FEATURE ARTICLE

A Cross-Sectional Study of Quality of Life Among Brazilian Adults With Type 1 Diabetes Treated With Insulin Glargine: Findings and Implications

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This article describes a cross-sectional study involving 401 adults with type 1 diabetes treated with insulin glargine in Minas Gerais, Brazil. Health-related quality of life was assessed, and worse scores were found to be associated with a low level of education, self-perceived health reported as poor/very poor, being bedridden and not physically exercised, having seen a doctor more than four times in the past year, and having reported comorbidities and episodes of hypoglycemia.

Type 1 diabetes is a chronic, costly disease, both for people living with it and for governments and society (1,2). The economic burden of type 1 diabetes is largely due to the costs of medicines and the complications of diabetes (3,4), with insulin treatments differing in terms of their pharmacokinetic parameters as well as their costs (5).

Long-acting human insulin analogs (insulin glargine [IGla], insulin degludec [IDeg], and insulin detemir [IDet]) were developed and introduced into clinical practice as an alternative to NPH insulin. Studies have documented an improvement in glycemic control and consequently a smaller number of hypoglycemic episodes alongside improved, health-related quality of life (HRQoL) (6,7). However, long-acting human insulin analogs (IGla and IDet) and ultra-long-acting human insulin analogs (IDeg and IGla U300) are considerably more expensive than intermediate-acting insulins such as NPH insulin (8,9). This is an especially important consideration for health technology assessment (HTA) authorities in low- and middle-income countries (LMICs), where insulin availability is a major concern, especially for people with type 1 diabetes, as well as for the sustainability of these countries' national health systems (10–12). There is also ongoing controversy regarding the level of patient benefit seen. Hemmingsen et al. (13) in their recent Cochrane review reported finding no clear differences when comparing IGla with NPH insulin for death, HRQoL, severe hypoglycemia (nocturnal), serious undesirable events, nonfatal complications of diabetes (e.g., nonfatal heart attacks and strokes), and A1C. However, Tricco et al. (7) came to a different conclusion in their systematic review, suggesting that both ultra-long-acting and long-acting insulins were superior to intermediate-acting insulins in reducing A1C, excess weight gain, and major, serious, and nocturnal hypoglycemia.

HTA authorities, which are independent recommendation agencies for the incorporation of health technologies into their respective national health services, have made recommendations for and against the incorporation of long-acting insulin analogs into health care systems, given their considerably higher costs compared with NPH insulin or similar insulins, as well as variable findings regarding the extent of clinical benefit in prac-

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tice (e.g., A1C lowering, HRQoL improvement, and hypoglycemia reduction) (6,7,12–16). HTA agencies that now recommend the incorporation of IDeg, IGla, and IDet into their national health system include the National Institute for Health and Care Excellence in the United Kingdom (17), the Scottish Medicine Consortium (18–20), and the Canadian Agency for Drugs and Technologies in Health (21,22). Brazil's HTA, the National Committee for Health Technology Incorporation into the Unified Health System (Conitec), in 2019 recommended the incorporation of IGla, IDet, and IDeg into the Brazilian unified health system (SUS) (23,24). This is important, as medicines indicated for incorporation by Conitec are provided free of charge to patients in Brazil (25). In addition, the different states of Brazil (i.e., Regions) can develop their own medicines lists and make accepted technologies available free to patients (12). For example, the state of Minas Gerais listed IGla in 2005 (25). IGla is the most prescribed long-acting insulin analog in Brazil and was incorporated in other Brazilian states before Conitec's decision in 2019 (23). In contrast to other HTAs, the National Commission of Medicines and Supplies, Ecuador's HTA, requested the exclusion of IGla in March 2013 (26). The German Institute for Quality and Efficiency in Healthcare also recommended the exclusion of long-acting human insulin analogs in 2010, as there appeared to be no studies demonstrating their superiority over NPH insulin (27). However, the situation has changed since then (6,15,28). As a result, long-acting insulin analogs have become the most prescribed insulins in high-medium–income and high-income countries (8,12). We are also seeing growing use in LMICs (9,12,29).

After Conitec's recommendation to incorporate IGla, IDeg, and IDet into SUS (23,24), the Brazilian Ministry of Health (MoH) created the Clinical Protocol and Therapeutic Guidelines (PCDTs) for type 1 diabetes (30). The PCDTs establish that there is no preferred analog among the three products; however, the clinical guideline gives consideration to the modest clinical benefit of long-acting insulin analogs in patients with recurrent episodes of hypoglycemia (30). Interestingly, even with the introduction of the biosimilar products Abasaglar (Eli Lilly) and Glargilin (Biomm) (31), the prices charged for IGla in public procurements, in 2020, remained high in Brazil compared with NPH insulin ($16.38 and $5.31 USD, respectively) (12,32,33). This issue is a continuing concern given the lower prices for biosimilar IGla in countries such as Bangladesh (29). It is worth noting that the PCDTs for type 1 diabetes recommend that Brazil's MoH should procure treatments with the best cost-minimization profile (30). However, the MoH has not yet taken a position on biosimilars in SUS, which may explain the lack of price reductions to date (34). It is also noteworthy that, even after the incorporation of IGla, IDet, and IDeg in March 2019, the MoH of Brazil was still unable to acquire any of these medicines in August 2021 (24,35). This inability was probably due to cost reasons since incorporation was conditional on the cost (general administration) of long-acting insulin analogs being equivalent to that of an NPH insulin pen (i.e., equivalent to $5.31 USD per NPH insulin pen of 100 units/mL on a similar patient-day basis) (23,24).

Adequate glycemic control minimizes episodes of hypoglycemia (whether nocturnal or severe) and improves HRQoL of people with type 1 diabetes (36). Alongside these benefits is the stark fact that ~10% of deaths of young people with type 1 diabetes are attributable to hypoglycemia (37). Fear of hypoglycemia increases the psychosocial burden of the disease and affects self-care behaviors, having a direct impact on glycemic control and increasing the risk of long-term macro- and microvascular complications, and contributing to worsening HRQoL among people with type 1 diabetes (14,38,39). In addition to hypoglycemic episodes, various factors are associated with HRQoL in people living with diabetes. These include, but are not limited to, prescribed antidiabetic treatments, overall glycemic control (i.e., A1C), the extent of comorbidities and diabetes-related complications, and psychological and family factors (38,40,41).

