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Evaluation of outpatient health services in diabetes mellitus in a middle-income setting: a retrospective cohort study involving secondary care

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ABSTRACT. In Brazil, it is necessary to assess the different levels of health care in diabetes mellitus (DM) in order to integrate them. In this retrospective cohort study, we analyzed 1,122 medical records of patients with DM from specialized services with interdisciplinary health teams (IHT) in the city of Ourinhos, São Paulo state, Brazil, to assess the impact of secondary care on glycemic control in patients with DM in those places and to compare baseline and follow-up DM care indicators concerning clinical evaluation and drug treatment regimens in the aforementioned health services. The study covered consultations carried out from September/2013 to September/2017. Data were collected from initial and final appointments in medical records and revealed an increase of 31.21% in insulin introduction and of 73.53% in regimens with three or more non-insulin antidiabetic (NIA) medications. Among the 570 patients with at least two glycated hemoglobin (A1C) measurements in the aforementioned review, 146 did not require any therapeutic adjustment between initial and final appointments, 123 required a subtle adjustment, 95, a moderate adjustment, and 206, an intense adjustment. There was a noticeably higher A1C reduction between initial and final appointments when patients who required an intense drug adjustment were compared to those who did not need any different NIA drug (p-value < 0.0001). In addition to optimizing drug treatment, essential exams in DM were performed with higher frequency, with an increase of 63% in ophthalmology evaluation performed during secondary care approach and 60.65% more individuals being screened for diabetic chronic kidney disease. IHT secondary care considered in this study, therefore, not only improved glycemic control of patients with DM, especially by optimization of NIA regimens and timely prescription of insulin, but also increased the screening for microvascular complications.

Keywords: diabetes mellitus; glycated hemoglobin A; secondary care; interdisciplinary health team; health services.

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Introduction

Diabetes mellitus (DM) is the fourth leading cause of death, 80% of which occur in low and middle-income countries (Alaofè et al., 2017) as Brazil, India, and China (Bahia et al., 2011). World Health Organization projects a prevalence of DM in about 11.3% of Brazilian population by 2030 (Coutinho & Silva, 2015; Ministério da Saúde, 2013). In 2021, data from the International Diabetes Federation ranked Brazil as the sixth country in number of people with DM in the world, with an estimated 15.7 million of cases (Sun et al., 2022).

Outpatient DM treatment in Brazil is offered through the Public Health System (SUS) in Primary Health Clinics (UBS) where patients are provided primary care (Ministério da Saúde, 2006; 2011; 2013) by interdisciplinary health teams (IHT) composed of physicians (general practitioners) and non-physician health care professionals (Guidoni, Borges, Freitas, & Pereira, 2013), and with secondary care provided by groups divided into specialized physicians (endocrinologists, ophthalmologists and others) and non-physician professionals (mostly pharmacists, nurses, nutritionists and social workers) (Guidoni et al., 2013). In some regions of São Paulo state (SP), secondary care is currently carried out by services such as Specialty Health Clinics (AME) (http://portal.saude.sp.gov.br/ses/perfil/cidadao/ambulatorio-medico-de-especialidades-

ames/ambulatorio-medico-de-especialidades-ames) and organizations such as Juvenile Diabetes Associations (ADJ) (https://adj.org.br/), which work on an IHT basis.

Several studies correlate a decrease in DM microvascular complications with the achievement of strict glycated hemoglobin (A1C) (American Diabetes Association, 2018) goals (see Table 1):

Table 1. A1C goals by different societies.

Society	ADA	IDF	AACE	SBD
A1C(% / mmolmol^{-1})	< 7 /< 53		< 6.5/< 48	
FPG(mgdL^{-1} / mmolL^{-1})				< 100/< 5.55
Preprandial blood glucose (mgdL^{-1} / mmolL^{-1})	90-130/ 4.99-7.21	100-110/ 5.55-6.1	< 110/ < 6.1	< 110/< 6.1
Postprandial blood glucose (mg dL^{-1} / mmol L^{-1})	< 180/ < 9.99	< 135/< 7.49	< 140/< 7.77	

ADA – American Diabetes Association, IDF – International Diabetes Federation, AACE – American Association of Clinical Endocrinologists and SBD – Brazilian Society of Diabetes.

