 20 \pm 5.7$.

Logistic regression analyses showed an association between non-adherence and heart failure OR = 2.3 (1.1–5.1) Table 2.

4. Discussion

Although this particular study design does not provide to establish if the occurrence of T2DM the first variable causes heart failure (HF) the other variable, the ‘relation of causality’, clinically, our findings contribute to the current literature by pointed an association between not following treatment recommendations, ‘non-adherence’ and HF in people with T2DM. Positive adherence to following therapeutic recommendations contributes to the better glycemic control and decreases the diabetes complications; lowering public health care costs. Clinically, the findings of our study contribute to identifying individual characteristics and clinical aspects related with complying with treatment recommendations, ‘adherence’ and individuals who will not or cannot follow recommended treatment regimens, ‘non-adherence’ in patients attended in the primary care clinics. Understanding the implications of not adhering to treatment recommendations made by health professionals and knowing which variables negatively affect medication usage in patients with T2DM, is imperative because this group of patients needs continuous education in Diabetes and ongoing support to be able to achieve glycemic goals.

The simultaneous presence of two or more chronic diseases or conditions in a patient, comorbidities increase diabetic complications. We see in patients with poor compliance, ‘non-adherence’ to treatment recommendations have poor glycemic control, increasing cardiovascular diseases, and burdening public health

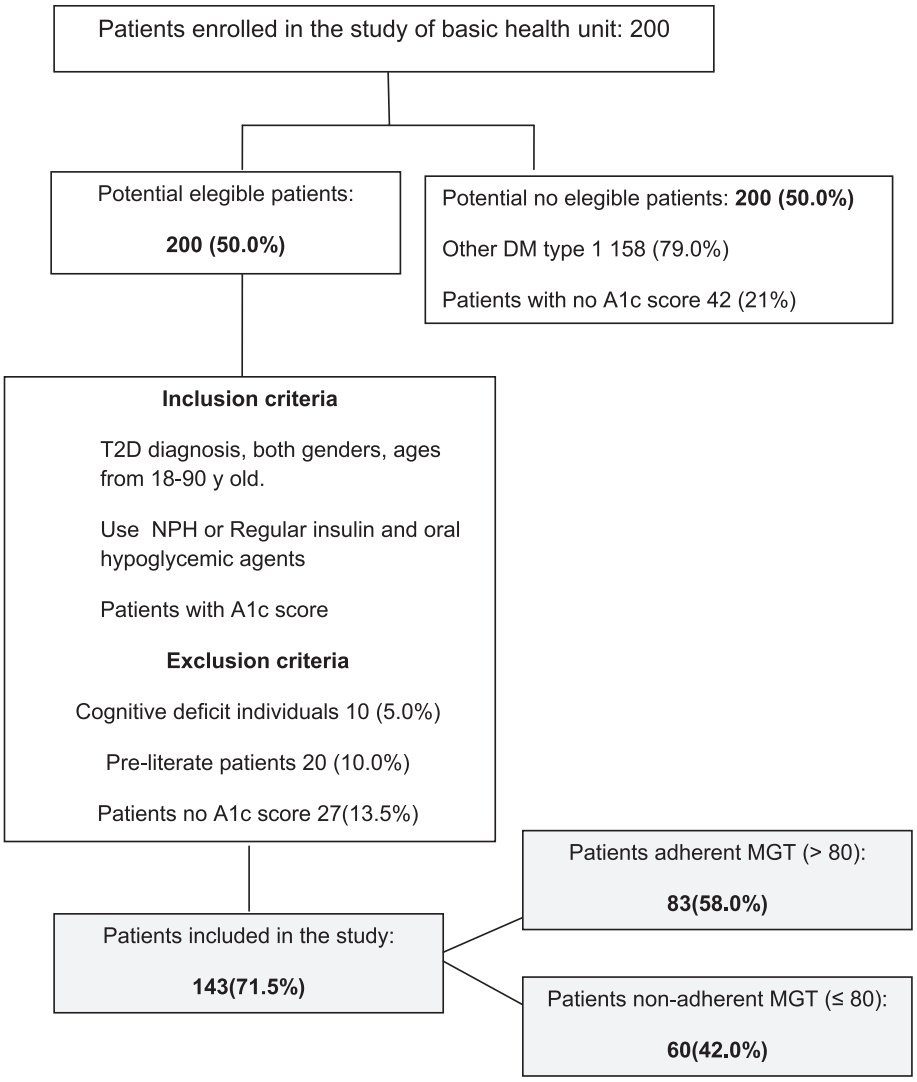

Fig. 1. Recruitment of patients for the study.

