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Clinical inertia in insulin prescription for patients with type 2 diabetes mellitus at a primary health care institution of Cartagena, Colombia

Inercia clínica en la prescripción de insulina en pacientes con diabetes mellitus tipo 2 de una institución de baja complejidad en Cartagena de Indias, Colombia

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| Abstract |

Introduction: Evidence has demonstrated clinical or prescriptive inertia along with an increased prescription of insulin, causing a delay in the change of prescription.

Objective: To determine the prescription pattern and clinical inertia of insulin use in the treatment of patients with type 2 diabetes mellitus (DM2) enrolled in a diabetes program at a primary health care institution of Cartagena, Colombia.

Materials and methods: Pharmacoepidemiology study that addresses drug utilization based on data collected through a review of medical records of 331 patients with DM2, aged 18 and older, who had at least 6 months of control.

Results: 64.4% of patients were treated with long-acting insulin analogues and 18.4% used insulin; 52.7% of the patients in which insuline use was required did not have a prescription of this drug.

Conclusions: There is clinical inertia related to insulin prescription. Strategies should be implemented to overcome prescriptive inertia for people with DM2 in order to achieve therapeutic goals earlier and effectively prevent the development and progression of chronic complications.

Keywords: Diabetes Mellitus Type 2; Insulin; Therapeutic Uses; Drug Prescriptions; Drug-related side effects and adverse reactions (MeSH).

| Resumen |

Introducción. Paralelo al aumento de la prescripción de la insulina se ha demostrado la inercia clínica o prescriptiva, de tal manera que la demora en cambiar la prescripción es prolongada.

Objetivo. Determinar el patrón de prescripción y la inercia clínica en la utilización de insulina al momento de estar indicada en el tratamiento de los pacientes con diabetes mellitus tipo 2 (DM2) que acuden a un programa de diabetes en una institución de baja complejidad de Cartagena, Colombia.

Materiales y métodos. Estudio de farmacoepidemiología dirigido al campo de los estudios de utilización de medicamentos que se basó en datos recogidos mediante la revisión de historias clínicas de 331 pacientes con DM2, mayores de 18 años y que tuvieran mínimo 6 meses de control.

Resultados. El 18.4% de los pacientes utilizaron insulina. 64.4% fueron tratados con análogos de insulinas de acción prolongada. 52.7% de los pacientes con indicación de insulina no tenían prescrito el fármaco.

Conclusiones. Existe inercia clínica para la prescripción de insulina. Se deben implementar estrategias que superen la inercia prescriptiva para que las personas con DM2 alcancen tempranamente las metas terapéuticas y prevengan de manera efectiva el desarrollo y la progresión de complicaciones crónicas.

Palabras clave: Diabetes mellitus tipo 2; Insulina; Indicación Terapéutica; Prescripción de medicamentos; Inercia; Efectos colaterales y reacciones adversas relacionados con medicamentos (DeCS).

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Introduction

The International Diabetes Federation (IDF) estimated that the regional prevalence of diabetes in 2015 was 9.4% among adults aged between 20 and 79 years in South and Central America. The increase of number of cases expected for 2040 is greater in these countries than in other areas, since 48.8 million cases are expected by then. Prevalence for Colombia, as reported in the seventh edition of the IDF Diabetes Atlas for the age-group 20-79 years is 9.6%, which provides an approximate figure of 3.04 million people with diabetes mellitus type 2 (DM2). (1)

Diabetes mellitus is a chronic disease that, if not treated early and properly, generates complications basically because of the poor control of glycemia and the years of evolution of the disease. Good control of diabetes eliminates symptoms, avoids acute complications and reduces the incidence and progression of chronic microvascular complications. Adding adequate control of other associated problems, such as high blood pressure and dyslipidemia, also prevents macrovascular complications; such prevention has proven to be cost-effective. (2,3)

Along with the epidemic of diabetes observed nowadays around the globe, a remarkable increase in the use of anti-diabetic drugs has also been reported in the last decades. The 57% increase in the use of insulin reported by the Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency of Medicines and Medical Devices) in Spain between 2000 and 2014 is particularly striking. (4)

As the prescription of insulin increases, clinical or prescriptive inertia, understood as the delay in the modification of the pharmacological treatment when the recommended therapeutic goals are not met, has also been reported. In this regard, HbA1c $\geq 8\%$ values prove that there is a delay in the change of prescription, amounting up to nearly 9 years when insulin is required. (5,6)