Diabetic retinopathy (DR) is the leading cause of irreversible blindness in the country and can be classified as absent; mild, moderate, or severe non-proliferative diabetic retinopathy (NPDR); and proliferative diabetic retinopathy (PDR) (Bertoldi et al., 2013). The parameters defining chronic kidney disease (CKD) are the estimated glomerular filtration rate (eGFR) < 60mLmin.$^{-1}$1.73m^{-2} and/or an albuminuria/creatinuria ratio (ACR) ⩾ 30mgg^{-1} (American Diabetes Association, 2018; Pedrosa & Martins, 2016; Satirapoj & Adler, 2015) (see Table 2):

Table 2. CKD prognostic classification.

eGFR stage	Description	eGFR (mLmin.$^{-1}$1.73m^{-2})[a]
G1	Normal or high	⩾ 90
G2	Slightly reduced	60-89
G3a	Moderately reduced	45-59
G3b	Markedly reduced	30-44
G4	Severely reduced	15-29
G5	Renal insufficiency	< 15
ACR stage	Description	ACR (mgg^{-1})
A1	Normal or high	10-29
A2	High	30-299
A3	Too high or nephrotic	⩾ 300

[a]eGFR was calculated by MDRD (Modification of Diet in Renal Disease) formula.

Symmetric polyneuropathy screening is performed to identify the foot at risk of ulceration and amputation (American Diabetes Association, 2018). Treating metabolic comorbidities such as dyslipidemia (DLP) and systemic arterial hypertension (SAH) is essential (American Diabetes Association, 2018; Faludi et al., 2017; Graham, Catapano,& Wong, 2017; Malachias et al., 2016).

DM treatment algorithms (Garber et al., 2018; Milech et al., 2016) recommend caution with use of insulin, glitazones, sulfonylureas and glinides. The use of non-insulin antidiabetic (NIA) drugs such as metformin, GLP-1 (glucagon-like peptide 1) analogues, SGLT 2 (sodium-glucose co-transporter type 2) inhibitors, DPP4 (dipeptidyl peptidase-4) inhibitors and α-glucosidase inhibitors is safer due to lower rates of hypoglycemia (Milech et al., 2016; Garber et al., 2018). Despite these numerous drug options, the Brazilian National List of Essential Medicines (RENAME) established, at the time the study was performed, only metformin, glibenclamide (glyburide) and gliclazide as primary NIA for DM treatment, alongside Neutral Protamine Hagedorn (NPH) and regular (R) insulin types (Almeida-Pititto et al., 2015; Ministério da Saúde, 2013; Ministério da Saúde, 2017). In Brazil, these medications are provided by SUS, which also offers medical supplies for self-monitoring of blood glucose (SMBG) (Coutinho & Silva, 2015).

Despite the high prevalence and economic burden of DM in Brazil, public health policymakers and authorities cannot accurately assess the real needs of these patients (Bahia et al., 2011). That is why the primary objective of this study was to assess the impact of secondary care on glycemic control in patients with DM in Ourinhos-SP and other municipalities of the micro-region, while secondary objectives were to compare baseline and follow-up DM care indicators concerning clinical evaluation and drug treatment regimens in the aforementioned health services, as well as to structure a DM database from those medical records.

Methodology

A retrospective cohort study was performed by reviewing medical records of patients with DM treated at IHT secondary services (AME and Diabetes Association of Ourinhos – ADO) in Ourinhos-SP, Brazil. Both services provide care exclusively by SUS to patients from Ourinhos-SP and 12 other cities of the micro-region.

First, we analyzed baseline data (obtained from initial appointment). After that, we analyzed follow-up data (obtained from final appointment). As specified below, all information deemed necessary regarded clinical evaluation and drug treatment regimens. Excel 2016 and Action 3.0 software were used for all data analysis.

Research Ethics Committee (REC) of Irmandade Santa Casa de Misericórdia de São Paulo approved the research online in Plataforma Brasil website, with Certificate of Presentation for Ethical Appreciation number 05991319.3.0000.5479. In this approval, REC dismissed the authors of obtaining a free and informed consent of participants.

Eligibility criteria

Researchers admitted all medical records with International Classification of Diseases (ICD) belonging to groups E10 and E11 whose appointments were carried out by Endocrinology at AME and ADO from September/2013 to September/2017.

Exclusion criteria

Exclusion criteria were wrongly reported ICD and diagnosis of gestational diabetes mellitus (GDM). The criteria were only observed during the review of the medical records.

Baseline data

We analyzed the following baseline data (obtained from initial appointment): age, gender, city of origin, age at diagnosis of DM, and presence or absence of fasting plasma glucose (FPG), A1C, ophthalmology evaluation and eGFR/ACR tests. Average weight, body mass index (BMI) and abdominal circumference (AC) measurements were obtained, type of DM (type 1 – T1DM, T2DM, LADA or others) was computed, as well as the prevalence of metabolic comorbidities (SAH, DLP, overweight and obesity), concomitant atherosclerotic cardiovascular disease (ASCVD) (myocardial infarction (MI), stroke (S) and others) and amputations by DM.