costs [2]. HFis a chronic, pathophysiologic, progressive condition in which the heart muscle is unable to pump enough blood through to meet the body's needs for blood and oxygen. Existing medical literature support a strong relationship between diabetes and cardiovascular disease, reporting 68% of elderly with DM patients die from some form of heart disease. DM is one of seven modifiable risk factors for cardiovascular diseases and adults with DM are two to four times more likely to die of heart disease compared to patients without DM. The risk of cardiovascular disease is increased in patients with DM2 due to hypertension, dyslipidemia, obesity and lack of physical activity [12], mirroring our research results in the patients with T2DM who are not adhering to their physician's treatment recommendations.

Significantly, in our study we found that patients not following treatment recommendations very well, the non-adherent 35% (21/60) of subject's suffer from HF, data that corroborates with the literature stating that patients with T2DM, suffering from HF are 2.3 times more likely to not follow treatment recommendations, 'non-adherent' [13]. 'Non-adherence' to therapeutic recommendations in people with HF is a strong predictor of repeated hospital readmission, which drains public health budgets [14,15]. Data from the "I Brazilian Registry of Heart Failure" (BREATHE) corroborate our findings, showing that most of the patients with HF are elderly, and the main feature for the HF, decompensation is poor adherence to pharmacotherapy and not following the current guidelines; contributing to high mortality and increased economic costs [16]. Additionally, data from the multicenter "Retirement in Action" (REACT) study done in Brazil, reported that suffering from Diabetes Mellitus insinuates there is a high risk for major clinical events in a short period of time; and insulin use, was associated with greater cardiovascular pathology in this population [17,18]. In this baseline, our group showed that increase insulin dosages both for insulin dependent type 1 Diabetes Mellitus (T1DM) and insulin resistant T2DM in patients using the medical services of the basic health unit clinics, do not ameliorate their medical condition, suffer from increased side effects, have more complexity of pharmacotherapy and gain more weight without non-pharmacologic interventions [19].

When analyzing the relationship between glycemic control and non-adherence to pharmacotherapy, we found no association. Comparing our data with current literature, a retrospective cohort study conducted in 2015 in Brazil reported that patients diagnosed with DM1 and DM2 disease more than 10 years did not reach glycemic goals [22]. Increasing adherence by 10% decreases

Table 1
Baseline demographic and clinical characteristics of patients.