Most patients with DM2 are treated exclusively by general practitioners, with an average of eight consultations per year. Several studies have confirmed that the prescription of insulin in primary care services is very low, with a range of 6-20%, and that the combination of oral therapy with insulin is also underutilized between 0% and 6%. (7,8)

Although insulin therapy is the most effective therapy, and even treating physicians accept its benefits, there is reluctance to prescribe insulin and prefer to initiate this treatment only "when necessary or absolutely essential." The barriers reported by physicians for the initiation of insulin are: 1) concern about adverse events, 2) considerations about the difficulty of use by the patient, 3) limited time to provide education in insulin therapy, and 4) inadequate training to start and continue insulin treatment. (9-12)

Hypoglycemia is common in patients with DM2; about 90% of all patients receiving insulin have experienced an episode of this type. (13) In view of this adverse event, clinical inertia is demonstrated based on the low percentage of primary care physicians who intensify drug treatment due to the lack of achievement of the expected goals, and a lower tendency to initiate insulin, even with elevated HbA1c values, showing little familiarity with insulin prescription. (14)

Hypoglycemia caused by insulin can be potentially avoidable, since education can reduce this index; adequate monitoring of blood glucose is also crucial for safe prescription. (15) These episodes can lead to lack of adherence to the treatment, which implies greater likelihood of worsening of the disease, increased health expenses and decreased quality of life in chronic patients. (16)

The drugs included in the Health Benefits Plan of the country for patients with DM2 treated by general practitioners are only metformin, glibenclamide and insulins (human and analogous). With the advent of MIPRES (Application for Reporting the Prescription of Services and Technologies not Covered by the Benefit Plan), patients of the

contributory scheme have access to medications that are not covered by the Capitation Payment Unit, while patients of the subsidized health scheme do not have access to this broad coverage.

All insulin analogues are available in Colombia and have new pharmaceutical forms in order to improve their administration and allow flexibility in daily administration, simplifying the dosage regimen.

The specific moment when insulin therapy should be initiated can be difficult to determine for each person, since there are no universal clinical guidelines. Indications for the initiation of insulin include non-achievement of goals with oral antidiabetics, contraindication of oral antidiabetics, ketonuria, ketoacidosis, acute hyperglycemic decompensation or marked hyperglycemia: fasting glycemia >250 - 300 mg/dL, HbA1c >9 - 10% . (17-22)

The objective of this study was to determine the prescription and clinical inertia pattern in the use of insulin at the time of indication in the treatment of patients with DM2 enrolled in a diabetes program of a primary health care institution of Cartagena de Indias, Colombia.

Material and methods

This is a pharmacoepidemiology study that specifically addresses descriptive studies on drug use, based on data collected after reviewing the medical records of patients with DM2, and over 18 years of age, who were enrolled in a diabetes care program during 2013 and 2014 for a minimum of 6 months of control in a primary health care institution. The population is composed of 1 340 patients and the investigation was approved by the Research Office of the Empresa Social del Estado Hospital Local Cartagena de Indias, which serves for the pertinent purposes as an institutional ethics committee by means of minutes issued on March 30, 2016.

With an expected prevalence of 50%, an error of 5% and a confidence interval of 95%, the sample obtained included 384 medical records. Since this was a finite population, the sample size was adjusted for a total of 299 clinical records. When adding 10% to cover losses, the final sample was 331. For sample selection, a simple random sampling of the list of patients was made using the tool Sample of Microsoft Excel. Data were collected through an instrument that investigated the pattern of insulin prescription and the adequacy of drug prescription, determining whether there was an indication for the use of insulin and prevention of adverse effects of the drug.

Based on the DM2 care guidelines of the Ministry of Social Protection, the institution defined that insulin prescription is indicated when the goals are not achieved using oral anti-diabetics, as a contraindication of anti-diabetics, in patients with weight loss or tendency to ketosis, when ketonuria or fasting glycemia >250 mg/dL and HbA1c $>9\%$. (19,20,22-24)

The established target for glycemic control was HbA1c $\leq 7\%$, as defined in the DM2 care guidelines used in Colombia, adopted at the respective institution and in force at the time of care. (21,24) Education on hypoglycemia was considered as performed when two parameters were found in the clinical records: education on the identification of hypoglycemia symptoms and prescription of glucometer, strips and lancets.

The data were stored in a Microsoft Excel spreadsheet and the analysis was carried out using the statistical program SPSS version 21.0. Statistical analysis yielded tables reporting absolute and relative frequencies, as well as measures of central tendency and dispersion for quantitative variables.