However, studies that have assessed HRQoL in people with type 1 diabetes who are prescribed long-acting insulin analogs are generally limited to the assessment of HRQoL scores of people taking the different analogs and do not typically assess factors associated with individual treatment outcomes, nor do they assess HRQoL in people with type 1 diabetes without regard to the treatments they use (14,38,42,43). There also appear to be no studies in Brazil that correlate HRQoL and A1C in people treated with IGla. Having said this, there are still uncertainties regarding HRQoL in people treated with IGla who have adequate glycemic control (14).

In view of the uncertainties regarding the role and value of long-acting human insulin analogs in people with type 1 diabetes with regard to HRQoL, especially in LMICs, and the fact that there have been no studies exclusively evaluating the HRQoL outcomes of people with type 1 diabetes treated with IGla in Brazil, we sought to address this issue. This study aimed to examine the factors associated with HRQoL in people living with type 1 diabetes and treated with IGla in Brazil.

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Research Design and Methods

Study Design, Setting, and Patient Recruitment

Using convenience sampling methods, a cross-sectional study was conducted in March 2017 with 401 people living with type 1 diabetes and treated exclusively with IGla, identified via the SUS database from the Secretary of State for Health of Minas Gerais (SES-MG). People with type 1 diabetes with a prescription for IGla in Minas Gerais are dispensed their insulin only by public pharmacies. This means that the public system only authorizes access to IGla after an assessment has been undertaken to appraise the conformity of the prescription with a clinical guideline specific for IGla use within the state (44). If approved, insulins are provided free of charge. However, patients are subject to a 100% copayment if the prescribing criteria are not met (12). The other long-acting human insulin analogs (IDet and IDeg) were not evaluated in this study, as most people with type 1 diabetes in Brazil are treated with Igla (i.e., IDet and IDeg do not have a large volume of prescriptions in Brazil, and other insulin formulations are subject to the 100% copayment).

The following inclusion criteria were adopted: adults (≥18 years of age) with type 1 diabetes treated with IGla for ≥6 months, with or without other insulins. The following exclusion criteria were applied: patients who were diagnosed with mental disorders (except for depression and bipolar disorder), bedridden, cognitively impaired, pregnant or lactating, or diagnosed with latent autoimmune diabetes in adults.

Study participants were interviewed by telephone. It is worth mentioning that only patients with type 1 diabetes, who had their prescriptions approved by the clinical guideline of the Minas Gerais Sanitary Authority of SES-MG (44), participated in this study. Participants answered a structured questionnaire administered by a trained interviewer. Up to five attempts were made to contact potential participants at different times. If telephone contact was unsuccessful, these individuals were excluded from the study. Overall, only eight potential participants could not be reached in this way. The eight patients who were not reached are not part of the 401 patients evaluated in this study.

Structured Survey Questionnaire, Measurements, and Definitions

A structured survey questionnaire was specially developed for this study to collect participant data. The survey included questions about the following: *1*) sociodemographic and occupational data, *2*) data on clinical factors and access to health services, and *3*) assessment of HRQoL (using the three-level EuroQol five-dimensional instrument [EQ-5D-3L]. These information categories are described in more detail in the subsections below.

Sociodemographic and Occupational Data

The data category included information on factors such as age, sex, race, marital status, education, housing, number of residents in the household, occupation, weekly workload, employment status, stress, and energy level after work. We developed this structured survey questionnaire especially for this study based on previous questionnaires and the considerable experience of the authors in researching the management of patients with diabetes in Brazil and elsewhere. However, it has not been validated.

A validated questionnaire based on the Brazilian economic classification criteria from the Brazilian Market Research Association (ABEP) was used to collect data on participants' economic status (45). The ABEP questionnaire takes into account the consumption patterns of families, public utility services, and householders' education. It provides scores for the number of household appliances, bathrooms, and domestic servants, scored with values between 0 and ≥4. Householders' education level is scored 0 for no schooling/incomplete elementary school up to 7 for a higher education degree. Public utility services (e.g., piped water and paved street) are scored as 4 points for "yes" and 0 points for "no." At the end of the questionnaire, a total score between 0 and 100 is generated. A score of 45–100 is classified as A1–A2 classes = best social conditions, whereas a score of 0–16 is classified as D–E classes = worst social conditions (45).

Clinical Factors and Access to Health Services

This category covered such topics as self-perceived health, physical exercise, being bedridden in the 15 days before the interview, doctor's visits and hospitalizations in the past year, health insurance plan, comorbidities, alcohol consumption, tobacco use, problems accessing health services, BMI, time since diagnosis, A1C, hypoglycemic episodes and type of hypoglycemia (e.g., severe or nocturnal) in the past 6 months, use of other insulins, insulin delivery method, and the number of medicines used. We again developed this structured survey questionnaire especially for this study. However, it has not been validated to collect these variables.

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BMI was assessed according to the recommendations of the World Health Organization, which lists the following cutoff points: <18.5 kg/m^2 = thin or underweight, 18.5–24.9 kg/m^2 = eutrophic or normal weight, 25–29.9 kg/m^2 = overweight, and ≥30 kg/m^2 = obesity (46).

A1C was classified with reference values recommended by the American Diabetes Association as follows: participants between 18 and 59 years of age with an A1C ≤7.0% and those >60 years of age with an A1C ≤8.0% were considered to have controlled glycemia, and those whose A1C was outside of their range of reference were considered to have uncontrolled glycemia (47,48).

HRQoL

The EQ-5D-3L, a generic instrument translated and validated in Brazil, was used to measure HRQoL (49,50). This instrument comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and three levels of severity (no problems, some problems, and extreme problems). The combination of these dimensions and levels identifies 243 health states, with respective utility scores for the Brazilian population (51,52).

Statistical Analysis

Categorical variables were presented as absolute frequency and relative frequency, and continuous variables as mean ± SD. To compare EQ-5D-3L mean utility scores, by variable, an independent samples *t* test was used—either the Student *t* test or ANOVA. Normality parameters were verified using the Kolmogorov-Smirnov test for the EQ-5D-3L utility values.

Multiple linear regression analysis was performed using the forward stepwise method with the EQ-5D-3L utility scores of patients treated with IGla as the dependent variable and all other variables as explanatory variables. The explanatory variables that yielded *P* values <0.05 remained in the final model. Model adequacy was checked by means of residual analysis.

We used IBM SPSS, v. 26.0, software (IBM Corp., Armonk, NY) for the statistical analyses, and a 95% CI was adopted.