	Non-adherent n = 60	Adherent n = 83
Sex		
Male	38	57
Female	22	26
Race		
White	27	39
Black	8	8
Brown	25	36
Marital Status		
Married	31	47
Single/Divorced	29	36
Schooling (years)		
0–8	45	68
9–12	15	15
Time diagnosis(months)	186 ± 100	205 ± 111
Number of comorbidities	4.6 ± 1.8	3.9 ± 1.9
Comorbidities		
Hypertension	41	68
Dyslipidemia	34	41
Congestive heart failure	21	16
Heart attack	11	8
Stroke	4	9
Depression	19	21
Retinopathy	25	36
Thyroid	11	13
Per capita income	592.5 ± 233	541.6 ± 254.6
Age	63 ± 10.5	64 ± 8.9
Body mass Index	30.9 ± 5.8	31.3 ± 5.8
Fasting blood glucose (mg)	183 ± 81	153 ± 63
Postprandial glucose (mg)	241.4 ± 96	219.8 ± 93
HbA1c (%)	9.2 ± 2	8.7 ± 1.5
NPH Insulin dosage (mg)	48.7 ± 25	45.9 ± 20.4
Regular Insulin dosage (mg)	16.8 ± 9.7	14.4 ± 8.8
Metformin (mg)	1.276 ± 724	1280 ± 626
Drug load	2.3 ± 0.8	2.2 ± 0.7
Number of medicines	6.6 ± 2.2	6.6 ± 2.4
Time medical services (minutes)	10 ± 4.9	10.8 ± 4
MedTake test	58.6 ± 19	65.8 ± 14.8
Complexity of Pharmacotherapy Index	20 ± 5.2	20 ± 6
Diabetes Complications Index	2.6 ± 1.3	2.3 ± 1.4
Auto Compliance Test	94.7 ± 8.3	99.2 ± 3.5
Pharmacotherapy		
Captopril	2	7
Hydrochlorothiazide	17	27
Losartan	21	28
Sinvatatin	24	34
Levothyroxine	7	17
Acetylsalicylic acid	20	32
Carvedilol	7	7
Amlodipine	5	7
Omeprazole	9	11
Enalapril Maleate	13	11
NPH and Regular Insulin	3	2
NPH and Regular Insulin and Metformin	23	37
NPH Insulin and Metformin	22	26
Insulin NPH, Metformin and Glibenclamide	8	12
Insulin NPH and Glibenclamide	1	1
Insulin NPH and Regular, Metfotmin and Glibenclamide	3	5

glycosylated hemoglobin, (HbA1c) levels by 0.1% [21] and adherence to adequate diet reduced mean (HbA1c) by 1.1% [23].

We found no statistically significant difference between the clinical and socio-demographic variables with those patients adhering and those not-adhering to pharmacotherapy. Our findings are in agreement, consonance with what is reflected in the literature. In the gender variable, women adhered better to pharmacological treatment recommendations compared to men, but without significant clinical changes [24]. The age variable, most of the patients with T2DM are older, which has age related issues and skews towards non-adherence to treatment. Taking several medicines, polypharmacy, coupled with low level education level achieved and low scores on patient's ability to manage their medication, the MT questionnaire, are predictors of non-adherence to pharmacotherapy recommendations [25]. Assessing attained education level, our data is reflective with studies reported in the literature that did not find evidence stating that education level is associated with non-adherence to pharmacotherapy [26,27,28,29]. Although there is no direct statistical association between education level and non-adherence, it should justify medical researchers and health professionals to pay heed, since it should contribute to the educational activities planning and evaluation provided health service.

Remarkably, our research uncovered that the average time spent in a medical consultation is, at most, eleven (11) minutes. It is highly unlikely to control any chronic disease, especially Diabetic Mellitus, with such a short time devoted to guiding relevant patient care. Moreover, the high Complexity of Pharmacotherapy increases patient's risk of over-medicating and can negatively influence 'non-adherence' to recommended therapy. However, we did not find a statistical association between the Complexity of Pharmacotherapy variable and adherence to pharmacotherapy. There is a paucity in medical literature reporting on Complexity of Pharmacotherapy (CP) among patients with T1DM and T2DM, and, hopefully further studies in the future will addressing this issue. In the future, we hope grants are made available to study further individuals dealing with Diabetes Mellitus (DM) and to identify possible factors that predispose patients to be unable or unwilling to follow treatment recommendations. Other designed studies could enable medical providers better tools to improve treatment efficacy and lower public health costs.

Among the limitations of this study, it is worth noting that, our study was designed as an exploratory endeavor; it might not be exempt from causality inferences or, possible biases that affect the resulting values. Self-reporting generally tends to yield inflated estimates in the MedTake (MT), Self-Reports Scale for Measuring Adherence to Medication, the Morisky-Green modified (MGT), Diabetes Complication (DC), and Complexity of Pharmacotherapy (CP) could have been somewhat lower than we observed. Our study was conducted in a single health unit, so the generalization of data should be performed with caution. In fact, our study has few patients with HF [21], regardless, we found significant differences.

