Cost-effectiveness of insulin analogs from the perspective of the Brazilian public health system

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Human insulin is provided by the Brazilian Public Health System (BPHS) for the treatment of diabetes, however, legal proceedings to acquire insulin analogs have burdened the BPHS health system. The aim of this study was to perform a cost-effectiveness analysis to compare insulin analogs and human insulins. This is a pharmacoeconomic study of cost-effectiveness. The direct medical cost related to insulin extracted from the Ministry of Health drug price list was considered. The clinical results, i.e. reduction in glycated hemoglobin (HbA1c), were extracted by meta-analysis. Different scenarios were structured to measure the uncertainties regarding the costs and reduction in HbA1c. Decision tree was developed for sensitivity of Incremental Cost Effectiveness Ratio (ICER). A total of fifteen scenarios were structured. Given the best-case scenario for the insulin analogs, the insulins aspart, lispro, glargine and detemir showed an ICER of R$ 1,768.59; R$ 3,308.54; R$ 11,718.75 and R$ 2,685.22, respectively. In all scenarios in which the minimum effectiveness was proposed, lispro, glargine and detemir were dominant strategies. Sensitivity analysis showed that the aspart had R$ 3,066.98 [95 % CI: 2339.22; 4418.53] and detemir had R$ 6,163.97 [95% CI: 3919.29; 11401.57] for incremental costs. We concluded there was evidence that the insulin aspart is the most cost-effective.

Keywords: Diabetes Mellitus/treatment/cost-effectiveness/evaluation. Prolonged Action Insulin. Short Action Insulin. Brazilian Public Health System.

INTRODUCTION

Diabetes Mellitus (DM) is a group of chronic metabolic disorders that cause hyperglycemia. If not controlled, DM may trigger vascular complications and impair the function of organs such as the kidneys, brain and heart (ADA, 2016; SBD, 2016; WHO, 2016a). Approximately 415 million people worldwide have DM, 75% from which live in low- and middle-income countries (IDF, 2016). In Brazil, the prevalence is 8.1% (WHO, 2016b).

The annual direct costs to the Brazilian Public Health System (BPHS) with DM management reaches 14.8 billion Reais, which represents outpatient spending of R$ 8,010.00/patient/year (SDB, 2016). This amount includes direct costs related to examinations, medicines and consultations, non-medical direct costs, such as transportation and absenteeism and indirect health care costs, such as those generated by the complications of uncontrolled DM. The treatment effectiveness results in sustained reduction in glycosylated haemoglobin (HbA1c) and cost savings associated to complications and to indirect costs which are the highest costs that burden the BPHS (Rascati, 2010; Do Livramento, Saleh, 2011; Wagner et al., 2001; Obreli-Neto et al., 2015; SDB, 2016).

DM type 1 (DMT1) is usually an autoimmune disorder that results in absolute insulin deficiency. DM type 2 (DMT2) is characterized by the resistance of tissues to the insulin and/or the relative deficiency of insulin. People with DMT1 are insulin-dependent and insulinization is a therapeutic option for DMT2. (ADA, 2016; SBD, 2016). Therapies with human Neutral Protamine Hagedorn (NPH) insulin, Regular (R) insulin and insulin analogs foster discussion about the DM treatment effectiveness

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Braz. J. Pharm. Sci. 2017;53(3):e00178

Page 1 / 8

and involved costs. NPH, a slow-acting insulin, has unfavorable characteristics such as its erratic absorption, causing unpredictable glycemic variations. R insulin has faster action and is used to control postprandial glycemia, but it presents relatively slow absorption considering its indication. This absorption and the irregular feeding of some patients can result in hypoglycemia and therapeutic failures (SBD, 2011).

