ORIGINAL ARTICLE
ARTIGO ORIGINAL

Reduction of glycated hemoglobin (HbA_{1c}) and cost analysis of treatment with insulin analogues in the state of Paraná: a retrospective cohort study

Redução de hemoglobina glicada (HbA_{1c}) e análise de custo do tratamento com análogas insulinas no estado do Paraná: estudo de coorte retrospectivo

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DOI: 10.21115/JBES.v8.n3.p221-226

Keywords:
Diabetes mellitus type 1, treatment outcomes, costs and cost analysis, insulin, comparative effectiveness research

ABSTRACT

Objective: Diabetes mellitus (DM) is a serious public health problem in Brazil. The goal of this study was to evaluate the effectiveness of long-acting insulin analogues in controlling glycemia in type 1 DM patients and to analyze the direct costs of the treatment. **Methods:** A retrospective cohort study was undertaken with data collected from the State Health Secretary's 2nd Regional Health Center from the State of Paraná. After randomization, socio-demographic data, the source of their drug prescriptions, and the pharmacotherapeutic profiles of the drugs were collected, along with clinical outcome information, such as glycated hemoglobin (HbA_{1c}) and fasting plasma glucose levels. The direct costs of treatment with analogue insulin were evaluated based on the drugs and supplies acquisition data from the Center for Drugs, Paraná Cemepar. **Results:** One hundred and forty-eight type 1 diabetes mellitus patients, older than 18 years of age, were included in the cohort study. The HbA_{1c} reduction after the insulin treatment was 0.36 ± 2.75, and the direct costs to reduce this parameter by 1% over a period of 24 months were U$ 1,806. The estimated costs to reduce HbA_{1c} by 1% are U$ 5,016. **Conclusions:** In this study, we were able to estimate the public health system costs of using insulin analogues to reduce HbA_{1c} by 1% in patients with type 1 DM. This information will assist clinicians in decision-making regarding insulin treatment.

Palavras-chave:
Diabetes mellitus tipo 1, resultado do tratamento, custos e análise de custo, insulina, efetividade

RESUMO

Objetivo: *Diabetes mellitus* (DM) é um grave problema de saúde pública no Brasil. O objetivo deste estudo foi avaliar a redução da HbA_{1c} em pacientes usuários de insulinas análogas de longa duração no controle glicêmico de pacientes com DM tipo 1 e avaliar custos diretos do tratamento com insulinas análogas. **Métodos:** O estudo é uma coorte retrospectiva e análise de custos para o tratamento de DM tipo 1, com pacientes pertencentes a 2ª Regional de Saúde do estado do Paraná. Após

Received on: 2/15/2016. **Approved for publication on:** 07/15/2016
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Acknowledgments: The authors gratefully acknowledge the financial support received from Araucária Foundation (Fundação Araucária), protocol 16752/2009.
Information on financial support: The authors gratefully acknowledge the financial support received from Araucária Foundation (Fundação Araucária), protocol 16752/2009.
Congress: This study has not been presented in any event so far.
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randomização dos pacientes, foram coletados dados sociodemográficos, origem da prescrição e seu perfil farmacoterapêutico, além dos desfechos clínicos, como hemoglobina glicada (HbA_{1c}) e glicemia em jejum. Foi realizada uma análise dos custos diretos do tratamento com insulinas análogas, e os valores foram obtidos por meio dos dados de compra dos medicamentos e insumos realizados pelo Centro de Medicamentos Básicos do Paraná (Cemepar). **Resultados:** Foram incluídos 148 pacientes maiores de 18 anos. A variável avaliada foi redução na HbA_{1c} que, entre os pacientes, foi de 0,36 ± 2,75. Os resultados médios dos custos diretos totais do tratamento com DM tipo 1 durante 24 meses foram de R$ 7.224,00, para obter redução em 0,36% dos valores de HbA_{1c}. O custo teórico para a redução em 1% de HbA_{1c} é de R$ 20.064,00. **Conclusões:** Neste estudo foi possível estimar o custo para o sistema público de saúde, da redução de 1% da HbA_{1c} em pacientes com DM tipo 1 usando insulinas análogas. Essa informação serve de subsídios para gestores e clínicos na tomada de decisão do tratamento com insulinas.