4.1. Recommendations for further study

There exists clinical data and experience suggesting an etiology for the development of T2DM and developing HF. Clinical experience shows when liver enzymes present with Gamma GT more than thirty units per liter (>30u/L), Aspartate transaminase (ASAT) between fifteen and thirty (15–30 u/L), and Aspartate transaminase (ALAT), the liver only enzyme, more than thirty units per liter (30 u/L) indicates the liver is deficient in bile production. The liver's production of bile is the major route for elimination of cholesterol that is converted in the liver with amino acids Taurine and Glycine. Hyperlipidemia in diabetes suggest the inability of the liver to produce adequate bile. Good quality, alkaline bile is needed for adequate digestion of protein and to emulsify dietary fats and facilitate their intestinal absorption.

Without decent quality bile, food is not digested properly and ferments. Seen in high triglycerides count. Elevated triglycerides are usually considered by many physicians to be the result of obesity, kidney disease, ingesting more calories than a person burns, excessive alcohol consumption, hypothyroidism and insufficiently controlled diabetes. Our position is that high triglycerides count, in individuals that do not drink alcohol, is from digestive fermentation. We have seen many patients where bacteria, yeasts and possibly other parasites existing in the upper gut, which

Table 2
Regression logistic of MGT modified with the variables related to adherence.

		Non-adherent (n = 60)		Adherent (n = 83)		Crude OR (95% CI)	Adjusted OR [a] (95% CI)
		n	%	*n*	%		
Sex	Male	22	36.7	26	31.3	Ref.	Ref.
	Female	38	63.3	57	68.7	0.8 (0.3–1.6)	0.8 (0.3–2.2)
Age (years)	≤40	4	6.7	0	–	–	–
	41–60	16	26.7	24	28.9	Ref.	Ref.
	61–70	26	43.3	38	45.8	1.0 (0.4–2.3)	1.2 (0.5–2.8)
	>70	14	23.3	21	25.3	1.0 (0.3–2.5)	1.3 (0.4–3.4)
Race	White	27	45.0	39	47.0	Ref.	Ref.
	Black	8	13.3	8	9.6	1.4 (0.4–4.3)	1.4 (0.4–4.5)
	Brown	25	41.7	36	43.4	1.0 (0.4–2.0)	1.1 (0.5–2.3)
Marital status	Single	4	6.8	5	6.0	Ref.	Ref.
	Married	31	52.5	47	56.6	0.8 (0.2–3.3)	0.9 (0.2–4.0)
	Divorced	7	11.9	18	21.7	0.4 (0.1–2.4)	0.5 (0.1–3.0)
	Widowed	17	28.8	13	15.7	1.6 (0.3–7.3)	2.5 (0.4–12.4)
Schooling (years)	0–8	45	75.0	68	81.9	Ref.	Ref.
	8–12	11	18.3	10	12.1	1.7 (0.6–4.2)	1.5 (0.5–4.0)
	>12	4	6.7	5	6.0	1.2 (0.3–4.7)	1.2 (0.2–4.9)
Time of diagnosis (months)	<120	11	18.3	16	19.3	Ref.	Ref.
	120–240	28	46.7	30	36.1	1.3 (0.5–3.4)	1.3 (0.5–3.5)
	>240	21	35.0	37	44.6	0.8 (0.3–2.1)	0.8 (0.3–2.2)
Per capita income	<400	21	35.0	41	49.4	Ref.	Ref.
	400–600	10	16.7	8	9.6	2.4 (0.8–7.1)	2.8 (0.8–9.2)
	>600	29	48.3	34	41.0	1.7 (0.8–3.4)	1.9 (0.8–4.0)
BMI (kg/cm2)	≤25	8	13.3	11	13.2	Ref.	Ref.
	(25,30]	23	38.3	31	37.4	1.0 (0.3–2.9)	0.9 (0.3–2.8)
	(31, 35]	16	26.7	23	27.7	0.9 (0.3–2.9)	0.9 (0.3–2.9)
	>35	13	21.7	18	21.7	1.0 (0.3–3.1)	0.9 (0.2–2.9)
Hypertension	No	18	30.0	16	19.3	Ref.	Ref.
	Yes	42	70.0	67	80.7	0.5 (0.2–1.2)	0.5 (0.2–1.3)
Dyslipedemia	No	26	43.3	42	50.6	Ref.	Ref.
	Yes	34	56.7	41	49.4	1.3 (0.6–2.6)	1.4 (0.7–2.8)
Heart failure	No	39	65.0	67	80.7	Ref.	Ref.
	Yes	21	35.0	16	19.3	**2.3 (1.1–4.8)***	**2.3 (1.1–5.1)***
Heart attack	No	48	80.0	75	90.4	Ref.	Ref.
	Yes	12	20.0	8	9.6	2.3 (0.8–6.2)	2.3 (0.8–6.3)
Stroke	No	56	93.3	74	89.2	Ref.	Ref.
	Yes	4	6.7	9	10.8	0.5 (0.1–2.0)	0.6 (0.1–2.4)
Depression	No	42	70.0	62	74.7	Ref.	Ref.
	Yes	18	30.0	21	25.3	1.3 (0.6–2.7)	1.3 (0.5–3.0)
Retinopathy	No	34	56.7	47	56.6	Ref.	Ref.
	Yes	26	43.3	36	43.4	1.0 (0.5–2.0)	0.9 (0.4–2.0)
Thyroid	No	49	81.7	70	84.3	Ref.	Ref.
	Yes	11	18.3	13	15.7	1.2 (0.5–2.9)	1.2 (0.5–3.0)
Fasting blood glucose (mg)	≤100	7	12.7	14	19.7	Ref.	Ref.
	100–125	8	14.6	10	14.1	1.6 (0.4–5.9)	1.7 (0.4–6.7)
	>125	40	72.7	47	66.2	1.7 (0.6–4.6)	1.5 (0.4–4.5)
Postprandial glucose (mg)	≤140	10	16.7	22	27.2	Ref.	Ref.
	>140	50	83.3	59	72.8	1.9 (0.8–4.3)	1.8 (0.7–4.2)
HbA1c (%)	≤7	5	9.1	10	14.3	Ref.	Ref.
	>7	50	90.9	60	85.7	1.7 (0.5–5.2)	1.8 (0.5–5.8)
NPH	≤40	24	40.0	38	45.8	Ref.	Ref.

