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ORIGINAL ARTICLE

Poor metabolic control in primary care

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Abstract

Introduction: *Poor metabolic control is a constant in patients with diabetes worldwide, despite resources demonstrated to achieve therapeutic targets. The object of this study was to identify causes of poor metabolic control in patients with diabetes treated in Family Medicine Clinics in metropolitan Mexico City at the Instituto Mexicano del Seguro Social.* **Material and Methods:** *We analyzed 638 of 1,170 patients studied between 2000 and 2006. Anthropometric variables, occurrence of infections, treatment adherence, medical prescriptions, diet, exercise, and laboratory results were recorded.* **Results:** *The proportion of patients with HbA1c < 7% worsened over time: from 38.9% at baseline it decreased to 21.4% (p < 0.001); LDL cholesterol decreased from 51.9 to 12.2% (p < 0.001), and controlled blood pressure from 35.6 to 23.3% (p < 0.001). A diet high in calories was associated with poor metabolic control (OR: 2.36; 95% CI: 1.34-4.13) and treatment intensification with elevated HbA1c (OR: 2.1; 95% CI: 1.14-4.14). Treatment was not intensified in 90% of patients outside targets. Infections, non-adherence, and drugs that interfere with oral hypoglycemic agents were not associated with higher HbA1c.* **Conclusions:** *The main factors associated with higher HbA1c were: disease progression, an inadequate diet, and lack of treatment intensification. Any program designed to improve the conditions of these patients must consider these factors.* (Gac Med Mex. 2016;152:314-20)

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Introduction

Over the past 50 years, the prevalence of diabetes has grown nearly 10-fold[1] to up to 14.4%[2]. Diabetes is the leading cause of death in Mexico[3]. The UKPDS trial showed that one third of patients with diabetes suffer from one chronic complication during the first 10 years of the disease, with half these cases being myocardial infarction; mortality in this period of time was 21%[4,5], and at 20 years of follow-up, at least 30% of the patients would have died[6]. Blood glucose poor control appears to be consistent in the world[7].

Diabetes complications can be prevented when the treatment achieves strict therapeutic goals. The STENO trial showed that with glucose, blood pressure (BP) and lipid control, a reduction of 59% in morbidity and mortality is achieved in a 14-year period[8]. This benefit is extended to long-evolution patients[9]; however, a stricter goal (< 6%) was associated with increased mortality[10].

In Mexicans, only 6% of patients with diabetes are estimated to reach the < 7% A1c goal[11]. This proportion might range from 18 to 20%[12-17] in patients who regularly attend their doctor's appointments, which is still far below the figures reported for similar patients in other countries (50 to 57%)[18-20]

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More recent studies in our country showed that this proportion of patients within blood glucose control target has improved; the ENSANUT 2012 survey showed that 25% of patients reach this goal (A1c < 7%), and a recent study by Pérez Cuevas et al. at the Mexican Institute of Social Security (IMSS – *Instituto Mexicano del Seguro Social*) found this proportion to be 23%. However, there are no reliable data on the proportion of patients reaching other therapeutic goals (BP and LDL cholesterol). On the other hand, it should be pointed out that although the proportion has improved (formerly it was 1%), only in 10% of patients is A1c routinely measured. Early search for chronic complications (screening for retinopathy, microalbuminuria and insensitive foot) is only made in a minority of patients.

This study was conducted with the purpose to estimate the proportion of diabetes-diagnosed patients who reach therapeutic goals and to find out possible causes of poor metabolic control.

Material and methods

To answer these questions, a secondary analysis was performed of a database of 1,170 type 2 diabetes patients who participated in any cohort study in our Research Unit. Only patients who had not participated in interventional trials (n = 638), who had type 2 diabetes according to the American Diabetes association (ADA) and that were within the first 3 years of the disease were analyzed. None of them was being treated with insulin or taking other drugs for the treatment of obesity and all of them belonged to a family care unit of Mexico City's metropolitan area.