Current treatment regimens for DM were discriminated in this initial appointment. Patients on insulin therapy had their insulin regimens analyzed as follows: only basal, multiple daily injections (MDI) with or without carbohydrate counting, or continuous subcutaneous insulin infusion (CSII). After that, long/ultra-long-acting and rapid/ultra-rapid-acting insulin types were detailed. For those who did not require insulin therapy, NIA were categorized into monotherapy, dual therapy or triple therapy/more than three NIA classes. After that, NIA classes prescribed to all patients were discriminated.

Follow-up data

We evaluated the number of appointments the patients attended from admission to the final consultation, as well as the time elapsed between patients' initial and last appointments. Staging of microvascular complications was then defined. Mean C-peptide values in those patient groups were also computed.

Afterwards, type of pharmacological treatment in use at the final appointment was analyzed and categorized in the same way as during initial appointment analysis.

For patients whose original reason for referral to AME was other than DM, and whose diagnosis of DM was reached during the consultations, the previously mentioned criteria referred to the period between the first appointment in which DM diagnosis was known and the discharge appointment.

Loss of follow-up was defined for those patients who, despite not having been discharged, no longer attended the appointments, or whose last appointment took place before May/2017 (as the final date considered for analysis of medical records data was September/2017 and four months is the maximum interval set for scheduling return appointments in both services). In these cases of loss of follow-up, the data considered in this study referred to the last appointment the patient attended.

Outcome

After performing baseline and follow-up data analysis, patients whose medical records presented at least two A1C measurements were classified according to the adjustments made in their therapeutic regimen between initial and final appointments, into the following groups: No adjustment – patients that did not require any treatment change. Subtle adjustment – addition of one NIA class. Moderate adjustment – addition of two NIA classes. Intense adjustment – addition of three or more NIA classes and/or prescription of insulin.

For each of these four groups, we evaluated the absolute variation of A1C between initial and final appointments. After that, we compared each group that was submitted to prescription alterations (subtle, moderate, or intense) with the group with no adjustment.

The outcome of this study was a statistically significant A1C reduction (p-value < 0.05) in any correlation between groups of patients submitted to medication adjustments with the group that required no adjustment.

Results

1,137 medical records initially met the inclusion criteria. 15 records were later found to be ineligible during analysis and were then excluded (11 with incorrect DM ICD classification and four cases of GDM), thus leaving 1,122 records.

Baseline data

Table 3 presents baseline clinical evaluation data. The mean age of all individuals was 56.24 years. 65% of DM patients treated in IHT secondary services were women. The mean age of diagnosis of DM was 46.1 years. Average weight, BMI and AC were, respectively, 79.8 kg (considering the 1,034 patients whose weight was evaluated), 30.34 kgm^{-2} (for the 1,010 patients whose BMI was calculated) and 104.9 cm (for the 812 patients whose medical records included this data). Among all the 1,122 medical records, prevalence of SAH and DLP were, respectively, 67 and 57%. Out of the 255 patients with ASCVD (22.72% of all the 1,122 patients), 60.6% had MI and 41.4%, stroke. 2.4% of all individuals had DM-related amputations. There was a higher prevalence of T2DM (85.7%) over other types of DM (7.3% of T1DM, 5.7% of LADA and 1.3% of other types). Only 32% of patients had A1C results collected within three months prior to the initial appointment. 106 of all 1,122 patients (9.44%) had no A1C collection during their appointments. The average initial FPG and A1C values for the remaining 1,016 patients were, respectively, 203.28$mgdL^{-1}$ (11.28$mmolL^{-1}$) and 9.9% (85 $mmolmol^{-1}$). Only 20% of all patients had had an ophthalmology evaluation in the last year, while only 7% had eGFR and ACR from the same period. At initial appointment, there was no information in any of the medical records reviewed about clinical screening for symmetric polyneuropathy performed at UBS.

Table 4 presents baseline drug treatment data. Regarding the treatment regimen being followed at the initial appointment, 26.47% of individuals were using insulin associated with NIA and 11.94% were using only insulin. 56.32% of the patients were only on NIA treatment. A fraction (5.25%) of all patients were on no medication at initial appointment. Among 431 patients (38.41% of 1,122 medical records) on insulin therapy at initial appointment, the predominance of prescriptions was exclusively basal regimen (62.64% of 431 individuals), in combination or not with NIA. Only 36.65% of the cases were on MDI therapy (36.42% on MDI with fixed doses and 0.23% on MDI with carbohydrate counting). 0.46% of all patients were on CSII treatment. Finally, 0.23% of individuals were exclusively on rapid or ultra-rapid-acting insulin. Out of the 428 patients using some long or ultra-long-acting insulin at the initial appointment, 81.54% were treated with NPH insulin, 11.91% with Detemir, 3.27% with 100 units/mL (U 100) Glargine, 0.23% with 300 units mL^{-1} (U 300) Glargine and 2.57% with Degludec. Out of the 161 patients using rapid or ultra-rapid-acting insulin at the initial appointment, 68.32% were treated with insulin R, 21.11% with Aspart, 10.55% with Lispro and none of them with Glulisine. In addition, 0.23% of insulin users were on premixed insulin types at initial appointment.