Table 2 (*continued*)

		Non-adherent (n = 60)		Adherent (n = 83)		Crude OR (95% CI)	Adjusted OR [a] (95% CI)
		n	%	*n*	%		
Insulin dosage (mg)	>40	36	60.0	45	54.2	1.3 (0.6–2.5)	1.4 (0.7–2.9)
Regular Insulin dosage (mg)	≤10	8	26.7	17	47.2	Ref.	Ref.
	>10	22	73.3	19	52.8	2.5 (0.8–7.0)	3.0 (0.9–9.4)
Drugload	≤1	3	5.1	2	2.4	Ref.	Ref.
	>1	56	94.9	80	97.6	0.4 (0.1–2.9)	0.4 (0.1–3.2)
Drugs	≤3	5	8.3	8	9.6	Ref.	Ref.
	>3	55	91.7	75	90.4	1.2 (0.3–3.8)	1.2 (0.3–3.9)
Time medical Services (m)	≤10	27	45.0	31	38.7	Ref.	Ref.
	>10	33	55.0	49	61.3	0.7 (0.3–1.5)	0.7 (0.3–1.5)
Med Take test	≤70	33	55.0	33	39.8	Ref.	Ref.
	>70	27	45.0	50	60.2	0.5 (0.1–1.5)	0.5 (0.2–1.1)
CPI	≤10	1	1.7	2	2.4	Ref.	Ref.
	>10	59	98.3	81	97.6	1.4 (0.1–16.4)	1.7 (0.1–20.6)
DC	≤2	28	48.3	39	52.0	Ref.	Ref.
	>2	30	51.7	36	48.0	1.2 (0.5–2.3)	1.2 (0.6–2.5)
ACT	≤80	6	10.0	1	1.2	Ref.	Ref.
	>80	54	90.0	82	98.8	0.1 (0.01–0.9)*	0.1 (0.01–1.1)

[a] OR adjusted by sex, age and time of diagnosis.

fermented foods, especially simple carbohydrates, instead of being digested. Screening for *Helicobacter pylori* and Rotavirus is recommended while checking liver function.