Introduction

Diabetes mellitus (DM) is a chronic disease associated with severe complications and death. Cardiovascular diseases have been the leading cause of death in Brazil since 1960, and DM is one of the main triggers for cardiovascular diseases (Barbosa *et al*., 2001). The number of subjects with diabetes increased 2.2-fold over a 28-year period (Danaei *et al*., 2011). The percentage of subjects with undiagnosed DM is high, and up to 25% of these individuals have microvascular complications at the time of clinical diagnosis (Narayan *et al*., 2000).

The government, diabetes associations, healthcare professionals, and patients need to be aware of the possibility of reducing the cost of this condition and increasing the effectiveness of disease control and treatment (International Diabetes Federation, 2014).

In 2002, the cost of diabetes in the United States was estimated to be US$ 132 billions. This figure is an underestimate, because it does not consider intangible costs such as quality of life (Hogan *et al*., 2003).

There are no studies in the literature evaluating the socio-economic impact of the poor metabolic control resulting from type 1 diabetes mellitus (T1D) in Brazil. According to data published by the Brazilian Diabetes Society in 2007, Brazil is the second worst performing country in the world with regard to DM management. DM treatment is a citizen's right in Brazil, which is guaranteed by the constitution (Brazil, Ministério da Saúde, 2008) and constitutes a major burden to the healthcare system.

Considering the importance of treatment for T1D, the need for insulin and the cost differences between the various types of insulin, studies assessing the effectiveness, the direct costs of treatment, and the proposed changes in the criteria for monitoring patients enrolled in the treatment program are of great importance. Such studies can contribute to the state by defining clinical protocols for the distribution of insulin analogues to T1D patients, providing the highest quality of patient care, and reducing public costs for treating this disease. Insulin is administered to all patients with T1D (American Diabetes Association, 2014; American Diabetes Association, 2011).

This study utilized T1D patients over 18 years of age from the second Regional Health Center in a Brazilian city (Curitiba – State of Paraná) and evaluated the reduction of glycated hemoglobin after treatment with insulin analogues and the direct costs of treatment. This study can contribute to the health system, because it evaluates data on the reduction of glycated hemoglobin and estimates its cost for the insulin analogue program in the State of Paraná.

Methods

To assess the effectiveness of insulin analogues, data were collected in Curitiba from the Central Database of Paraná Medicines and the medical records of patients available in the second Health Region of Curitiba, State of Paraná (registration protocol CEP/SD: 820.155.09.10).

The study population consisted of patients diagnosed with T1D who were over 18. To be included in the study, the patients must belong to the insulin analogue administration protocol (glargine or detemir) from the Ministry of Health and be registered in the program of the State of Paraná for a minimum of 18 months, with a maximum of 24 months, among the baseline and final examinations. Patients with incomplete records or who abandoned the use of the drug during the period of the study were excluded. The sample size was calculated using the t-test. The following information was used for the calculation: the estimated average HbA_{1c} in patients with DM type 1 in Brazil is 9.0%, and the mean HbA_{1c} in the patients studied was 9.5%, with a standard deviation of 2%. The level of HbA_{1c} in the general population was estimated based on findings from a Brazilian population study,

published in 2010 (Mendes *et al*., 2010). The sample size calculation was performed using the program Biostat 5.0, applying a statistical power of 80% and an alpha level of 5% with a two-sided test. The sample size was estimated to be 125 patients; however, we chose to collect data from 150 patients.

The profiles of survey participants were recorded on a data collection form developed specifically for the project, which gathered information on the socio-demographic profile, the source of the prescription, and the pharmacotherapeutic profile of the drug (which was evaluated with regard to insulin type, dose and mode of treatment). The HbA_{1c} and fasting plasma glucose data were recorded from the medical records and any relevant doctors' files from the 2nd Health Region of Curitiba, State of Paraná. We recorded all the available results for patients who had data from at least 18 months of participation in the program. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) Statistics 17.0, using the method of descriptive statistics. Descriptive statistics and continuous data with a normal distribution of the mean and standard deviation and data with a non-normal distribution arranged in median and range were obtained. When a statistical method was applied, we used a nonparametric assessment with the analysis of variance (ANOVA) test.

Calculation of the cost of treatment with insulin analogues (both long-acting and rapid-acting types) was conducted from the perspective of the Brazilian public health system. In this perspective, only the direct costs were considered.