All patients were taken a history that included: family history, medications, comorbidities, infections, treatments, adherence, medical appointments, diet, physical activity (standardized questionnaires and medical record) and physical examination. Laboratory tests: A1c, glucose, lipids (LDL, HDL, triglycerides), creatinine, microalbuminuria, with the usual techniques, and electrocardiogram, electromyography (neuroconduction velocity), retinal stereoscopic photograph (7 fields/eye that were assessed with the modified Ayre scale).

The proportions of patients who had achieved therapeutic goals (A1c < 7%, systolic BP < 130 mmHg and diastolic BP < 80 mmHg and LDL cholesterol < 100 mg/dl)[21,22] were estimated for the 2000-2003 and 2006-2009 periods. Additionally, the proportion of patients in compliance with the ADA recommendations on nutritional medical therapy and physical activity was estimated, as well as the possible association of goals' achievement with:

- Treatment adherence: With a questionnaire asking the patient how often did he/she forget to take his/her medications. This questionnaire was previously validated with a visit to the patient's domicile, where the doctor´s prescription was contrasted with the medications remaining in the original container.
- Caloric contents of the diet: Average calories/day intake was estimated using a semi-quantitative food consumption questionnaire that was previously validated for this purpose in Mexico City[23]. In addition, the "appropriate weight" was estimated; i.e.; with the patient´s height, the weight he/she should have to reach a body mass index (BMI) below 24.9 kg/m^2 was calculated. Caloric content of the diet was regarded as being appropriate if average daily consumption did not exceed 30 kcal/kg "appropriate weight" when the BMI was < 25 kg/m^2, and if it was ≥ 25 kg/m^2, average daily consumption should not exceed 25 kcal/kg "appropriate weight".
- Presence of infections over the past year: Based on a questionnaire that inquired on the presence of fever episodes and upper airway (cough, expectoration, etc.) and urinary tract (dysuria, urgency, etc.) symptoms, urinalysis result (leukocytes, nitrites, etc.), gastrointestinal symptoms (diarrhea) and in women leukorrhea, itching, etc. None of these infections was corroborated with cultures.
- Drug interactions: Patients taking the following drugs with known interactions with oral hypoglycemic agents were recorded: barbiturates, rifampicin, thiazides and loop diuretics, steroids, estrogens, diphenylhydantoin and β-blockers.
- To assess if the oral hypoglycemic agents prescription was appropriate, the A1c value of a period of at least 3 months was used. In this period, an evaluation was made for prescription changes. Patients were considered to be within the targeted goal when the A1c concentration was < 7%, regardless of the drug, and off-goal with A1c higher values.

Results

Six hundred and thirty-eight patients were studied, out of which 435 were women (68.2%); average age was 51.8 ± 10.6 years, with an average time of evolution of 1 year ± 11 months, and 301 patients (47.2%) had been diagnosed within the previous 6 months. Average BMI was 30.3 ± 4.8 kg/m^2. Among all patients,

Table 1. Patient demographics

Characteristic	2003	2006
Age (years)	51.8 (± 10.6)	57.3 (± 10.6)
Sex		
Females	435 (68.2%)	435 (68.2%)
Males	203 (31.8%)	203 (31.8%)
Time since diagnosis		
0-6 months	301 (47.2%)	
6-35 months	309 (48.4%)	–
≥ 36 months	28 (4.4%)	
Body mass index	30.3 (± 4.8)	29.5 (± 5)
< 25	68 (10.7%)	103 (16.1%)
25-29.9	260 (40.8%)	269 (42.2%)
≥ 30	310 (48.6%)	266 (41.7%)
Body weight	72.8 (± 12.3)	71.2 (±12.5)
Chronic complications:	242 (37.9%)	
Cardiovascular		
Myocardial infarction	51 (8.0%)	
Stroke/TIA	45 (7.05%)	
Arrhythmias	8 (1.2%)	
Heart failure	20 (3.1%)	
Angina pectoris	13 (2.0%)	
Intermittent claudication	1 (0.1%)	
Microvascular		
Retinopathy	37 (5.7%)	
Nephropathy	32 (5.0%)	
Neuropathy	68 (10.6%)	

Frequency and (percentage) are shown.