Not digesting means food means 'essential' amino acids are not being absorbed and to keep up with the metabolic requirements, the body catabolizes muscle. Seen when Creatine phosphokinase (CPK) rises above 100 units/Liter that reflects muscle reabsorption, resulting in sarcopenia. Seen as developing woman's flabby upper arms, triceps and in men a reduction in size of the leg calf, Gastrocnemius muscle. Seen as results of diabetes, the decline in muscle mass, strength and function associated with diabetes that leads to sarcopenia, frailty and eventually disability, [V1] is, a pre-existing condition. Muscle catabolism includes the heart and can be diagnosed with elevated myoglobin.

Metformin is the primary anti-diabetic drug in patients with T2DM. Metformin reduces mitochondrial respiration and enhances anaerobic metabolism [V2]. Anaerobic metabolism produces a limited amount of Adenine Triphosphate (ATP). Because ATP is needed to pump back calcium in endoplasmic reticulum (=sarcoplasmic reticulum) before the muscle cells can relax. Diabetic patients, especially taking diabetes medication suffer from 'stiff' muscles [V3]. Diabetic's muscles stay in contracted state till the nervous stimulus is withdrawn and until ATP is available to supply energy for 'cross-bridge' formation (ATP is spent to change the orientation of myosin head which helps in sliding actin filament during contraction). The heart, a muscle also becomes 'stiff' and can be diagnosed as increased analyte levels of Brain natriuretic peptide (NT-proBNP (BNPT) that reflects a 'stiff heart' is effective in screening and diagnosing acute congestive heart failure (CHF). Enabling the heart to more fully 'relax' the greater opening draws in more blood volume.

5. Conclusions

Heart failure is a factor associated with non-adherence to treatment in patients with T2DM. Clinical trial with large size must be made in future for the decrease non-adherence to therapeutic recommendations. For the clinical practice, the screening for the heart failure and interventions may improve adherence to pharmacotherapy.

Conflicts of interest statement

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2018.12.013.

References

[1] International Diabetes Federation – IDF. Diabetes atlas. fourth ed. Brussels: International Diabetes Federation; 2013 [Acesso em: 12 jan. 2018] http://www.diabetesatlas.org/content/diabetes.
[2] Fowler Michael J. Microvascular and macrovascular complications of diabetes. Clin Diabetes 2008;26(2):77–82.
[3] Sociedade Brasileira de Diabetes – SBD. Diretrizes da Sociedade Brasileira de Diabetes: 2015–2016. São Paulo: AC Farmacêutica; 2016.
[4] Blackburn DF, Swidrovich J, Lemstra M. Non-adherence in type 2 diabetes: practical considerations for interpreting the literature. Patient Prefer Adherence 2013;7:183–9.
[5] Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO multinational study of vascular disease in diabetes. Diabetologia 2001;442. S14–S2.
[6] Peres HA, Freitas MCF, Pereira LRL. Low scores in the auto-compliance method and fast medical care influence the PoorAdherence in diabetics attended in the basic health unit. Biol Med 2017;9(3):2–8.
[7] Sweileh WM, Zyoud SH, Abu Nab'a RJ, Deleq MI, Enaia ML, et al. Influence of patients' disease knowledge and beliefs about medicines on medication adherence: findings from a cross-sectional survey among patients with type 2 diabetes mellitus in Palestine. BMC Public Health 2014;14(1):94.