Results

61.3% (n=203) of the study population were females and the average age was 54.3 years ($\sigma=12.2$). 73.7% (n=244) of patients with type

2 diabetes had BMI ≥ 25 kg/m² and only 1.5% (n=5) had BMI < 18.5 kg/m². 63.1% (n=209) had data on HbA1c in their medical records and 20% had no urinalysis reports. Of 263 patients with urinalysis reports, none had ketonuria (Table 1).

Table 1. Characteristics of patients with type 2 diabetes mellitus included in the study. Cartagena de Indias, Colombia.

Characteristics		n	%
Sex	Female	203	61.3
	Male	128	38.7
Body Mass Index	Underweight	5	1.5
	Normal weight	82	24.8
	Obesity	117	35.3
	Overweight	127	38.4
Information on HbA1c	No	122	36.9
	Yes	209	63.1
Urinalysis report	No	68	20.5
	Yes	263	79.5
Total		331	100

Source: Own elaboration.

18.4% (n=61) of patients used insulin, regardless it was long-acting, intermediate-acting, rapid-acting or ultra-rapid. The most widely used basal insulin was glargine, as its use was reported in 57.6% (n=34) of the patients requiring this type of insulin. 62% (n=38) of patients were treated with long-acting insulin analogues (glargine and detemir), while 34% (n=21) received NPH insulin as basal insulin. Crystalline insulin was the most used as prandial insulin (Table 2).

Table 2. Prescription pattern in patients with type 2 diabetes mellitus included in the study. Cartagena de Indias, Colombia.

Type of prescription		n	%
Basal insulin	Detemir	4	6.6
	Glargina	34	55.7
	NPH	21	34.4
	No basal insulin	2	3.3
Prandial insulin	Aspart	3	4.9
	Crystalline	10	16.4
	Glulisine	5	8.2
	Non-prandial	43	70.5
Total		61	100

Source: Own elaboration.

It was found that 39% (n=129) of the clinical records evaluated showed some indication for the initiation of insulin treatment, either definitively or temporarily. Among patients with insulin indication, only 47.3% (n=61) were prescribed insulin.

In decreasing order, the main conditions indicated for the initiation of insulin therapy were: fasting glucose > 250 mg% (54.3%), HbA1c

$> 9\%$ (24%), contraindicated oral anti-diabetics (17.9%), symptomatic patients with weight loss (15%) and failure to achieve HbA1c goals despite the use of the two oral anti-diabetics available in the mandatory health plan (metformin and glibenclamide) (11.6%) (Table 3).

Table 3. Conditions that indicate insulin prescription in patients with type 2 diabetes mellitus included in the study. Cartagena de Indias, Colombia.

Indications	n	%
Fasting glucose > 250 mg%	70	54.3
HbA1c $> 9\%$	31	24.0
Oral anti-diabetics contraindicated	23	17.9
Symptomatic patients and weight loss	20	15.5
Failure to achieve HbA1c goals	15	11.6

Source: Own elaboration.

Of 61 patients with insulin prescription, only the clinical records of 52.5% (n=32) reported receiving education to identify hypoglycemia early and the prescription of the glucometer kit.

Discussion

Exposure to chronic hyperglycemia leads to glucotoxicity in several cells; there is a strong correlation between toxicity and vascular endothelial dysfunction, particularly damaging endothelial cells in the capillaries of the retina, the mesangial cells in the renal glomerulus, and the microvasculature that supplies the nerves. (25)

Strict glycemic control of diabetes is fundamental to prevent micro and macrovascular complications that increase the economic burden for the health system and affect healthy life years in these patients. (26) In addition, it has been evidenced that early and effective insulin intervention is important because inhibiting glucotoxicity and decreasing the onset of complications may be beneficial to preserve functional beta-cell mass. (27,28)

The percentage of patients who used insulin was 18.4%, which is relatively similar to the figures reported in Colombia by Villegas *et al.* (29) and Machado-Alba *et al.* (30): 19.6% and 23.5%, respectively; it is worth noting that these authors included patients with type 1 and type 2 diabetes (10.5% and 4.9%, respectively).

A figure of 18.4% of insulin use is higher than that found in Italy by Pellegrini *et al.* (31), who reported 15.3% among patients attended by general practitioners, but lower than Machado-Duque *et al.* (32) with 26.1% in Pereira in a retrospective cohort followed up for 5 years, and than Alba *et al.* (33), who reported a 54% use of insulin in a study conducted in Bogotá with patients of a university hospital program.