57.4% had hyperglycemia symptoms, and the median of these symptoms (polyuria, polyphagia, polydipsia, fatigue, blurry vision) was 2.4 symptoms/patient. Seventy-five of them had some comorbidity (median: 2.6 additional diagnoses/patient), 41% were hypertensive and 62.6% were treated with oral hypoglycemic drugs. The dietetics department had been attended by 73.8% at least once. In the initial study, at least one chronic complication was detected in 38% (Table 1).

Average A1c concentration in the 2000-2003 period was 8.1 ± 2.6% and for the 2006-2009 period, it was 8.9 ± 2.2% ($p < 0.001$). In these same periods, LDL cholesterol concentrations were 101 ± 29 mg/dl and 137 ± 35 mg/dl ($p < 0.001$). Systolic BP average values were 120 ± 15 mmHg and 134 ± 22 mmHg ($p < 0.001$), and for diastolic BP, 76.4 ± 7.9 mmHg and 78.3 ± 10.8 mmHg ($p < 0.001$), respectively.

Table 2 shows the proportions of patients reaching different therapeutic goals. In the initial period, the A1c goal was achieved in 38.9% and, in the follow-up, it was only achieved in 21.4% ($p < 0.001$); the LDL cholesterol goal, in 51.9 and 12.2% ($p < 0.001$); and the BP goals, in 35.6 and 23.3% ($p < 0.001$), respectively. No significant changes were detected in the proportion of patients who consumed a recommendable amount of calories/day, but some qualitative aspects of the daily diet did improve (less fat, saturated fat and cholesterol). The proportion of patients who consume recommendable amounts of vegetal fiber was very low and only one third of the patients practiced the recommendable physical activity (the latter, was only measured in the first period).

Diet adherence: 216 (87.1%) patients with A1c < 7% and 367 (94.1%) patients with A1c ≥ 7% consumed a diet with inadequate caloric content in the initial period, OR: 2.36 (1.34-4.13); $p = 0.003$ (Table 3).

Treatment adherence: 230 (97.2%) and 351 (90%) patients within the targeted goal (A1c < 7%) or off-goal (A1c ≥ 7%) referred always or nearly always taking their medications (this corresponds to a consumption of at least 80% of their medications, OR: 0.97 [0.75-1.27]; $p = 0.873$).

Drug interactions: 39 (15.7%) patients within the targeted goal (A1c < 7%) and 48 (1.3%) off-goal (A1c ≥ 7%)

Table 2 . Metabolic control parameters

Parameter	2003 n (%)	2006 n (%)	p
A1c (< 7%)	248 (38.9)	137 (21.4)	0.001
LDL-C (< 100 mg/dl)	331 (51.9)	78 (12.2)	0.001
BP (< 130/80 mmHg)	499 (78.2)	299 (46.9)	0.001
Nutrients			
+ Carbohydrates (50-55%)	97 (15.2)	142 (22.3)	0.001
+ Protein (≥ 15%)	327 (51.3)	445 (69.7)	0.124
+ Fat (< 30%)	376 (58.9)	378 (59.2)	0.904
+ Saturated fat (≤ 7%)	141 (22.1)	207 (32.4)	0.001
+ Cholesterol (< 200 mg/day)	121 (19.0)	203 (31.8)	0.001
+ Fiber (≥ 14 g/1,000 kcal)	4 (0.6)	0 (0.0)	0.045
Body weight	72.8 (± 12.3)	71.2 (± 12.5)	

Frequency (n) and percentage (%) are shown.

Table 3. Factors associated with metabolic control

Indicator	A1c < 7% n (%)	A1c ≥ 7% n (%)	p	OR (95% CI)
Treatment adherence	230 (92.7%)	351 (90%)	0.873	0.979 (.75-1.27)
Drug interaction	39 (15.7%)	48 (1.3%)	0.221	0.752 (.47-1.18)
Inadequate caloric consumption (2003)	216 (87.1%)	367 (94.1%)	**0.003**	2.36 (1.34-4.13)

Frequency (n) and percentage (%), odds ratio (OR) and its corresponding 95% confidence interval (CI) are shown.

referred taking drugs that interact with the treatment, OR: 0.75 (0.47-1.18); p = 0.221.