Among the 632 patients who were not taking any insulin type at initial appointment (56.32% of all 1,122 medical records), the predominant NIA treatment regimen was dual therapy (58.7% of the 632 subjects). Patients under monotherapy accounted for 31.18%. Finally, 10.12% of these individuals were already using triple therapy or more than three NIA classes. Considering that the total absolute number of NIA in use at initial appointment was 1,808 (whether or not patients were on concomitant insulin therapy), 46.9% of these medications belong to

the biguanides class (metformin) and 32.9% to sulfonylureas (23.1% of all patients receiving glibenclamide, 8.2%, gliclazide, and 1.6%, glimepiride). 9.4% of all individuals were using other NIA classes than those two offered by RENAME (1.4% on thiazolidinediones – pioglitazone; 0.2% on GLP-1 analogues – liraglutide; 6.7% on DPP4 inhibitors – alogliptin, linagliptin, saxagliptin, sitagliptin or vildagliptin, 1% on SGLT2 inhibitors – canagliflozin, dapagliflozin or empagliflozin; and 0.1% on α-glucosidase inhibitors – acarbose).

Table 3. Baseline clinical evaluation data.

Socio-demographic data		
Mean age (years)	56.24	
Gender	65% female / 35% male	
Mean age of DM diagnosis (years)	46.1	
Percentage of patients by city of origin	Ourinhos	44.1%
	Santa Cruz do Rio Pardo	18.6%
	Ipaussu	6.3%
	Ribeirão do Sul	4.8%
	Chavantes	4.7%
	Bernardino de Campos	4%
	Salto Grande	3.9%
	São Pedro do Turvo	3.8%
	Óleo	2.6%
	Espírito Santo do Turvo	2.4%
	Canitar	2.2%
	Timburi	1.6%
	Ibirarema	0.5%
	Other (Assis, Cerqueira César, Palmital, Pacaembu and Candido Mota)	0.5%
Clinical data at first appointment		
Average weight (kg)	79.8	
Average BMI (kgm^{-2})	30.34	
Average AC (cm)	104.9	
SAH prevalence	67%	
DLP prevalence	57%	
Overweight prevalence	29.11%	
Obesity prevalence	40.54%	
Amputation prevalence	2.14%	
ASCVD prevalence[a]		
MI	60.6%	
S	41.1%	
Other[b]	4%	
DM types		
T2DM	85.7%	
T1DM	7.3%	
LADA	5.7%	
Other types[c]	1.3%	
Percentage of patients with essential exams at first appointment		
FPG[d]	29%	
A1C[d]	32%	
Ophthalmology evaluation[e]	20%	
eGFR and ACR[e]	7%	

[a]percentages calculated for 255 patients with ASCVD (867 individuals did not present ASCVD). No distinction was made between stroke and transient ischemic stroke, both being computed as stroke. As a same patient may have more than one ASCVD type, the percentages will result more than 100%. [b]other ASCVD: renal artery stenosis (1%), acute arterial occlusion (1%), carotid stenosis (1%), subclavian artery stenosis (0.5%) and previous pulmonary embolism (0.5%). Only cases of stenosis considered as hemodynamically significant by Vascular Surgery were computed in this study. [c]other types: 4 patients (0.36%) with DM induced by corticotherapy, 2 (0.18%) with lipodystrophy, 2 (0.18%) with pheochromocytoma, 1 (0.09%) with post pancreatitis DM and 1 (0.09%) with Cushing's syndrome. [d]FPG and A1C tests collected up to three months before initial appointment were accepted.[e]ophthalmology evaluation and eGFR/ACR performed in the twelve months preceding initial appointment were accepted.

Follow-up data

Table 5 contains follow-up clinical evaluation data. 220 of all 1,122 subjects (19.6%) lost follow-up. For the remaining 902 patients, the mean number of appointments in both services was 3.57 and the mean number of months elapsed between initial and final appointments was 11 months. For the data reported below, the total number of 1,122 medical records remained under analysis. For the cases with loss of follow-up, information was obtained from the last appointment the patient attended.

Table 4. Baseline drug treatment data.