Ethical Approval

The study was approved by the Ethics and Research Committee of the Federal University of Minas Gerais, Brazil, under protocol no. 55876816.0.0000.519 and opinion no. 1.572.257, observing the principles of confidentiality of patient information, according to the Declaration of Helsinki.

We declare that patients did not receive any monetary or other incentives to participate in the study (i.e., patient participation in the study was entirely voluntary).

Results

The study comprised 401 individuals with type 1 diabetes who were treated with IGla. There were statistically significant differences in mean utility scores of people treated with IGla with regard to sex, age, education, occupation, employment status, weekly workload, stress, and energy level after work (Table 1).

There were also statistically significant differences in the mean utility scores of people treated with IGla with regard to self-perceived health, bedridden or engaged in physical activity in the last 15 days before the interview, doctor's visits and hospitalizations in the past year before the interview, problems in accessing health services, number of comorbidities, systemic arterial hypertension, cardiovascular disease, stroke, kidney disease, diabetic retinopathy, dyslipidemia, diabetic neuropathy, chronic obstructive pulmonary disease (COPD), hearing problems, depression, cancer, BMI, time since diagnosis, hypoglycemic episodes and type of hypoglycemia in the past 6 months before the interview, alcohol consumption, and number of medicines used (Table 2).

Moderate problems that have an impact on HRQoL were reported by patients treated with IGla in the dimensions of anxiety/depression (36%), pain/discomfort (31%), mobility (13.8%), usual activities (e.g., work, study, or household chores), family or leisure activities (13%), and self-care (5.8%) (Table 3).

Patients treated with IGla obtained a mean utility value of 0.796 ± 0.009 (95% CI 0.778–0.813).

Multiple regression analysis showed that a level of education ≥9 years, self-perceived health reported as very good/good, not being bedridden and having exercised in the past 15 days before interview, having had a maximum of three doctor's visits in the past year, not having other comorbidities such as diabetic neuropathy or COPD, and not having reported episodes of hypoglycemia in the past 6 months all contributed to optimal HRQoL in individuals living with type 1 diabetes and treated with IGla (Table 4). The variables that remained in the final model explained 39.7% of the variability in EQ-5D-3L utility scores.

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TABLE 1 Sociodemographic Data, Occupational Characteristics, and Mean Utility Scores of Individuals With Type 1 Diabetes Treated With IGla (n = 401)

Variable	Participants, n, %	Utility		P*
		Mean ± SD	95% CI	
Sex				0.001
Male	202 (51)	0.826 ± 0.012	0.801–0.852	
Female	199 (49)	0.764 ± 0.012	0.740–0.789	
Age, years (mean 40.76 ± 0.841)				<0.001
18–40	223 (56)	0.841 ± 0.010	0.821–0.861	
41–60	117 (30)	0.763 ± 0.015	0.731–0.794	
61–90	61 (14)	0.695 ± 0.030	0.634–0.756	
Ethnicity				0.225
Non-Black	233 (58)	0.805 ± 0.011	0.783–0.827	
Black	168 (42)	0.783 ± 0.014	0.753–0.812	
Marital status				0.295
Has a partner	187 (47)	0.785 ± 0.014	0.757–0.814	
No partner	214 (53)	0.804 ± 0.011	0.782–0.827	
Education				<0.001
≥9 years	324 (81)	0.815 ± 0.009	0.797–0.832	
≤8 years	77 (19)	0.716 ± 0.026	0.664–0.768	
Housing				0.790
Owner	326 (81)	0.797 ± 0.010	0.777–0.817	
Nonowner	75 (19)	0.791 ± 0.018	0.753–0.828	
Residents in the household				0.734
With other people	374 (93)	0.796 ± 0.009	0.778–0.815	
Alone	27 (7)	0.784 ± 0.037	0.708–0.860	
Social class				0.435
A1-A2	199 (50)	0.784 ± 0.012	0.759–0.809	
B1	194 (48	0.808 ± 0.013	0.782–0.833	
B2	8 (2)	0.797 ± 0.052	0.674–0.920	
Occupation				0.001
Nonworkers†	193 (48)	0.763 ± 0.014	0.735–0.792	
Worker	208 (52)	0.826 ± 0.010	0.804–0.847	
Employment status				0.001
Nonworkers†	193 (48)	0.763 ± 0.014	0.735–0.792	
Formal employment	132 (33)	0.836 ± 0.013	0.810–0.863	
Informal employment	76 (19)	0.807 ± 0.018	0.771–0.844	
Weekly workload				0.005
Nonworkers†	193 (48)	0.763 ± 0.014	0.735–0.792	
≥41 hours	120 (30)	0.840 ± 0.013	0.814–0.867	
40 hours	58 (15)	0.807 ± 0.021	0.763–0.851	
30 hours	20 (5)	0.834 ± 0.034	0.760–0.907	
20 hours	5 (1)	0.840 ± 0.070	0.645–0.999	
10 hours	5 (1)	0.717 ± 0.088	0.471–0.962	
Stress				<0.001
Nonworkers†	193 (48)	0.763 ± 0.014	0.735–0.792	
Yes	107 (27)	0.805 ± 0.015	0.775–0.836	
No	101 (25)	0.851 ± 0.014	0.821–0.880	

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TABLE 1 Sociodemographic Data, Occupational Characteristics, and Mean Utility Scores of Individuals With Type 1 Diabetes Treated With IGla (n = 401) *(Continued)*

Variable	Participants, n, %	Utility		P*
		Mean ± SD	95% CI	
Energy after work				<0.001
Nonworkers†	193 (48)	0.763 ± 0.014	0.735–0.792	
Yes	151 (38)	0.841 ± 0.012	0.816–0.866	
No	57 (14)	0.792 ± 0.020	0.751–0.833	

*P <0.05 is statistically significant. †Nonworkers = students, retirees, pensioners, or unemployed; A1–A2 classes = best social conditions, and D–E classes = worst social conditions (45).

Discussion

We believe this is the first study in Brazil examining the factors associated with the HRQoL of people living with type 1 diabetes treated with IGla. Most participants were young, White, from the highest social classes, and highly educated. Our findings are not surprising because, in Brazil, there is a great barrier to access to medicines provided in the SUS's Specialized Component of Pharmaceutical Assistance (CEAF) among the lower economic strata (25).