The data regarding the consumption of drugs, tests, and supplies were obtained through analyzing the medical records of the patients included in the study. The cost of treatment was calculated for each patient individually, taking into account a time horizon of 24 months from the date of inclusion in the insulin analogue program. Costs were also calculated as a mean monthly cost and a mean annual cost per patient.

For the tests, we used the list price for these services through the Brazilian public health system (Brazil, Decreto no. 7.508, de 28/06/2011). The drug's costs were evaluated based on the real price paid by the Center for Drugs, Paraná (Centro de Medicamentos Básicos do Paraná, Cemepar) after a bidding process in the first half of 2011.

Results

During the data collection period until April 2010, 685 subjects were enrolled in the Second Regional Health Center – Curitiba, receiving medication and supplies for application and glycemic control. Three hundred patients were randomized from the 685 subjects enrolled in the program until the period of data collection. Out of the 300 patients, 148 met the inclusion criteria and were included in the study. The referral origin of the subjects included in the study is described in Table 1. Only 18.2% of the patients were from the public health system.

The socio-demographic profile of the patients reveals that the group was composed of 84 (56.8%) women with a mean age of 34.0 ± 13.1 years. Patient characteristics at the time of inclusion in the Type 1 Diabetes Optimization Program in the State of Paraná, the results of the baseline and final HbA_{1c} and fasting plasma glucose levels are shown in Table 2.

Figure 1 shows the progress of disease control, which was monitored through laboratory results.

Within the first six months of use of the new technology, the patients demonstrated a decrease in HbA_{1c} and fasting plasma glucose; however, these results were not statistically significant (ANOVA, $P > 0.05$). Between the month of entry of the patient into the insulin analogue program and the eighteenth month of follow-up, fasting plasma glucose decreased by 47.8 mg/dL, which was a statistically significant result ($P < 0.05$) that was not maintained in the following semester.

The type of insulin and the combinations used by the patient at the beginning of treatment are shown in Figure 2.

When initiating treatment with insulin analogues, 131 (88%) of the patients combined treatment of their long-term insulin analogue with a rapid-acting insulin analogue, and in 100% of cases, this option was the insulin lispro.

Table 1. Distribution of patients in the study according to their route of referral

		Referring physician		
	Number of patients	Public Health System	Private	Unidentified
Total N (%)	148	27 (18.2%)	107 (72.3%)	14 (9.5%)

N: number of patients.

Table 2. Characteristics and results of laboratory biomarkers for glycemic control over a period of 24 months, from the patients belonging to the Type 1 Diabetes Mellitus Optimization Program of the State of Paraná

Demographic characteristics and glycemic variables	Results
Gender N (%)	84 (56.7%) Female
	64 (43.3%) Male
Age (years)	34.0 ± 13.1
Number of exams	6.0 ± 2.3
Baseline HbA_{1c} (%)	9.2 ± 2.1
Difference in HbA_{1c} (%)	-0.36 ± 2.75
Baseline fasting plasma glucose (mg/dL)	192.2 ± 99.8
Difference in fasting plasma glucose (mg/dL)	-30.8 ± 121.4

N: number of patients; HbA_{1c}: glycated hemoglobin.

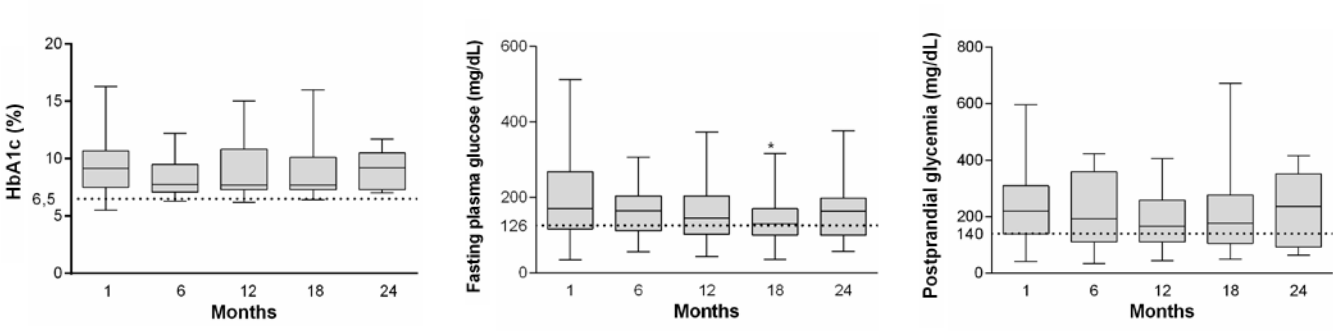
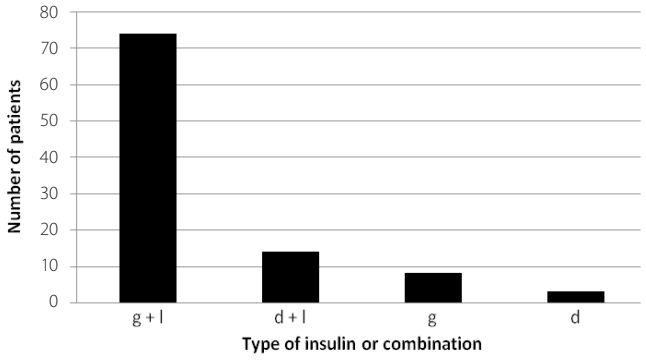