Human NPH and R insulin are provided by the BPHS. However, access to human insulin analogs generally occurs through lawsuits (Do Livramento, Saleh, 2011; Figueiredo, Osorio-de-Castro, Pepe, 2013). These unforeseen expenses in the health budget with higher cost medicines burden the BPHS and this increase of expenses to the BPHS has been associated with arbitrary decisions related to provision of the insulin analogs. They have been available through judicial processes in different regions and municipalities of Brazil. The number of lawsuits involving lispro and glargine insulins is twice the number of lawsuits to require other insulin analogs (Lima *et al.*, 2015). Decision-making for health care should be a rational process which does not result in excessive and unnecessary health care costs because this can compromise the system equity and the access to health (Shafie *et al.*, 2016). The decision to provide or to incorporate to BPHS for any insulin analog should be supported by economic analysis and clinical evidence (Brasil, 2014).

In this context, the knowledge about cost-effectiveness of insulin analogs can subsidize health planning and possible incorporation of insulin analogs into the BPHS. The aim of this study was to perform a cost-effectiveness analysis to compare insulin analogs and human insulins.

METHODS

This is a pharmacoeconomic study of cost-effectiveness to perspectives of BPHS. This study was developed based on data from the literature concerning the treatment of DM with insulin therapy. The cost data refer to the month of June 2016 and were recorded in monetary values in Brazilian currency, the Real. The calculation referred to the cost per patient/year.

For this study the direct medical costs of insulin treatment were ranked. The therapeutic regimen for each type of insulin was measured in accordance with the dose described as an International Unit (IU) per kg of the patient, considering for the calculation of the annual cost, 360 days of a year and body weight of 70 kg, being the mean of the normal distribution for the Brazilian population, according to the Brazilian Institute of Geography and Statistics (Brasil, 2016). Thus, the cost per IU of the drug was multiplied by

the mean daily dose in IU recommended for each type of insulin, and calculated per patient/year. The mean dose values assigned to each type of insulin were extracted from the studies used in the meta-analysis by Sanches *et al.* (2013) (Anderson Jr *et al.*, 1997; Home, 2000; Hermansen *et al.*, 2004; Heller, Koenen, Bode, 2009).

Data related to the reduction of HbA1c were used to compare treatment with human insulin and treatment with insulin analogs, being obtained from the meta-analysis by Sanches *et al.* (2013). The meta-analysis examined sixteen studies, totaling 5,733 patients using rapid-acting insulin analogs (glulisine, arpart, lispro) and 4,771 patients using long-acting insulin analogs (glargine and detemir). The mean age was 39.2 years and all patients were receiving diabetes treatment with insulin only. Glulisine was excluded from this study because it was not analyzed in the meta-analysis, being as it was found only in a clinical trial that analyzed glulisine vs. insulin R. The meta-analysis considered the significance level of 5% and the figures were interpreted for 95% confidence interval (Sanches *et al.*, 2013).

The costs were extracted from the Market of Regulation of the Market of Medicines (*CMED*). It was considered the price of the sale of medicine to the government and the tax rate of 18%, linked to most Brazilian states. The values of each insulin existing in the table were considered: NPH INSUNORM N (ASPEN PHARMA) 100 IU mL, 10 mL injectable suspension; Regular INSUNORM R (ASPEN PHARMA) 100 IU/mL, 10 mL injectable solution; NOVORAPID aspart (NOVO NORDISK) 100 IU/mL, 10 mL injectable solution; lispro HUMALOG (ELI LILLY) 100 IU/mL, 10 mL injectable solution; detemir LEVEMIR (NOVO NORDISK) 100 IU/mL, 3 mL injectable solution; and glargine VELUXUS (MEDLEY) 100 IU/mL, 3 mL injectable solution (ANVISA, 2016).

Calculating cost-effectiveness

For cost-effectiveness analysis the Incremental Cost Effectiveness Ratio (ICER) was calculated, the calculation of which is the ratio of the cost variation by variation of the effectiveness, designated by the expression (Rascati, 2010):

$$ICER = \frac{(\text{cost of human insulin} - \text{cost of insulin analog})}{(\text{reduciton of HbA1c by human insulin} - \text{reduction of HbA1c by insulin analog})}$$

The ICER refers to the extra cost with the insulin analog in order to obtain an improvement in the outcome, the reduction in HbA1c. Thus, it can be understood that when there is no higher cost and there is an improvement of the outcome, the option becomes dominant in the scenario of the analysis, and when there is a higher cost and worsening outcome, the option becomes dominated in the respective scenario of analysis.