Barriers that contribute to insulin access problems for Brazilians with type 1 diabetes are numerous and complex (25). For example, patients in Minas Gerais must present at the clinic and receive a new medical prescription every 6 months (53), which includes having a current A1C test result every 6 months (30). However, these barriers are easily overcome by people from higher socioeconomic strata who have more regular access to health services, including private medical offices, private clinics, and periodic diagnostic testing than individuals belonging to the lowest economic strata in Brazil (54,55). These equity differences need to be addressed moving forward, as they also occur with other technologies and treatments for other chronic diseases (e.g., monoclonal antibodies in metastatic colorectal cancer and access to early diagnosis in breast cancer) (56,57). This effort requires medium- and long-term planning by the MoH in Brazil, mainly to improve access to CEAF medicines among the population from the lower social strata (58), and we will be monitoring this.

Individuals who were professionally active in our study reported experiencing stress resulting in worse HRQoL, which is similar to findings from other studies that have assessed HRQoL, occupational status, and level of education in patients with diabetes (59). This finding is a warning because, in addition to having a direct impact on HRQoL, stress may increase the psychosocial burden of type 1 diabetes and decrease self-care behavior and may even affect glycemic control, leading to increased macro- and microvascular complications over time (60). Consequently, people with type 1 diabetes should be monitored regularly for their mental health status.

Regarding participants' HRQoL data, low EQ-5D-3L scores were evident in those with poor/very poor self-perceived health and in those who had been bedridden and had not exercised in the past 15 days before the interview, as well as in those who had had two to four doctor's visits in the past year or had been hospitalized at least twice in the past year before the interview. These findings are similar to those found in a case-control study with 1,074 participants that compared individuals with and without diabetes (at the 1:2 ratio). The results demonstrated worse HRQoL and poor/very poor self-perceived health in individuals with diabetes (61). Negative perspectives of people with type 1 diabetes regarding their life and living with the disease may also negatively affect adherence to prescribed insulins (62). Consequently, adherence to insulin needs to be carefully monitored alongside measures to help improve HRQoL. We recognize this is more difficult in LMICs, where there can be affordability issues with monitoring equipment such as glucose testing strips, especially if these are not provided free of charge by the health service (8,10); however, hopefully the situation is changing through donor programs and other support mechanisms.

Our findings suggest worse HRQoL in people with a greater number of comorbidities, including both microvascular and macrovascular complications, which is similar to findings of previous Brazilian studies (43,63),

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TABLE 2 Clinical Data, Lifestyle Factors, Access to Health Services, and Mean Utility Scores of Individuals With Type 1 Diabetes Treated With IGla (n = 401)

Variable	Participants, n, %	Utility		P*
		Mean ± SD	95% CI	
Self-perceived health				<0.001
Very good/good	227 (57)	0.856 ± 0.010	0.836–0.876	
Fair	155 (39)	0.735 ± 0.014	0.706–0.764	
Poor/very poor	19 (4)	0.569 ± 0.032	0.501–0.638	
Bedridden in the past 15 days				<0.001
Yes	40 (10)	0.666 ± 0.033	0.599–0.734	
No	361 (90)	0.810 ± 0.009	0.792–0.828	
Physical exercise in the past 15 days				<0.001
Yes	257 (64)	0.827 ± 0.010	0.807–0.847	
No	144 (36)	0.739 ± 0.016	0.707–0.772	
Number of doctor's visits in the past year				<0.001
DK/NR	8 (2)	0.768 ± 0.063	0.617–0.919	
0–3	250 (63)	0.840 ± 0.010	0.820–0.861	
≥4	143 (35)	0.719 ± 0.015	0.689–0.750	
Number of hospitalizations in the past year				<0.001
0	312 (78)	0.840 ± 0.009	0.801–0.839	
1	72 (18)	0.729 ± 0.023	0.682–0.775	
≥2	17 (4)	0.626 ± 0.043	0.534–0.718	
Medical insurance				0.937
Yes	224 (56)	0.796 ± 0.011	0.773–0.819	
No	177 (44)	0.795 ± 0.014	0.766–0.823	
Problems accessing health services				0.025
Scheduling a doctor's appointment	143 (36)	0.787 ± 0.015	0.758–0.817	
None	110 (28)	0.836 ± 0.014	0.807–0.864	
Access to medicines	109 (26)	0.784 ± 0.017	0.749–0.820	
Others	39 (10)	0.744 ± 0.037	0.668–0.820	
Number of comorbidities (mean 1.55 ± 0.064)				<0.001
0–3	373 (93)	0.809 ± 0.008	0.791–0.826	
4–6	22 (5)	0.649 ± 0.034	0.577–0.722	
≥7	6 (2)	0.521 ± 0.111	0.234–0.807	
Systemic arterial hypertension				<0.001
Yes	62 (15)	0.676 ± 0.026	0.623–0.730	
No	339 (85)	0.817 ± 0.009	0.800–0.835	
Cardiovascular disease				<0.001
Yes	24 (6)	0.608 ± 0.042	0.519–0.697	
No	377 (94)	0.808 ± 0.008	0.790–0.825	
Stroke				<0.001
Yes	5 (1)	0.482 ± 0.058	0.319–0.645	
No	396 (99)	0.800 ± 0.008	0.782–0.817	
Kidney disease				0.006
Yes	24 (6)	0.698 ± 0.042	0.609–0.786	
No	377 (94)	0.802 ± 0.009	0.784–0.820	
Diabetic retinopathy				<0.001
Yes	41 (10)	0.646 ± 0.029	0.587–0.705	
No	360 (90)	0.813 ± 0.009	0.795–0.831	

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TABLE 2 Clinical Data, Lifestyle Factors, Access to Health Services, and Mean Utility Scores of Individuals With Type 1 Diabetes Treated With IGla (n = 401) *(Continued)*