Infections: 162 (65.3%) patients with an A1c concentration < 7% and 280 (71.8%) with an A1c concentration ≥ 7% reported some infection within the last year, OR: 1.35 (0.96-1.90); p = 0.85. Table 4 shows patient-reported infections, by type of infection; only vaginal infections (27 vs. 35.1%) were associated with higher A1c concentration (Table 4).

Appropriate drug prescription: 59.2 and 71.9% of the patients received drug treatment in both observation periods. The rest reported being treated with diet and exercise. Table 5 shows patient's control according to the treatment they received (monotherapy, combination therapy, insulin) and whether they received the maximum or lower than maximum, for both observation periods. The proportion of patients assigned to the different treatment modalities changed significantly (p < 0.001)

Table 4. Infections

Infection	A1c < 7% 248 (38.8%) n (%)	A1c ≥ 7% 390 (61.1%) n (%)	p	OR (95% CI)
Urinary tract	99 (39.9%)	170 (43.6%)	0.360	1.16 (.84-1.60)
Vaginal	67 (27%)*	137 (35.1%)*	**0.033**	1.46 (1.03-2.07)
Airway	78 (31.5%)	125 (32.1%)	0.874	1.02 (.73-1.44)
Gastrointestinal	18 (7.3%)	28 (7.2%)	0.970	0.988 (.53-1.82)
Any infection	162 (65.3%)	280 (71.8%)	0.85	1.35 (.96-1.90)

Frequency (n) and percentage (%), odds ratio (OR) and its corresponding 95% confidence interval (CI) are shown.
*p < 0.05

Table 5. Prescription

Treatment	2003		2006	
	A1c < 7% 248 (38.8%) n (%)	A1c ≥ 7% 390 (61.1%) n (%)	A1c < 7% 137 (21.4%) n (%)	A1c ≥ 7% 501 (78.5%) n (%)
Monotherapy	100 (40.3%)	206 (52.8%)	48 (35%)	129 (25.7%)
Sub-maximum dose	97 (97%)	177 (85.9%)	48 (100%)	119 (92.2%)
Maximum dose	3 (3%)	29 (14.1%)	0	10 (7.8%)
Oral combination therapy	11 (4.4%)	57 (14.6%)	29 (2.1%)	198 (39.5%)
Sub-maximum dose	11 (100%)	50 (87.7%)	25 (86.2%)	162 (81.8%)
Maximum dose	0	7 (12.2%)	4 (13.8%)	36 (22.2%)
Insulin alone or combined	0	4 (1%)	3 (2.2%)	52 (10.3%)
Treatment	111 (44.8%)	267 (68.4%)	80 (58%)	379 (75.6%)
Without treatment	137 (55.2%)	123 (31.6%)	57 (41.6%)	122 (24.4%)
Treatment intensification made	13 (5.2%)	42 (10.7%)	7 (5.1%)	45 (9%)

Frequency (n) and percentage (%) are shown.

between both periods. However, and judging by the A1c concentration, 61.1 and 78.5% of patients required some treatment adjustment (starting drugs, increase to maximum dose, adding another drug or insulin). In summary, treatment intensification was made in 13 (5.2%) patients with A1c < 7% and in 42 (10.7%) patients in the year 2003 (p = 0.015) and in 7 (5.1%) patients with A1c < 7% and 45 (9%) patients with A1c ≥ 7% (p = 0.129) in the year 2006.

Discussion

The main causes of poor metabolic control that we observed in this analysis were disease progression, inadequate nutrition and failure to opportunely intensify drug treatment.