Page 2 / 8

Braz. J. Pharm. Sci. 2017;53(3):e00178

Simulation of uncertainties

Different scenarios were structured to measure the possibilities of variation of costs and reduction in HbA1c achieved by each type of insulin (Drummond *et al.*, 2005). The calculation of the ICER for variations in cost was performed for the mean, minimum, and maximum values, which relate to the cost difference between the mean, minimum, and maximum values of insulin, respectively. The cost was also varied for the largest possible difference and smallest possible difference obtained by the difference between the lowest cost of human insulin and the highest cost of insulin analog, and between the highest cost of human insulin and the lowest cost of insulin analog, respectively. To compose the scenarios of different possibilities for insulin cost-effectiveness, the variation in costs was combined with variation of effectiveness, whether mean, minimum and maximum, for the reduction of HbA1c. The cost-effectiveness threshold was measured by the amount of three times the GDP per capita for the year 2015 as recommended by the Brazilian Network of Technology Assessment in Health (Brasil, 2014).

Sensitivity analysis

Sensitivity analysis was performed in order to support decision-making regarding the analysis of ICER variation of each type of insulin analog (Drummond *et al.*, 2005; Rascati, 2010). For this, a decision tree was drawn which through the confidence interval for the reduction of HbA1c demonstrated the sensitivity of the analysis, given the variation of effectiveness. In this model of analysis, calculated probabilities were considered with a 95% confidence interval for the minimum and maximum variation in HbA1c, and for the variation in the minimum and maximum cost of each insulin types . For construction of the decision tree the first node of the tree was defined as being the decision node between two representatives of each insulin-class of fast and long-acting action. This node branched into a probability node related to the probability of minimum and maximum effectiveness of each insulin. Each probability node branched into a terminal node with the probability of variation in maximum and minimum cost for each insulin.

The probabilities were obtained within the confidence interval itself. For the probability of the minimum value the ratio between the minimum value and the sum of the values within the interval was calculated, and the probability of the maximum value followed the expression: (1 - probability of minimum value). Thus, the smaller the amplitude between the maximum and minimum values of the confidence interval, the lower the probability for values to differ from the mean, both for effectiveness and cost, i.e. the result is more consistent with the mean which was used for calculating the cost-effectiveness ratio.

RESULTS

When insulin analogs were compared with human insulin, fast acing R and long-acting NPH, the insulin analogs that presented greater effectiveness were aspart and detemir, which showed a further reduction of -0.13% [95% CI: -0.17; -0.09] and -0.11% [95% CI: -0.32; 0.11] in mean HbA1c, respectively. It should be highlighted that among the insulin analogs, aspart and detemir were the options that presented the lowest mean cost of treatment per patient/year, R$ 665.34 [95% CI: 591.41; 739.26] and R$ 1,752.66 [95% CI: 1448.86; 2056.45], respectively. It was observed that the highest cost that aspart could present was still lower than the lowest cost of the analog option analyzed, namely lispro. A similar situation was not verified for the long-acting insulin analogs (Table I).

TABLE I - Effectiveness of insulin analogs in reducing HbA1c compared to human insulins and the annual cost for treatment

Insulins	Reduction in HbA1c (CI 95 %)	Daily dose IU/Kg (CI 95 %)	R$ Cost of treatment patient/year		
			Minimum	Mean	Maximum
Fast acting					
REGULAR	Reference	0.68 (0.62; 0.73)	500.75	549.20	589.59
Aspart	-0.13 (-0.17; -0.09)	0.36 (0.32; 0.40)	591.41	665.34	739.26
Lispro	-0.08 (-0.24; 0.08[+])	0.67 (0.61; 0.70)	1,084.80	1,191.50	1,244.85
Long acting					
NPH	Reference	0.34 (0.32; 0.36)	258.45	274.60	290.75
Glargine	-0.04 (-0.12; 0.05[+])	0.33 (0.30; 0.37)	1,995.84	2,195.42	2,461.53
Detemir	-0.11 (-0.32; 0.11[+])	0.37 (0.31; 0.44)	1,448.86	1,752.66	2,056.45

[+] = confidence interval shows that there is a possibility of increased HbA1c. Reference = the glycated reduction values were the benchmarks for insulin analogs. Costs were obtained according to the CMED Table 2016 and were calculated for the annual cost of treatment in accordance with the recommended regimen for each type of insulin.