Variable	Participants, *n*, %	Utility		*P**
		Mean ± SD	95% CI	
Dyslipidemia				0.002
Yes	10 (2)	0.623 ± 0.081	0.439–0.807	
No	391 (98)	0.800 ± 0.008	0.782–0.818	
Diabetic foot				0.164
Yes	4 (1)	0.670 ± 0.122	0.281–0.999	
No	397 (99)	0.797 ± 0.009	0.779–0.815	
Diabetic neuropathy				<0.001
Yes	27 (7)	0.582 ± 0.032	0.516–0.649	
No	374 (93)	0.811 ± 0.008	0.793–0.829	
COPD (e.g., emphysema, asthma, bronchitis)				0.001
Yes	11 (3)	0.614 ± 0.061	0.477–0.750	
No	390 (97)	0.801 ± 0.009	0.783–0.819	
Hearing problems				0.041
Yes	7 (2)	0.657 ± 0.081	0.457–0.857	
No	394 (98)	0.798 ± 0.009	0.780–0.816	
Depression				<0.001
Yes	23 (6)	0.635 ± 0.038	0.556–0.715	
No	378 (94)	0.805 ± 0.009	0.787–0.823	
Hyperthyroidism				0.318
Yes	68 (17)	0.776 ± 0.020	0.734–0.817	
No	333 (83)	0.800 ± 0.010	0.780–0.819	
Obesity				0.067
Yes	7 (2)	0.671 ± 0.076	0.483–0.859	
No	394 (98)	0.798 ± 0.009	0.780–0.816	
Any type of cancer				0.008
Yes	3 (1)	0.522 ± 0.028	0.397–0.646	
No	398 (99)	0.798 ± 0.009	0.780–0.815	
Time since diagnosis, years (mean 17.93 ± 0.519)				0.015
1–10	119 (30)	0.823 ± 0.015	0.792–0.853	
11–20	147 (35)	0.808 ± 0.014	0.780–0.835	
21–30	83 (21)	0.770 ± 0.023	0.723–0.816	
31–40	42 (11)	0.759 ± 0.023	0.713–0.806	
≥41	10 (3)	0.661 ± 0.078	0.484–0.838	
A1C (mean 7.76 ± 0.059%)				0.306
Uncontrolled	260 (65)	0.783 ± 0.016	0.750–0.816	
Controlled	141 (35)	0.802 ± 0.010	0.781–0.823	
Number of hypoglycemic episodes in the past 6 months				<0.001
1–6	183 (46)	0.797 ± 0.012	0.772–0.822	
≥7	96 (24)	0.735 ± 0.019	0.697–0.772	
0/DK	122 (30)	0.841 ± 0.016	0.809–0.874	
Type of hypoglycemia in the past 6 months				<0.001
None/NS	122 (30)	0.841 ± 0.016	0.809–0.874	
Severe hypoglycemia (needed help or medical care)	56 (14)	0.723 ± 0.027	0.668–0.779	
Nocturnal hypoglycemia	67 (17)	0.757 ± 0.022	0.712–0.801	
Hypoglycemia (did not need help or medical care)	156 (39)	0.802 ± 0.012	0.777–0.828	

Continued on p. 320 »

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« Continued from p. 319

TABLE 2 Clinical Data, Lifestyle Factors, Access to Health Services, and Mean Utility Scores of Individuals With Type 1 Diabetes Treated With IGla (n = 401) *(Continued)*

Variable	Participants, n, %	Utility		P*
		Mean ± SD	95% CI	
Alcohol consumption				0.012
No	282 (70)	0.781 ± 0.011	0.758–0.803	
Yes	119 (30)	0.831 ± 0.013	0.803–0.858	
Tobacco use				0.827
No	373 (93)	0.796 ± 0.009	0.778–0.815	
Yes	28 (7)	0.788 ± 0.037	0.711–0.866	
Glargine injection delivery				0.375
Syringe	220 (56)	0.787 ± 0.014	0.758–0.815	
Pen	181 (44)	0.803 ± 0.011	0.780–0.826	
Other insulins				0.071
NR	113 (28)	0.773 ± 0.019	0.734–0.811	
Lispro	140 (35)	0.815 ± 0.012	0.790–0.841	
Aspart	86 (21)	0.816 ± 0.018	0.779–0.835	
Glulisine	60 (15)	0.772 ± 0.024	0.772–0.822	
Other	2 (1)	–	–	
Other insulin injection delivery				0.078
NR	113 (28)	0.773 ± 0.019	0.734–0.811	
Syringe	76 (19)	0.777 ± 0.020	0.735–0.819	
Pen	212 (53)	0.817 ± 0.011	0.795–0.839	
Number of medicines used (mean 2.36 ± 0.111)				<0.001
0	11 (3)	0.776 ± 0.055	0.651–0.900	
1–4	337 (84)	0.818 ± 0.009	0.800–0.836	
≥5	53 (13)	0.656 ± 0.026	0.603–0.709	

*P <0.05 is statistically significant. DK, did not know; NR, did not respond.

as well as a study conducted among patients from Minas Gerais (40). These results suggest an association with the age profile of patients with type 1 diabetes in that our study included mostly people who were young (18–40 years of age). Young individuals appear to have greater difficulty accepting complications and comorbidities with type 1 diabetes, which may cause social stigmatization, increase their psychosocial burden, and decrease their freedom. All of these issues should be considered by health professionals when reviewing treatment options with younger patients (64,65).

Our participants reported a number of types of hypoglycemic episodes, with nocturnal episodes being the second most frequent one. In addition, hypoglycemic episodes were responsible for worse HRQoL scores. However, these findings differ from those of some other studies (66,67) that demonstrated a lower number of hypoglycemic episodes with IGla. On the other hand, Raskin et al. (68) and Yamamoto-Honda et al. (69) did not find lower numbers of hypoglycemic episodes with IGla. In addition, 71% of the participants in our study were also treated with rapid-acting insulins (i.e., lispro, aspart, and glulisine). A recent systematic review indicated that rapid-acting insulins were associated with fewer hypoglycemic episodes (total, nocturnal, and severe) when compared with regular insulins (70). We are not sure why our results conflict with this finding, and we will explore this issue in future studies. It is worth pointing out that the number of hypoglycemic episodes is directly related to worse HRQoL because of increased fear, anxiety, and emotional burden of the disease in people with type 1 diabetes. For this reason, some individuals may reduce the amount of insulin they administer as a response to their fear of hypoglycemia. Consequently, their glycemic control will be lower, as the results of our study demonstrate (71).

People treated with IGla in our study did not have adequate glycemic control. Our findings are similar to those found by Marra et al. (72) and Braga de Souza et al.

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TABLE 3 Descriptive States of EQ-5D-3L in Participants With Type 1 Diabetes Treated With IGla (N = 401)

EQ-5D-3L Dimensions	Severity*	*n* (%)
Mobility	1	350 (86)
	2	50 (13.8)
	3	1 (0.2)
Self-care	1	375 (94)
	2	25 (5.8)
	3	1 (0.2)
Usual activities	1	344 (86)
	2	52 (13)
	3	5 (1)
Pain/discomfort	1	244 (61)
	2	124 (31)
	3	33 (8)
Anxiety/depression	1	200 (50)
	2	143 (36)
	3	58 (14)

*Severity: level 1, no problem; level 2, some problems; and level 3, extreme problems.