Diabetes is a progressive disease[24,25], and our observations confirm that fact, since, in the course of a few years, average A1c increased and the proportion of patients reaching therapeutic goals (A1c < 7%) was reduced by 17%. Worsening of LDL cholesterol concentration and BP was also observed. For this reason, modern treatment of diabetes includes therapeutic goals frequent verification and appropriate treatment adjustments as many times as it is required.

Another relevant point is the absence of non-pharmacological interventions. Our patients' usual diet was characterized by an excessive consumption of energy. Previous studies have shown that, with adequate nutritional counseling, A1c can be reduced by 1 to 2%[26]. The participation of nutrition professionals has an impact, but it is more of a qualitative nature, since patients consume less and higher-quality fat, although, 5 years post-diagnosis, energy intake was still excessive.

Diabetes-care programs should offer nutritional counseling with efficacious techniques[27-29]. The lack of an efficacious program for the management of non-pharmacological measures is acknowledged to be one of the most important deficiencies in diabetes-care programs[30]. It should be pointed out that this part of the treatment is the patient's responsibility[31,32].

Institutional basic formularies have hypoglycemic agents available. Pioglitazone is limited to specialists, but it is within reach for general practitioners by means of a transcription procedure. Sub-optimal treatment of these patients cannot be attributed to a lack of therapeutic options. In our system, patients are not required to make out of pocket expenditures to obtain their medications[33].

Our data show that, over time, general practitioners made treatment adjustments, but not with the required intensity or frequency. The ADOPT trial showed the probability of secondary failure in a period of time similar to that of our observations[34]. The delay to intensify treatment has been estimated to be between 1 and 5 years[35-37]. Therapeutic inertia is the absence of modifications to a treatment plan that is not being effective in the control of a chronic condition[38,39], and it is not limited to pharmacologic treatment, since other important preventive measures, such as referral to the ophthalmologist, are also delayed[40]. It relates to attitudes, fear of adverse effects and inexperience of both the

physician[41,42] and the patient[43]. The doctor is an important player in the achievement of therapeutic goals[44]; specialists are not much better than first-contact physicians[45] in this regard, and some measures have been proposed to solve this problem[46]. It should be noted that, although treatment intensification was twice as frequent in patients with A1c ≥ 7%, and that this difference was statistically significant, this only happened in 10.7% of cases, when it should have happened in all of them. This way, in 89% of the patients who required treatment intensification (dose increase, addition of new drugs, start insulin), it was not done. As the disease advances, the proportion of off-therapeutic goal patients in whom treatment was intensified was a little lower and showed no statistical significance.

Other possible causes of poor control showed minor effects: infections, in general, were not more frequently associated with poor metabolic control when it was assessed by means of A1c, although this did occur in the cases of vaginal infection. We attributed this to the fact that most infections occur in an acute form[2] and are likely to be self-limited or to receive opportune treatment[48], whereas vaginal infections are usually sub-acute and not always opportunely detected and treated[49,50]. Additionally, these infections might be bilaterally related to poor metabolic control, i.e, one increases the risk for the other[51].

Medication non-adherence has been associated with poor control, more hospitalizations and visits to the emergency room and higher mortality[52]. It should be noted that the measurement of treatment adherence is complex and the questionnaire has not been the most sensitive measuring tool[53]. Although this questionnaire showed high concordance with the doctor's prescription and the remaining tablets (the cutoff point corresponds to 80% adherence to the prescription). However, in this case we think the problem is not related to non-adherence, but rather to insufficient prescription by the physician.

There are drugs that can interfere with the medications' mechanism of action[54,55]. We expected for a proportion of patients to be out of control for this reason. The proportion of controlled patients who took this type of drugs was higher, but the difference was not statistically significant.

In conclusion: An elevated proportion of patients who are attended to in primary care fail to reach the therapeutic goals of treatment. The main causes of the problem are related to the nature of the disease and the progressive loss of pancreatic reserve, inefficacious programs for non-pharmacological treatment and delay in pharmacological treatment intensification.

In order to achieve efficacious and quality medical care, programs focused on the care of diabetes should consider how to solve these problems.

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