Fifteen scenarios were structured for the simulation of uncertainty in cost-effectiveness analysis. The mean, minimum, and maximum cost combinations, and largest and smallest cost difference with the mean, minimum and maximum effectiveness of each insulin showed that in face of the best-case scenario for the insulin analogs, i.e. least difference in cost and maximum effectiveness, the insulins aspart, lispro, glargine and detemir showed the ICER of R$ 1,768.59; R$ 3,308.54; R$ 11,718.75 and R$ 2,685.22, respectively. Additionally, in face of the worst-case scenario, i.e. largest cost difference and lowest effectiveness, all options were the dominated strategies, except aspart. The same was interpreted for all other scenarios in which minimal effectiveness was proposed (Table II).

Sensitivity analysis showed that in face of the probabilities of the effectiveness and cost variations, the insulin analogs aspart, lispro, glargine and detemir presented the ICER of R$ 3,066.98; R$ 5,960.39; R$ 22,414.37; and R$ 6,163.97, respectively. It is possible to highlight by sensitivity analysis that the option of the most cost effective fast acting insulin analog was aspart and long acting was detemir (Figure 1).

DISCUSSION

In direct cost analysis for the treatment of DM was possible to predict with 95% certainty that the minimum cost of insulin analog options was not less than the maximum cost of human insulin options, and the same evidence holds in the comparison between aspart and lispro. According to Holden *et al.* (2011), human insulins are preferred over insulin analogs in merit of cost savings to the government, given the expected effectiveness for the treatment of DM.

In all scenarios in which the lowest possible effectiveness is projected, the options lispro, glargine and detemir were dominated strategies and only aspart had ICER in trade-off, able to present an incremental cost for additional improvement in the outcome. When considering the mean effectiveness range, the most cost effective long-acting insulin option was detemir, R$ 14,142.73 and, among the fast acting options the most cost effective was aspart, R$ 3,698.54, being values added to the treatment for an additional reduction of 1 % in HbA1c per patient/year. In all scenarios, all options had an ICER less than the threshold of cost-effectiveness of R$ 86,628.00 (amount equal to three times the per capita GDP of the year 2016). According to the opinion of the National Commission on Technology Incorporation in the BPHS (CONITEC, 2013), the ICER attributed to insulin analogs are not able to exceed the cost-effectiveness threshold.
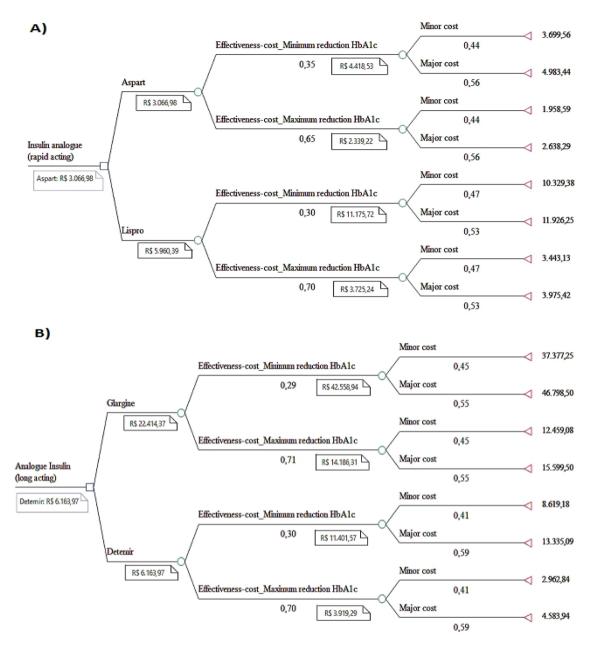
Considering the best possible scenario for comparison of insulin analogs, among the fast-acting and long-acting insulins, aspart and detemir were the options that presented the best incremental cost effectiveness, being R$ 1,768.59 and R$ 2,685.22 per patient/year to reduce by an additional 1 % HbA1c respectively. In the worst and best scenario, aspart and detemir insulin analogs had the lowest ICER compared with lispro and glargine. It is important that a 1 % reduction in HbA1c reduces by 43% the risk of amputation, in 14% the risk of acute myocardial infarction, and in 37% microvascular complications (SBD, 2016), so that the incremental cost represent the long-term economy of resources for the BPHS.