(43), with >60% of patients having poor glycemic control as indicated by A1C. Two additional Brazilian studies (73,74) also found poor glycemic control in people with diabetes, which needs to be addressed moving forward. However, Machado-Alba et al. (42) reported that people with type 1 diabetes treated with long-acting insulin analogs reported better HRQoL than those treated with human insulin, although the difference was not statistically significant. Overall, it seems that IGla yields better results in controlled environments, but when the effectiveness of IGla treatment is assessed in real-world scenarios, the results appear to be less positive (14,25,72,75–77). Such findings may be the result of greater monitoring of patients in formal studies, encouraging greater adherence to treatment; however, this theory remains to be proven. In any event, we are seeing greater use of long-acting insulin analogs across a range of countries in view of their perceived benefits (8,12,29,78). Consequently, more studies are needed in real-world settings within LMICs to fully assess the role and value of long-acting insulin analogs if considerable price differences remain. The advent of biosimilar products may potentially reduce such price differences (12,29,72).

The HRQoL results in this study, measured by the EQ-5D-3L instrument, were similar to those found in other studies involving people living with type 1 diabetes (40,41). Overall, participants reported good health and "some problems" in the five domains of the EQ-5D-3L. Multiple regression analysis showed worse HRQoL in individuals who had a lower level of education, had poor/very poor self-perceived health, had been bedridden and had not exercised in the past 15 days, had seen a doctor more than four times in the past year, had comorbidities (systemic arterial hypertension, diabetic neuropathy, or COPD), and had seven or more episodes of hypoglycemia in the 6 months before the interview. These findings are similar to those observed by the Brazilian Type 1 Diabetes Study Group (BrazDiab1SG) (43), which identified A1C, physical activity, time since diagnosis, age, and micro- and macrovascular complications as variables associated with worse HRQoL. Conversely, in the BrazDiab1SG's work, the variables only explained 7.1% of the HRQoL variability of people with type 1 diabetes. This finding contrasts with our study, in which the associated variables explained 39.7% of the variability in EQ-5D-3L's utility score. This contrast can be partially explained by differences between the investigated populations, as the selection of participants for the current study took into account only those being treated with IGla, which was a more homogeneous population. In addition, not all of the variables that could be associated with HRQoL in people with type 1 diabetes are known; thus, results may vary between studies. On the other hand, it is known that people living with diabetes have worse HRQoL than populations without diabetes (38).

A correlation was observed between the numbers of hypoglycemic episodes, especially in individuals who had seven or more episodes, and worse HRQoL scores in our study. However, Bahia et al. (79) found no statistically significant difference in the number of hypoglycemic episodes. Again, we are not sure why these findings differed. There is a consensus that patients with more hypoglycemic episodes have worse HRQoL scores than patients who report no hypoglycemic episodes (80). Furthermore, two other studies found an association between worse HRQoL and the presence of hypoglycemia in patients with diabetes, thereby confirming the results of our regression model (39,81).

There are a number of limitations with our study. First, this is a cross-sectional study and cannot be used to analyze behavior over a longer period of time. Second, the results drew on individuals' self-reports; clinical data on treatment with other insulins and time since diagnosis were self-reported, and medical records were not available for checking. This limitation compromises the accuracy of the data. Third, the

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TABLE 4 Multiple Regression Analysis Using the Forward Stepwise Method of Factors Associated With HRQoL in Participants With Type 1 Diabetes Treated With IGla ($N = 401$)

Variable	Utility			
	Coefficient	SE	95% CI	*P**
Education, years				
<8	−0.099	0.022	−0.143 to −0.055	<0.001
≥9	0			
Self-perceived health				
Fair	−0.121	0.017	−0.154 to −0.087	<0.001
Poor/very poor	−0.286	0.039	−0.364 to −0.209	<0.001
Very good/good	0			
Bedridden in the last 15 days				
Yes	−0.144	0.029	−0.201 to −0.086	<0.001
No	0			
Physical exercise in the last 15 days				
No	−0.088	0.018	−0.124 to −0.052	<0.001
Yes	0			
Number of doctor's visits in the past year				
≥4	−0.011	0.018	−0.154 to −0.083	<0.001
1–3	0			
Systemic arterial hypertension				
Yes	−0.141	0.024	−0.188 to −0.094	<0.001
No	0			
Diabetic neuropathy				
Yes	−0.229	0.034	−0.296 to −0.161	<0.001
No	0			
COPD (e.g., emphysema, asthma, bronchitis)				
Yes	−0.187	0.055	−0.295 to −0.080	<0.001
No	0			
Number of hypoglycemic episodes in the past 6 months				
1–6	−0.044	0.021	−0.085 to −0.004	0.033
≥7	−0.107	0.024	−0.154 to −0.059	<0.001
0	0			

*P <0.05 is statistically significant.

data on type 1 diabetes diagnosis were obtained from the SUS database for the entire state of Minas Gerais and were confirmed by patient self-reports; however, there may have been outliers. Furthermore, we used some nonvalidated questionnaires to collect information on sociodemographic, occupational, clinical, and health care access variables. However, despite these limitations, we believe our findings are robust.

Conclusion

Our results suggest that there is a barrier to access to medicines in the SUS. Consequently, the Brazilian MoH needs to reassess the CEAF medicines access policy, especially for the population from lower economic strata. Another important aspect of our findings was the number of factors associated with HRQoL in individuals living with type 1 diabetes treated with IGla, and especially episodes of hypoglycemia and other comorbidities. Overall, we believe our results can provide useful information to guide future policy-making and planning for the treatment of people with type 1 diabetes in Brazil, particularly in prioritizing the follow-up of individuals with low HRQoL scores, and we will be monitoring this. Finally, we recommend continuous monitoring by the MoH of IGla and the other long-acting human insulin analogs (IDet and IDeg) in the SUS and carrying out comparative post-incorporation analyses (real-world data). These are considerations for the future.