[8] Vieira LB, Ueta J, Pereira LRL. Adherence to medication before and after the use of a Drug- Dispensing System with usage control. Brazilian J Pharm Sci 2015;51:327–9.
[9] Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care 1986;24(1):67–74.
[10] Fincke BG, Clark JA, Linzer M, Spiro A, Miller DR. Assessment of long-term complications due to type 2 diabetes using patient self-report: the diabetes complications index. J Ambul Care Manag 2005;28(3):262–73.
[11] Raehl CL, Bond CA, Woods T, Patry RA, Sleeper RB. Individualized drug use assessment in the elderly. Pharmacotherapy 2002;22(10):1239–48.
[12] Melchiors AC, Correr CJ, Fernández-Llimos F. Translation and validation into Portuguese language of the medication regimen complexity index. Arq Bras Cardiol 2007;89(4):210–8.
[13] Farsaei S, Radfar M, Heydari Z, Abbasi F, Qorbani M. Insulin adherence in patients with diabetes: risk factors for injection omission. Prim Care Diabetes 2014;8(4):338–45.
[14] International language for drug utilization research. https://www.whocc.no/atc_ddd_methodology/purpose_of_the_atc_ddd_system/Accessed 15 January 2018.
[15] American Diabetes Association Standards of medical care in diabetes - 2013. Diabetes ARDUINO F. O diabetes através dos tempos. In: Arduino F, editor. Diabetes mellitus e suas complicações. 2ª ed. Rio de Janeiro: Guanabara Koogan; 1973. p. 1–4.
[16] Tang HY, Sayers SL, Weissinger G, Riegel B. The role of depression in medication adherence among heart failure patients. Clin Nurs Res 2014;23(3):231–44.
[17] Lee D, Mansi I, Bhushan S, Parish R. Non-adherence in at-risk heart failure patients: characteristics and outcomes. J Nat Sci 2015;1(5):95.
[18] Wu JR, Lennie TA, Dekker RL, Biddle MJ, Moser DK. Medication adherence, depressive symptoms, and cardiac event–free survival in patients with heart failure. J Card Fail 2013;19(5):317–24.
[19] Albuquerque DCD, Souza-Neto JDD, Bacal F, Rohde LEP, Bernardez-Pereira S, Berwanger, et al. I Brazilian registry of heart failure-clinical aspects, care quality and hospitalization outcomes. Arq Bras Cardiol 2015;104(6):433–42.
[21] Schaan BD, De Figueiredo Neto JA, Moreira LB, Ledur P, Mattos, et al. Diabetes and cardiovascular events in high-risk patients: insights from a multicenter registry in a middle-income country. Diabetes Res Clin Pract 2017;127:275–84.
[22] Peres HA, Foss MCF, Pereira LRL. High dosage insulin, low adherence and low knowledge about pharmacotherapy- face to face with reality in the health public system Brazilians. Prensa Med Argent 2017;103(4):2–5.
[23] Zhu VJ, Tu W, Marrero DG, Rosenman MB, Overhage JM. Race and medication adherence and glycemic control: findings from an operational health information exchange. In AMIA annual symposium proceedings (Vol. vol. 2011, p. 1649). American Medical Informatics Association.
[24] Rozenfeld Y, Hunt JS, Plauschinat C, Wong KS. (2008). Oral antidiabetic medication adherence and glycemic control in managed care. Am J Manag Care 2008;14(2):71–5.
[25] Baptista DR, Thieme RD, Reis WCT, Pontarolo R, Correr CJ. Proportion of Brazilian diabetes patients that achieve treatment goals: implications for better quality of care. Diabetol Metab Syndrome 2015;7(1):113.
[26] Davison KA, Negrato CA, Cobas R, Matheus A, Tannus L, et al. Relationship between adherence to diet, glycemic control and cardiovascular risk factors in patients with type 1 diabetes: a nationwide survey in Brazil. Nutr J 2014;13(1):19.
[27] Tiv M, Viel JF, Mauny F, Eschwege E, Weill A, Fournier C, Penfornis A. Medication adherence in type 2 diabetes: the ENTRED study 2007, a French population-based study. PLoS One 2012;7(3), e32412.
[28] Park K, Kim JG, Kim BW, Kam S, Kim KY, et al. Factors that affect medication adherence in elderly patients with diabetes mellitus. Kor Diabet J 2010;34(1):55–65.
[29] Peres HA, Freitas MCF, Pereira LRL, Viana CM. New insights for the polypharmacy use in elderly with diabetes-an update about effect of education level. J Endocrinol Diab. 4(5): 1-6.