Figure 1. The laboratory parameters assessed over 24 months, presented as mean values.



g + l: glargine + lispro; d + l: detemir + lispro; g: glargine; d: detemir.

Figure 2. Frequency of use of insulin analogues, combined or single.

Table 3. Direct cost of the type 1 diabetes mellitus treatment with long-acting insulin analogues from the perspective of the public health system

	Mean cost (U$)	Minimum cost (U$)	Maximum cost (U$)
Insulin	3,153	762	8,509
Total cost	3,153	762	8,509
HbA_{1c} reduction	Mean (CI 95% Upper; CI 95% Lower)		
	-0,36 (0.086; -0.807)		

HbA_{1c}: glycated hemoglobin; FPG: fasting plasma glucose; CI: confidence interval.

Treatment costs with long-acting insulin analogues

The doses used in the direct cost analysis for the 148 patients were evaluated based on the amounts paid by Cemepar for the purchase of drugs and supplies in the first half of 2011. For the costs of the tests, parameter values from SIGTAP (Sistema de Gerenciamento da Tabela de Procedimentos) 0909141204 version 1.2 (SIGTAP, 2011) were used (Table 3).

Our results indicate that the average of the total direct costs for the treatment of T1D for 24 months is U$ 1,806 to obtain a 0.36% reduction in HbA_{1c} concentration. Thus, the theoretical cost of a 1% reduction in HbA_{1c} is U$ 5,016. After univariate sensitivity analysis (considering cost), the minimum and maximum theoretical values (U$ 408 to U$ 4786/24 months) were obtained.

Discussion

As required by the Regional Health Center, the patients were submitted to an appropriate number of tests and laboratory monitoring. The difference in the HbA_{1c} values of the patients between the time of admission to the program and the end of data collection was small (-0.36 ± 2.75%), whereas the fasting plasma glucose values for the same period were -30.8 ± 121.4.

Gough conducted a review of insulin analogues compared with human insulin and showed that the benefits of this latest treatment are low with regard to the change in HbA_{1c} values (Gough, 2007). The same results were reported in a meta-analysis of the insulin glargine versus neutral protamine Hagedorn (NPH), published by Singh *et al.*, which found a mean difference in HbA_{1c} of -0.11% in adult patients. The same authors stated that the difference between the conventional treatment and insulin analogues is minimal and therefore clinically insignificant (Singh *et al.*, 2009).

A study conducted by BRATS (the Brazilian Health Technology Assessment Bulletin) noted that in Brazil, the monthly costs of treatment among the three insulins differ significantly. This difference can reach 530% when comparing the insulin glargine with NPH insulin (Brazil, Boletim Brasileiro de Avaliação de Tecnologias em Saúde, 2010). The direct cost is high for treatment with human insulin, and such treatment is still regarded as necessary to maintain clinical improvement. In addition, non-pharmacological measures are required (Borges *et al.*, 2010). The lack of advantages from using human insulin analogues for glycemic control, was also reported by other authors (Tran *et al.*, 2007; Warren *et al.*, 2004). The clinical benefit associated with the use of insulin analogues is still slight compared to