Treatment schemes at initial appointment		
No medication		5.25%
Only NIA		56.32%
Insulin plus NIA		26.47%
Only insulin		11.94%
Insulin schemes at initial appointment[a]		
Only basal		62.64%
MDI		36.42%
MDI with carbohydrate counting		0.23%
CSII		0.46%
Only bolus		0.23%
Percentages of insulin types at initial appointment		
Long or ultra-long-acting insulin types[b]		
NPH		81.54%
Detemir		11.91%
U 100 Glargine		3.27%
Degludec		2.57%
U 300 Glargine		0.23%
Rapid or ultra-rapid-acting insulin types[c]		
R		68.32%
Aspart		21.11%
Lispro		10.55%
Glulisin		None
Percentages of NIA schemes at initial appointment[d]		
Monotherapy		31.18%
Dual therapy		58.7%
Triple therapy or more than three NIA		10.12%
Percentage of NIA classes at initial appointment[e]		
Biguanides (metformin)		46.9%
Sulphonylureas	Glibenclamide (glyburide)	23.1%
	Gliclazide	8.2%
	Glimepiride	1.6%
Glitazones (pioglitazone)		1.4%
GLP-1-analogues (liraglutide)		0.2%
DPP-4 inhibitors	Alogliptin	0.3%
	Linagliptin	1.9%
	Saxagliptin	0.3%
	Sitagliptin	1%
	Vildagliptin	3.2%
SGLT2 inhibitors	Canagliflozin	0.1%
	Dapagliflozin	0.3%
	Empagliflozin	0.6%
α-glucosidase inhibitors (acarbose)		0.1%
Without any NIA class		10.7%

[a]percentages calculated for 431 patients who used insulin at initial appointment. [b]percentages calculated for 428 patients who used insulin at initial appointment. [c]percentages calculated for 161 patients using rapid or ultra-rapid-acting insulin at initial appointment. All CSII users were on Lispro insulin at the moment of evaluation. [d]percentages calculated for 632 patients who did not use any type of insulin at initial appointment (exclusive use of NIA). [e]a same patient can use two or several NIA types (classes). The absolute total number of NIA in use at initial appointment was 1,808, from which these percentages were calculated.

As mentioned previously, 106 of all 1,122 patients (9.44%) had no A1C collection during their appointments. In addition, 446 individuals (39.75%) performed a single A1C collection during the appointments, leaving 570 subjects (50.8% of all medical records analyzed) for whom it was possible to estimate a variation between initial and final values. If we consider those 570 patients with at least two A1C collections during their follow-up, we have an average initial A1C of 10.2% (88mmol/mol) and an average final value of 8.5% (69mmolmol^{-1}), thus corresponding to a mean reduction of 1.7% between both moments.

17% of all patients were not screened for retinopathy, while 32.35% were not screened for diabetic nephropathy. All patients were screened for neuropathy, as this assessment is clinical. 23% of all 1,122 medical records contained patients with DR. If we consider only the 930 patients who were evaluated by Ophthalmology, 27.9% of them had some degree of DR. 24.53% of all 1,122 individuals had eGFR < 60mLmin.-11.73m-2 and/or ACR ⩾ 30mgg-1. When we consider only the 759 patients who had these tests collected, however, 36.36% of them had some degree of CKD. Ultimately, 41% of all individuals whose medical records were reviewed had somatic neuropathy. When comparing initial and final appointments, there was an increase of 63% in ophthalmology evaluations performed during

secondary care approach. 60.65% more individuals were screened for diabetic CKD with eGFR/ACR tests. Finally, there was an increase of 100% in clinical screening for symmetric polyneuropathy. For the 307 patients whose C-peptide measurement was performed, average results were 2.5ngmL-1. Among the 17 patients with T1DM, the average C-peptide was 0.66ngmL-1. Finally, the average C-peptide among 50 patients with LADA was 0.62ngmL-1.

Table 5. Follow up clinical evaluation data.

Data concerning consultations at secondary care services								
Mean number of appointments					3.57[a]			
Mean time between initial and final appointments (in months)					11[a]			
Percentage of patients who missed follow-up					19.6%			
Prevalence of microvascular complications								
Retinopathy			Nephropathy			Somatic Neuropathy		
Stage	Number of patients	%	Stage	Number of patients	%	Stage	Number of patients	%
			Not evaluated	363	32.35%			
Not evaluated			G1A1	232	20.67%			
	192	17%	G1A2	36	3.2%			
			G1A3	6	0.5%			
			G2A1	251	22.37%	Present	460	41%
Absent	670	60%	G2A2	25	2.22%			
			G2A3	9	0.8%			
			G3aA1	71	6.32%			
Mild NPDR	81	7%	G3aA2	21	1.87%			
			G3aA3	7	0.6%			
			G3bA1	32	2.85%			
Moderate NPDR	111	10%	G3bA2	13	1.2%			
			G3bA3	14	1.2%			
			G4A1	7	0.6%			
Severe NPDR	28	2%	G4A2	4	0.4%	Absent	662	59%
			G4A3	21	1.87%			
			G5A1	None	None			
PDR	40	4%	G5A2	None	None			
			G5A3	10	0.9%			
Total	1122	100%	Total	1122	100%	Total	1122	100%
C-peptide average values ($ngmL^{-1}$)								
All C-peptide tests[b]					2.5			
T1DM C-peptide tests[c]					0.66			
LADA C-peptide tests[d]					0.62			

[a]regarding 902 patients (220 missed follow-up). [b]regarding 307 patients whose C-peptide was tested. [c]regarding 17 patients with T1DM whose C-peptide was tested. [d]regarding 50 patients with LADA whose C-peptide was tested.