According to the sensitivity analysis by the decision

TABLE II - Incremental cost effectiveness in different scenarios for the simulation of the uncertainties in the comparison of insulin analogs with human insulin

	Mean Effectiveness				Minimum Effectiveness				Maximum Effectiveness			
	Aspart	Lispro	Glargine	Detemir	Aspart	Lispro	Glargine	Detemir	Aspart	Lispro	Glargine	Detemir
Mean Cost	3,005.69	11,461.25	41,155.50	10,940.55	4,341.56	Dominated	Dominated	Dominated	2,298.47	3,820.42	13,718.50	3,760.81
Minimum Cost	2,561.23	10,329.38	37,377.25	8,619.18	3,699.56	Dominated	Dominated	Dominated	1,958.59	3,443.13	12,459.08	2,962.84
Maximum Cost	3,450.08	11,926.25	46,798.50	13,335.09	4,983.44	Dominated	Dominated	Dominated	2,638.29	3,975.42	15,599.50	4,583.94
Largest difference in cost	3,698.54	12,330.00	49,019.50	14,142.73	5,342.33	Dominated	Dominated	Dominated	2,828.29	4,110.00	16,339.83	4,861.56
Smallest difference in cost	2,312.77	9,925.63	35,156.25	7,811.55	3,340.67	Dominated	Dominated	Dominated	1,768.59	3,308.54	11,718.75	2,685.22

Largest difference = difference between the lowest cost of human insulin and the highest cost of insulin analog. Smallest difference = difference between the highest cost of human insulin and the lowest cost of insulin analog. Dominated = represents the strategy in which the insulin analog had a larger cost and a lower effectiveness when compared to human insulin.

Page 4 / 8

Braz. J. Pharm. Sci. 2017;53(3):e00178

FIGURE 1 - Sensitivity analysis structured in a decision tree model for the Incremental Cost Effectiveness Ratio (ICER) of insulin analogs. A) structured sensitivity analysis for fast acting insulin analogs. B) Structured sensitivity analysis for long-acting insulin analogs. For the construction of the decision tree, the first node of the tree was considered as the decision node (square symbol) between the two types of insulin in each category, i.e. fast-acting and long-acting. The respective node of each insulin had a branch to two probability nodes (circle symbol), a node associated with the minimum and maximum effectiveness and another with the maximum and minimum cost. For the probabilities of each branch the 95 % confidence interval was calculated, based on the range between the minimum and maximum reduction of glycated hemoglobin and minimum and maximum cost of insulin. The terminal node (triangle symbol) had values in Reais of incremental cost effectiveness for each possibility, taken from Table II. For the respective insulin of the dominated strategy when considering minimum effectiveness, the ICER was ranked from the scenario of minimum and maximum cost with the mean effectiveness of the insulins.

tree, the most cost effective fast-acting insulin analog was aspart, R$ 3,066.98 [95% CI: 2339.22; 4418.53] and the most cost effective long-acting insulin was detemir, R$ 6,163.97 [95% CI: 3919.29; 11401.57]. The result in face

of the uncertainty simulation scenarios was maintained with sensitivity analysis, i.e., aspart and detemir were the most cost effective from the options. However, it was possible to identify increased ICER of aspart and

detemir in accordance with the probabilities. This positive difference in the mean was R$ 61.29 and R$ 4,776.58, respectively. When comparing with the worst-case scenario, there was a negative difference of R$ 631.56 and R$ 7,978.76, respectively, and in the best scenario, a positive difference of R$ 1,298.39 and R$ 3,478.75 for aspart and detemir respectively.