treatment costs (Siebenhofer-Kroitzsch *et al*., 2009). A meta-analysis comparing the efficacy of long-lasting insulin analogues with NPH insulin in 20 randomized controlled trials found that the mean difference between the initial and final HbA_{1c} was 0.4% for insulin analogues and 0.3% for NPH, and the overall result was in favor of the insulin analogue (-0.07% 95% confidence interval, CI [-0.13, -0.11]) (Monami *et al*., 2009). There is a poor difference in HbA_{1c} results, with little significance from the standpoint of glycemic control (Gough, 2007). The results presented in the meta-analysis described in this paper showed no statistically significant results favoring any of the treatments (MD -0.06 [95% CI -0.14 to 0:02], P = 0.16). Cameron and Bennett found that the cost effectiveness of insulin analogues depends on the type of insulin analogue that the individual receives and the type of diabetes that is being treated. Based on a comprehensive evaluation of the limited financial resources for health, insulin analogues, from the point of view of glycemic control, do not represent the best clinical or financial option (Cameron and Bennett, 2009).

The cost required to reduce HbA_{1c} by 1% is U$ 5,016. According to the BRATS, the glycemic control results do not allow us to say that there are differences between the insulin analogues glargine, detemir and NPH, although the outcomes of the evaluations indicate the superiority of insulin analogues in reducing the risk of hypoglycemia. However, biases identified in the studies may compromise the validity of these findings (Brazil, Boletim Brasileiro de Avaliação de Tecnologias em Saúde, 2010). According to a study conducted in Canada by Cameron and Bennett, to evaluate the management and complications of diabetes, the insulin detemir is less cost-effective than NPH insulin. It is important to note that hypoglycemic episodes were not noted in the medical records; therefore, information about the safety of analogues could not be assessed.

During patient monitoring, it was observed that although there are maintenance criteria in the distribution protocol of insulin analogues that affirm the need to cut 50% of the surplus target of HbA_{1c} (7.0 ± 1.0%) in the first year of participation in the program, only 60 patients achieved it. The Brazilian Diabetes Society (Sociedade Brasileira de Diabetes, SBD) published a paper in 2011 that reviews the nominations and recommendations for the provision of insulin analogues by public health services. Such material analyzes the availability of similar protocols already in place in Brazil and makes a proposal including the scope, inclusion criteria, and criteria for evaluating the effectiveness and exclusion. Comparing this proposal with the protocols available in several states in Brazil, none of them presents a monitoring plan to evaluate the reduction in the frequency of hypoglycemic episodes, a factor that, according to the literature, is more useful in insulin analogues compared with human insulin (Brazil, Boletim Brasileiro de Avaliação de Tecnologias em Saúde, 2010). This document from SBD provides guidance on the other behaviors importants for glycemic control, and suggests that a satisfactory control of this parameter supports the triad of adequate supervisory responsibilities + continuing education + effective pharmacological intervention, and should be adapted according to the local conditions of each program or service (Brazil, Boletim Brasileiro de Avaliação de Tecnologias em Saúde, 2010).

Considering the current situation of the health system, where advanced drugs with high costs are available to patients without a return on the investment (adequate glycemic control), we find that the situation needs to be reviewed. Studies have shown that diabetic patients have a poor adherence to treatment (Cramer, 2004). Disease duration and the complexity of treatment are aggravating factors in this situation (Fihn *et al*., 2004). However, meta-analysis results show that direct interventions (patient-health professional), combining technical, cognitive, behavioral, and patient education with information that leads to a better understanding of the disease and its care, resulted in improved compliance to treatment. The study by BRATS argues that investment in self-management programs for patients with diabetes has promoted a relevant and sustained clinical gain (Brazil, Boletim Brasileiro de Avaliação de Tecnologias em Saúde, 2010).

The findings regarding the reduction of HbA_{1c} and the limitations of the insulin analogue program in Paraná showed that it is necessary to make changes regarding effective monitoring of the outcomes of hypoglycemia. Furthermore, the criteria for the maintenance program should be followed; we established the fact that this monitoring has not occurred.

This study has some limitations, such as being a retrospective observational study rather than an interventional one. For this reason, some important information was not found in the records, such as the frequency and severity of hypoglycemic episodes during the treatment.

Conclusions

The therapeutic option of human insulin seems to be an effective alternative and less costly than the insulin analogues. According to the therapeutic guidelines, that option (i.e., human insulin) should be exhausted before the use of insulin analogues, leading to inferior costs for the health system. Furthermore, educational measures can have a greater impact on disease control than merely changing the type of insulin.

Studies assessing other outcomes, such as indirect costs and quality of life of T1D patients using insulin analogues, should be conducted to assist clinicians and healthcare professionals in making decisions about therapeutic protocols.

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