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DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

P.H.R.F.A. contributed to the conceptualization, literature review, data curation, formal analysis, methodology, writing, and review/editing of the submitted article. B.G. and J.A-T. contributed to conceptualization, literature review, writing, and review/editing. V.d.S.N.-N., L.L.P.d.L., F.d.A.A., A.A.G.-J., V.E.d.A., and A.M.A. contributed to writing and review/editing. All authors provided final approval of the submitted article. P.H.R.F.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1. Oliveira GL, Guerra Júnior AA, Godman B, Acurcio FA. Cost-effectiveness of vildagliptin for people with type 2 diabetes mellitus in Brazil: findings and implications. Expert Rev Pharmacoecon Outcomes Res 2017;17:109–119

2. Chan JCN, Lim L-L, Wareham NJ, et al. The Lancet Commission on diabetes: using data to transform diabetes care and patient lives. Lancet 2021;396:2019–2082

3. American Diabetes Association. 1. Improving care and promoting health in populations: *Standards of Medical Care in Diabetes—2019*. Diabetes Care 2019;42(Suppl. 1):S7–S12

4. Bommer C, Sagalova V, Heesemann E, et al. Global economic burden of diabetes in adults: projections from 2015 to 2030. Diabetes Care 2018;41:963–970

5. Guney Z. Insulin and its analogues: what are they for? (pros and cons). Trends Diabetes Metab 2019;2 (doi: 10.15761/tdm.1000113)

6. Laranjeira FO, Andrade KRC, Figueiredo ACMG, Silva EN, Pereira MG. Long-acting insulin analogues for type 1 diabetes: an overview of systematic reviews and meta-analysis of randomized controlled trials. PLoS One 2018;13:e0194801

7. Tricco AC, Ashoor HM, Antony J, et al. Comparative efficacy and safety of ultra-long-acting, long-acting, intermediate-acting, and biosimilar insulins for type 1 diabetes mellitus: a systematic review and network meta-analysis. J Gen Intern Med 2021;36:2414–2426

8. Ewen M, Joosse H-J, Beran D, Laing R. Insulin prices, availability and affordability in 13 low-income and middle-income countries. BMJ Glob Health 2019;4:e001410

9. Godman B, Haque M, Kumar S, et al. Current utilization patterns for long-acting insulin analogues including biosimilars among selected Asian countries and the implications for the future. Curr Med Res Opin 2021;37:1529–1545

10. Godman B, Basu D, Pillay Y, et al. Ongoing and planned activities to improve the management of patients with type 1 diabetes across Africa: implications for the future. Hosp Pract (1995) 2020;48:51–67

11. Mainul H, Salequl I, Abdullahi Rabiu A, et al. Utilization and expenditure on long-acting insulin analogs among selected middle-income countries with high patient co-payment levels: findings and implications for the future. J Appl Pharm Sci 2021;11:172–182

12. Godman B, Haque M, Leong T, et al. The current situation regarding long-acting insulin analogues including biosimilars among African, Asian, European, and South American countries: findings and implications for the future. Front Public Health 2021;9:671961

13. Hemmingsen B, Metzendorf M-I, Richter B. (Ultra-)long-acting insulin analogues for people with type 1 diabetes mellitus. Cochrane Database Syst Rev 2021;3:CD013498

14. Almeida PHRF, Silva TBC, Assis Acurcio F, et al. Quality of life of patients with type 1 diabetes mellitus using insulin analog glargine compared with NPH insulin: a systematic review and policy implications. Patient 2018;11:377–389

15. Semlitsch T, Engler J, Siebenhofer A, Jeitler K, Berghold A, Horvath K. (Ultra-)long-acting insulin analogues versus NPH insulin (human isophane insulin) for adults with type 2 diabetes mellitus. Cochrane Database Syst Rev 2020;11:CD005613

16. Dawoud D, O'Mahony R, Wonderling D, Cobb J, Higgins B, Amiel SA. Basal insulin regimens for adults with type 1 diabetes mellitus: a systematic review and network meta-analysis. Value Health 2018;21:176–184

17. National Institute for Health and Care Excellence. Type 1 diabetes in adults: diagnosis and management. Available from https://www.nice.org.uk/guidance/ng17/chapter/1-Recommendations#insulin-therapy-2. Accessed 4 August 2021

18. Scottish Medicine Consortium. Insulin glargine (Lantus): summary of recommendation. Available from https://www.scottishmedicines.org.uk/media/1859/insuline_glargine_final.pdf. Accessed 19 August 2019

19. Scottish Medicine Consortium. 2nd Re-submission insulin degludec (Tresiba) 100 units/mL solution for injection in pre-filled pen or cartridge and 200units/mL solution for injection in pre-filled pen. Available from https://www.scottishmedicines.

Downloaded from http://ada.silverchair.com/clinical/article-pdf/40/3/312/685508/diaclincd210068.pdf by guest on 09 April 2024

org.uk/media/1850/insulin_degludec_tresiba_2ndresub_final_july_2016_updated_300716_for_website.pdf. Accessed 8 April 2021

20. Scottish Medicine Consortium. Product update: insulin detemir 100 units/mL, solution for injection in cartridge (Penfill), pre-filled pen (FlexPen) and pre-filled pen (InnoLet) (Levemir). Available from https://www.scottishmedicines.org.uk/media/1852/insulin_detemir_levemir_abbreviated_final_february_2016_for_website.pdf. Accessed 8 April 2021

21. Canadian Agency for Drugs and Technologies in Health. Insulin glargine: a long-acting insulin for diabetes mellitus. Available from https://www.cadth.ca/sites/default/files/pdf/259_insulin_glargine_cetap_e.pdf. Accessed 4 August 2021

22. Canadian Agency for Drugs and Technologies in Health. Optimal therapy recommendations for the prescribing and use of insulin analogues. Available from https://www.cadth.ca/sites/default/files/pdf/compus_IA_OT_rec_report.pdf. Accessed 4 August 2021

23. National Committee for Health Technology Incorporation into the Unified Health System. Long-acting insulin analogues for or treatment of type I diabetes mellitus. Available from http://conitec.gov.br/images/Relatorios/2019/Relatorio_Insulinas_Analogas_DM1.pdf. Accessed 6 August 2021 [in Portuguese]

24. Official Journal of the Union. Ordinance no. 19, of March 27, 2019. Available from http://conitec.gov.br/images/Relatorios/Portaria/2019/PortariaSCTIE-18-19.pdf. Accessed 22 August 2021 [in Portuguese]