Table 6 contains follow-up drug treatment data. Regarding the treatment regimen at the final appointment, no patient remained without prescription. 432 patients were using insulin at the initial appointment, while, at the final appointment, this number rose to 628 individuals. It represents therefore an increase of 31.21% in insulin prescription. At the final appointment, no patient was exclusively on rapid or ultra-rapid-acting insulin, 51.28% of the 624 individuals on insulin therapy were only on basal regimen, 45.99% were on MDI with fixed doses, 1.92%, on MDI with carbohydrate counting, and 0.8%, on CSII. Out of the 619 individuals on long or ultra-long-acting insulin at final appointment, 50.08% were treated with NPH insulin, 18.57%, with Detemir, 13.57%, with U 100 Glargine, 1.45%, with U 300 Glargine and 16.31%, with Degludec. Out of the 304 patients using rapid or ultra-rapid-acting insulin at final appointment, 26.61% were treated with insulin R, 65.13%, with Aspart, 5.92%, with Lispro, and 0.32%, with Glulisine. No patient was on premixed insulin at final appointment.

43.93% of all subjects were exclusively on NIA at the final appointment, while 36.89% were using NIA plus insulin and 19.16%, only on insulin therapy. 64 patients were under triple therapy or more than three NIA classes at the initial appointment, while, at the final appointment, this number rose to 233 individuals. It represents therefore an increase of 73.53% on triple therapy or more than three NIA classes prescription. Among the 492 individuals who were not taking any insulin at final appointment, the predominant NIA regimen was triple therapy or more than three NIA classes (47.35%). Patients under monotherapy accounted for 26.21%. Finally, 26.42% of these subjects were using dual therapy. Considering that total absolute number of NIA in use at final appointment was 2,507 (whether or not patients were on concomitant insulin therapy), it was

noted that 30.1% of these medications belong to the biguanide class (metformin) and 24.9%, to the sulfonylureas (0.3% of all patients receiving glibenclamide, 24.3%, gliclazide, and 0.3%, glimepiride). 36.4% of these subjects were on other NIA classes than those two offered by RENAME (5.2% using thiazolidinediones, 1.5% using GLP-1 analogues, 21.6% using DPP4 inhibitors and 8.1% using SGLT2 inhibitors).

Table 6. Follow-up drug treatment data.

Treatment schemes at final appointment		
No medication		None
Only NIA		43.93%
Insulin plus NIA		36.89%
Only insulin		19.16%
Treatment schemes at final appointment[a]		
Only basal		51.28%
MDI		45.99%
MDI with carbohydrate counting		1.92%
CSII		0.8%
Only bolus		None
Percentages of insulin types at final appointment		
Long or ultra-long-acting insulin types[b]		
NPH		50.08%
Detemir		18.57%
U 100 Glargine		13.57%
Degludec		16.31%
U 300 Glargine		1.45%
Rapid or ultra-rapid-acting insulin types[c]		
R		28.61%
Aspart		65.13%
Lispro		5.92%
Glulisin		0.32%
Percentages of NIA schemes at final appointment[d]		
Monotherapy		26.21%
Dual therapy		26.42%
Triple therapy or more than three NIA		47.35%
Percentages of NIA classes at final appointment[e]		
Biguanides (metformin)		30.1%
Sulphonylureas	Glibenclamide (glyburide)	0.3%
	Gliclazide	24.3%
	Glimepiride	0.3%
Glitazones (pioglitazone)		5.2%
GLP-1 analogues (liraglutide)		1.5%
DPP-4 inhibitors	Alogliptin	1.5%
	Linagliptin	6.9%
	Saxagliptin	0.2%
	Sitagliptin	0.8%
	Vildagliptin	12.2%
SGLT2 inhibitors	Canagliflozin	1.2%
	Dapagliflozin	1.4%
	Empagliflozin	5.5%
Without any NIA class		8.7%

[a]percentages calculated for 624 patients who used insulin at final appointment. [b]percentages calculated for 619 patients using ultra-long-acting insulin analogue types at final appointment. [c]percentages calculated for 304 patients using ultra-rapid-acting insulin analogues at final appointment. [d]these values were calculated for 492 patients who were not taking any form of insulin at final appointment (were exclusively on NIA therapy). [e]a same patient can use two or several NIA types (classes). The absolute total number of NIA in use at final appointment was 2,507, from which these percentages were calculated.