It is important to stick to the scenarios of uncertainties, which showed that in the lowest-effectiveness hypothesis, the only option not dominated was aspart. This may be related to the effectiveness of lispro, which presented no evidence of better effectiveness compared with R insulin in clinical trials, unlike aspart which promoted significant improvement in glycemic control (Gale, 2000; Home, Lindholm, Riis, 2000). The same has been shown for long-acting insulin analogs, which have not presented evidence of better efficacy when compared with NPH (Venancio *et al.*, 2013).

The investment decision in aspart to improve glycemic control in diabetic patients can initially bring clinical benefits to patients and future financial benefits to the BPHS. However, this decision should have a plan, since budget impact studies indicate that the impact of the addition of insulin analogs into the BPHS can reach about 202.8 million Reais (CONITEC, 2013). In this way, the system cannot enjoy adequate capital for the initial investment which results in future financial benefits. Any poorly planned investment may compromise other sectors of health in Brazil.

One of the benefits highlighted for the use of insulin analogs over human insulin has been the significant reduction in the incidence of cases of hypoglycemia. Studies have shown that the improvement occurs in episodes of nocturnal hypoglycemia (Crasto *et al.*, 2009; SDB, 2011; SDB, 2016). However, due to the data source used, this study did not consider episodes of diurnal, nocturnal and pre-prandial hypoglycemia, but instead, total hypoglycemic episodes. Thus, it is possible to emphasize that when evaluating the total episodes of hypoglycemia, the options of long and fast-acting insulin analogs poses no greater risks than NPH and Regular (Hermansen *et al.*, 2001; CONITEC, 2013; Venancio *et al.*, 2013).

According to the analysis by the values of Odds Ratio (OR) between the comparisons of total episodes of hypoglycemia, the meta-analysis used in this study has shown: detemir vs. NPH, OR=0.88 [0.52 to 1.51]; glargine vs. NPH, OR=1.12 [0.69 to 1.81]; lispro vs. insulin R, OR=0.72 [0.21 to 2.55]; and aspart vs. insulin R, OR=0.71 [0.43 to 1.16]. These results mean that all insulins present the same risk to cause hypoglycemia (Sanches *et al.*, 2013). It is noteworthy that the analysis performed in this study did not consider the cost of adverse reactions of the insulins.

It is relevant to point out that the assessment of cost-effectiveness of this study considered adult diabetic individuals, according to analysis performed by meta-analysis which provided the data for the study. We highlight there was no need to obtain other types of costs, such as indirect medical costs and non-medical costs since, given the perspective of this study (Rascati, 2010; CONITEC, 2013). Additionally, the effectiveness of each type of insulin was pertinent to insulin monotherapy, without adjuvant to DM treatment.

However, it is noteworthy that this study presents well-delineated results consistent with reality for Brazilian adult diabetic patients, and insulin without adjuvant treatment of DM. A relevant form of costing to the perspective of this study was used, in face of the BPHS and clinical data with high value of evidence (Savi, Silva, 2009). In addition, sensitivity analysis was performed based on a robust method for decision making, which uses statistical and mathematical tools that summarize in the decision tree model the best choice (Drummond *et al.*, 2005; Rascati, 2010).

CONCLUSION

Assessing only the cost of treatment by direct cost analysis performed in this study, it was possible to conclude that Regular insulin and NPH were the best options for the treatment of DM. Still considering direct cost analysis, the insulins aspart and detemir were alternatives as the best choice among the insulin analog options, and aspart presented no possibilities of being more costly than the other fast-acting insulin options evaluated. According to sensitivity analysis, the best options among the insulin analogs were detemir and aspart. However, the insulin detemir was a dominated option according to uncertainty scenarios. Thus, our study showed there was evidence for aspart to be the most cost-effective insulin option when targeting an increment in reducing HbA1c and possible improvement in glycemic control.

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Page 6 / 8

Braz. J. Pharm. Sci. 2017;53(3):e00178

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CONFLICT OF INTEREST

The authors confirm that the content of this paper has no conflict of interest.

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