With this in mind, it can be said that due to the difference in the inclusion criteria, the follow-up time and the scope of the studies, an exact comparison cannot be performed. However, despite the difficulties, it is possible to conclude that there is a low prescription rate of insulin in the diabetes care program studied here.

Currently available insulin analogs offer the same clinical effectiveness as conventional human insulins, with benefits in terms of hypoglycemia and less weight gain. Basal insulin analogues are preferred over NPH insulin because a single dose of insulin provides a lower serum insulin concentration for about 24 hours, resulting in significantly less hypoglycemia. (18,34)

A change in the prescription pattern of insulins has been observed worldwide, as the use of long-acting drugs analogous has

increased, causing the detriment of intermediate-acting and human-derived insulins. (4,35) The use of long-acting insulin analogues is predominant with 64.4%, and an a significant use of ultrafast-acting insulin analogues is also observed, which shows that the percentage of use of insulin analogues is increasing since their introduction in the mandatory health plan.

To support the positive aspects of this change in insulin prescription trends, a reduction in the risk of nocturnal hypoglycemia with the use of long-acting insulin analogues compared to NPH insulin has been reported by the literature, as well as a lower risk of hypoglycemia with ultra-fast insulin analogs compared to crystalline insulins. (36,37)

Regarding the increase of anti-diabetics prescription, a greater percentage increase of oral anti-diabetics is observed in relation to insulin; this could be related to the clinical inertia of physicians, who unjustifiably delay the initiation of insulin therapy. Primary care physicians state that they feel safer using oral anti-diabetics; therefore the prescription of the hormone is late and at a very low percentage, as only 6-20% of patients with DM2 are treated with it. In addition, an average delay in the initiation of insulin between 7.7 and 9.2 years is observed in cases in which it is required. (5,38)

The United Kingdom Prospective Diabetes Study (UKPDS) revealed that only 33% of patients treated with metformin and sulfonylureas had HbA1c <7% after 3 years of treatment. (39) It reports 18.4% of patients with insulin prescription, but the most interesting thing about said study is that 52.7% of patients with some insulin indication had not been prescribed, proving the inertia in the prescription of this drug for the patients treated by the program.

The Collaborative Drug Therapy Management Service shows that the introduction of insulin in patients with HbA1c >9% improves glycemic control and that it is less frequent than recommended. (40) In the UKPDS, each year, about 3% of patients treated with insulin experience a severe episode of hypoglycemia; in addition, 40% had an episode of hypoglycemia of any degree of severity. (37) The prevention of hypoglycemia requires some major considerations, including the appropriate use of capillary blood glucose monitoring and self-management supported by education. Furthermore, the patient needs to be well informed about the risk factors for hypoglycemia, its symptoms, prevention and treatment, and must constantly monitor glucose; consequently, education on hypoglycemia is fundamental to prevent this complication. (13)

No information regarding education on hypoglycemia or prescription of a glucometer kit was found in 47.5% of the clinical records evaluated. It is necessary to consider the possibility that these activities have been carried out and not reported; however, it should be noted that the professionals of this institution have limited time for conducting these educational strategies and there is no educational support provided after the medical consultation.

Following this train of thought, and considering all the reasons for the low prescription of insulin, this scenario leads to inadequate control of diabetes and is one of the causes of the onset of complications. Insulin is traditionally the last therapeutic option, and once it is initiated, complications have already appeared. Therefore, it is necessary to sensitize clinicians on the importance of initiating insulin in a timely manner.

These findings confirm the need to implement strategies that overcome the prescriptive inertia for patients with DM2 to reach early therapeutic goals and effectively prevent the development and progression of chronic complications. Given that greater inertia in the prescription of insulin has been observed, these strategies should place special emphasis on their proper use in a timely manner.

A limitation of the study was that a significant percentage of patients did not have HbA1c or ketone urine tests, so the number

of patients who would have an insulin indication for glycosylated hemoglobin >9% or ketonuria could be higher. The duration of the disease in patients attending this program is unknown. The longer it takes to diagnose the disease, the greater the need for insulin.

Conclusion

Adequate metabolic control in type 2 diabetic patients decreases the incidence of complications. Using all therapeutic options available is fundamental to achieve good control; insulin is the most effective medication and should be used without delay in all patients with this indication. Therefore, it is very important to educate primary care physicians on specific indications. It is imperative to provide training by disclosing the advantages that the Colombian health system has when making available all the types of insulin covered by the health plan.

Conflicts of interest

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WILLIAM SMELLIE, M.D. (1754)

*"A Sett of Anatomical Tables with explanations and an
abridgement of the Practice of Midwifery"*