Outcome results

Among the 570 patients that presented at least two A1C measurements in the aforementioned medical records review, 146 did not receive any therapeutic adjustment between initial and final appointments, 123 were submitted to a subtle adjustment, 95, to a moderate adjustment, and 206, to an intense adjustment.

Mean A1C values of individuals with no therapeutic adjustment were 10.2% (88mmolmol^{-1}) at the initial appointment and 8.6% (70mmolmol^{-1}) at the final consultation. Patients submitted to subtle adjustments presented mean A1C values at initial and final appointments of 9.2% (77mmolmol^{-1}) and 7.7% (61mmolmol^{-1}), respectively. Individuals that required moderate adjustments in medications exhibited 10% (86mmolmol^{-1}) of initial mean A1C and an average result of 8.3% (67mmolmol^{-1}) at the final appointment. Finally, mean A1C

at the initial and final consultations of patients submitted to intense adjustments were 11.4% (101mmolmol^{-1}) and 9.3% (78mmolmol^{-1}), respectively. Wilcoxon test for paired data showed that those A1C reductions were significant for all groups in isolation (p-value < 0.0001).

Wilcoxon test for independent samples showed more significant A1C reduction between initial and final consultations when the group that received intense therapeutic adjustment was compared to the group that required no adjustment (p < 0.0001). Nevertheless, there was no significant A1C variation when the group submitted to subtle adjustment was compared to the group with no adjustment (p = 0.361), as well as when the group submitted to moderate adjustment was compared to the group that received no adjustment (p = 0.148). Figure1 presents these outcome results.

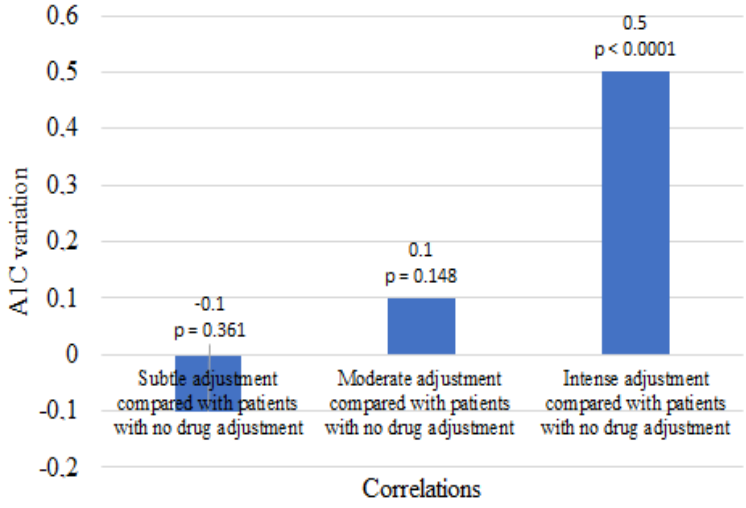

Figure 1. outcome data.

Discussion

This was a retrospective cohort study. Researchers obtained data from medical records of patients with DM treated at IHT secondary services (AME and ADO) in the micro-region of Ourinhos-SP. Data from initial and final appointments of these records were compared and provided a fair evaluation of the evolution and impact of secondary care on clinical and therapeutic indicators.

Initial data highlighted the need for an improved approach to the management of DM among men, implementation of lifestyle change interventions, and an increase in A1C testing, eGFR/ACR screening and ophthalmology evaluation among patients with DM. The findings require a reassessment of the causes of the high percentage of patients who interrupted follow-up. High rates of DR – almost 28% among patients evaluated for the complication – underlined the importance of improving access by ophthalmology among individuals with DM in Ourinhos-SP and micro-region. Prevalence of CKD in these cities (36.36% among patients who were evaluated for the complication) is similar to that presented in the national literature (Bertoldi et al., 2013). On the other hand, the higher rates of neuropathy in our survey compared to other national studies (Bertoldi et al., 2013) suggest the need for a greater focus on implementing measures for adequate glycemic control, and for foot care guidelines for all patients with DM. These potential complications of DM require comprehensive screening in all the evaluated municipalities.

Increase in insulintherapy rates is clear when final prescribing frequencies are compared with distribution of the therapeutic regimen at initial appointment, with an increase of 10.42% in patients using insulin plus NIA and an increase of 7.22% in subjects exclusively on insulin. In addition, insulin regimens at final appointment were more complex, with an increase of 9.57% of MDI with fixed doses, as well as an increase of 1.69% in carbohydrate counting and 0.34% in CSII indication. Compared with therapeutic regimens at initial appointment, prescriptions for all ultra-long-acting insulin increased by 31.92%, while NPH insulin prescriptions decreased by 31.46%, reflecting migration from NPH to ultra-long-acting insulin analogues. Likewise, prescriptions for all ultra-rapid-acting insulin increased by 48.97%, while insulin R prescription decreased by 39.71%. Both timely insulin therapy and an increased use of insulin analogues are recommended by the Brazilian Society of Diabetes (SBD) guidelines (Milech et al., 2016).

The potential effects of the use of glibenclamide (glyburide) on ischemic preconditioning (Loubani, Fowler, Standen,& Galiñanes, 2005) and its prescription for geriatric patients ignoring Beers criteria (Martin, Tamblyn, Benedetti, Ahmed & Tannenbaum, 2018) are alarmingly in contrast with its widespread use in Ourinhos-SP and micro-region. Association between different NIA classes changed from a higher frequency of dual therapy at initial appointment to a predominance of triple therapy/more than three NIA classes at final appointment, as supported by the guidelines presented (Garber et al., 2018; Milech et al., 2016). When comparing NIA classes, there was a 16.8% reduction in prescription of biguanides (metformin), perhaps due to contraindications that might not have been contemplated in primary evaluations. Sulfonylureas prescription also decreased by 8%, with clear change in the profile of the drug in use, characterized by a 22.8% reduction in glibenclamide use and a 16.1% increase in treatment with gliclazide compared to therapy regimens in practice at initial appointment. Prescriptions of all other NIA classes increased between initial and final appointments. There was an increase of 14.9% in DPP4 inhibitors prescription, 1.3% in GLP-1 analogues, 7.1% in SGLT2 inhibitors and 3.8% in thiazolidinediones. An increase in the prescription of these classes is in line with current guidelines (Milech et al., 2016; Garber et al., 2018). Besides, it reflects a trend observed when evaluating the indirect costs of DM treatment and stressed in a study which revealed that 24.6% of patients purchased medication from private pharmacies. The findings highlight the need to discuss enhancing NIA options provided by RENAME (Bahia et al., 2011).

Significant A1C reduction between baseline and follow-up data confirms the positive impact of secondary care approach on glycemic control. Once patients were classified according to the intensity of the therapeutic adjustment made between initial and final appointments, individuals who required no adjustment were deemed potentially treatable at primary health care level. A1C reduction in these patients is most likely due to lifestyle changes and adherence to treatment orientations. Relevant A1C reductions were also observed in all groups of patients that received therapeutic adjustments. Comparison between the groups whose patients were submitted to medication adjustments with the group that required no therapeutic adjustments exhibits the distinctive character of secondary health care for patients with refractory DM, for whom prescription of more complex NIA schemes or insulin introduction is necessary.

Nevertheless, the study has some limitations. First, there was no evolutionary comparison of weight, BMI, and AC between initial and final appointments. The major bias was to analyze services that receive patients whose DM had mostly already proved to be refractory to the medications available in the Brazilian SUS, thus justifying the need to prescribe different types of medication out of the RENAME scope. Another limitation was that the study did not categorize the severity of somatic neuropathy or the extent of amputations, but merely reported its presence or absence. In addition, it did not track several manifestations of autonomic neuropathy. Moreover, NIA and insulin doses in use by patients were not detailed. Lastly, it is important to highlight that a more expressive reduction in A1Cis commonly observed in patients withhigher baseline levels in tests (Esposito, Chiodini, Bellastella, Maiorino,& Giugliano, 2012).

Despite limitations, the study does have its strengths. To the best of our knowledge, no other research has yet provided a more comprehensive review of secondary care in DM in Brazil. It is important to highlight that this was the first study to focus on patients from Ourinhos-SP and municipalities in the micro-region and to evaluate the use of NIA out of the RENAME scope in SUS. Similarly, these efforts go beyond previous reports as this paper considered both clinical evaluation and drug treatment in the Brazilian SUS, something difficult to analyze (Bahia et al., 2011).

Finally, we believe data here obtained are particularly important to implement more effective policies in the SUS for the different levels of DM care. Our database can now extend its effects to Ourinhos-SP and micro-region. Similar studies are certainly required in different regions of Brazil, given its large territory, to be truly representative on a national basis.

Conclusion

Secondary care performed by IHT teams, here considered, improved glycemic control of DM patients, and revealed itself to be important to enhance prescription of more complex NIA classes and timely insulin therapy. This improvement was achieved through a clinical-pharmacological approach of patients and resulted in an expressive increase of microvascular complication screening.

Information obtained during this analysis now structures a regional database for future health planning. Similar studies are certainly required in different regions of Brazil, given its large territory, to be truly representative on a national basis.

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