25. Almeida PHRF, Godman B, Lemos LLP, et al. A cross-sectional study of the quality of life of patients living with type 1 diabetes treated with insulin glargine and neutral protamine Hagedorn insulin and the implications. J Pharm Health Serv Res 2021;12:332–342

26. Castellanos CG, Sánchez A, Lucio R. Disinvestment in health technologies: the case of insulin glargine in Equador. National Commission of Medicines and Supplies of the National Health Council. Health Technology Assessment Network of the Americas. Available from https://redetsa.org/wp/?p=3666. Accessed 4 August 2021 [in Spanish]

27. Institute for Quality and Efficiency in Health Care. Long-acting insulin analogues in the treatment of diabetes mellitus type 1: executive summary of final report A05-01, version 1.0. Available from https://www.ncbi.nlm.nih.gov/books/NBK84131. Accessed 4 August 2021

28. Gururaj Setty S, Crasto W, Jarvis J, Khunti K, Davies MJ. New insulins and newer insulin regimens: a review of their role in improving glycaemic control in patients with diabetes. Postgrad Med J 2016;92:152–164

29. Haque M, Islam S, Kamal ZM, et al. Ongoing efforts to improve the management of patients with diabetes in Bangladesh and the implications. Hosp Pract (1995) 2021;49:266–272

30. National Committee for Health Technology Incorporation into the Unified Health System. Clinical protocol and therapeutic guidelines for type 1 diabetes. Available from http://conitec.gov.br/images/Consultas/Relatorios/2019/Relatrio_Diabetes-Mellitus-Tipo-1_CP_51_2019.pdf. Accessed 8 June 2021 [in Portuguese]

31. Brazilian Health Regulatory Agency. Consultations – medicines. Available from https://consultas.anvisa.gov.br/#/medicamentos. Accessed 11 July 2021 [in Portuguese]

32. Heath Prices Database. Public report (medicines, medical-hospital materials and medicinal gases). Available from https://bps.saude.gov.br/visao/consultaPublica/relatorios/geral/index.jsf. Accessed 6 August 2021 [in Portuguese]

33. Central Bank of Brazil. Exchange rates. Available from https://www.bcb.gov.br/estabilidadefinanceira/historicocotacoes. Accessed 3 February 2020 [in Portuguese]

34. Ascef BO, Silva RGLD, Oliveira Júnior HA, Soárez PC. Interchangeability and substitution of biosimilars: is health technology assessment (HTA) a tool for decision-making? Cad Saude Publica 2019;35:e00087219 [in Portuguese]

35. Official Journal of the Union. Electronic auction 22/2021-UASG 250005. Available from https://www.in.gov.br/en/web/dou/-/aviso-de-licitacao-306326488. Accessed 22 August 2021 [in Portuguese]

36. Rosner B, Roman-Urrestarazu A. Health-related quality of life in paediatric patients with type 1 diabetes mellitus using insulin infusion systems: a systematic review and meta-analysis. PLoS One 2019;14:e0217655

37. Seaquist ER, Chow LS. Hypoglycemia in diabetes: does insulin type matter? JAMA 2017;318:31–32

38. Rwegerera GM, Moshomo T, Gaenamong M, et al. Health-related quality of life and associated factors among patients with diabetes mellitus in Botswana. Alexandria Journal of Medicine 2018;54:111–118

39. Solli O, Stavem K, Kristiansen IS. Health-related quality of life in diabetes: the associations of complications with EQ-5D scores. Health Qual Life Outcomes 2010;8:18

40. Mata AR, Álvares J, Diniz LM, et al. Quality of life of patients with diabetes mellitus types 1 and 2 from a referal health centre in Minas Gerais, Brazil. Expert Rev Clin Pharmacol 2016;9:739–746

41. Raymakers AJN, Gillespie P, O'Hara MC, Griffin MD, Dinneen SF. Factors influencing health-related quality of life in patients with type 1 diabetes. Health Qual Life Outcomes 2018;16:27

42. Machado-Alba JE, Medina-Morales DA, Echeverri-Cataño LF. Evaluation of the quality of life of patients with diabetes mellitus treated with conventional or analogue insulins. Diabetes Res Clin Pract 2016;116:237–243

43. Braga de Souza ACC, Felício JS, Koury CC, et al.; Brazilian Type 1 Diabetes Study Group (BrazDiab1SG). Health-related quality of life in people with type 1 diabetes mellitus: data from the Brazilian Type 1 Diabetes Study Group. Health Qual Life Outcomes 2015;13:204

44. Secretary of State for Health of Minas Gerais. SES-MG no. 2359 of June 17, 2010. Available from www.saude.mg.gov.br/images/documentos/resolucao_2359.pdf. Accessed 6 August 2021 [in Portuguese]

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45. Kamakura W, Mazzon JA. Socioeconomic stratification criteria and classification tools in Brazil. Revista de Administração de Empresas 2016;56:55–70 [in Portuguese]

46. World Health Organization. Global health observatory data: mean body mass index: situation and trends. Available from https://www.who.int/data/gho/data/themes/topics/topic-details/GHO/body-mass-index. Accessed 8 August 2021

47. American Diabetes Association. 6. Glycemic targets: *Standards of Medical Care in Diabetes—2019*. Diabetes Care 2019;42(Suppl. 1):S61–S70

48. American Diabetes Association. 12. Older adults: *Standards of Medical Care in Diabetes—2019*. Diabetes Care 2019;42(Suppl. 1):S139–S147

49. Andrade MV, Noronha K, Reis CB, et al. Value system of the EQ-5D instrument for measuring health-related quality of life: an analysis for the state of Minas Gerais. Available from https://www.researchgate.net/publication/266416984_SISTEMA_DE_ VALORES_DO_INSTRUMENTO_EQ5D_DE_MENSURAO_DE_QUALIDADE_DE_VIDA_RELACIONADA_SADE_UMA_ANLISE_PARA_O_ESTADO_DE_MINAS_GERAIS. Accessed 11 August 2021 [in Portuguese]

50. Santos M, Cintra MACT, Monteiro AL, et al. Brazilian valuation of EQ-5D-3L health states: results from a saturation study. Med Decis Making 2016;36:253–263

51. EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208

52. EuroQol Group. EQ-5D-3L: user guide basic information on how to use the EQ-5D-3L instrument. Available from https://euroqol.org/publications/user-guides. Accessed 8 July 2018

53. Brazilian Ministry of Health. Consolidation ordinance no. 2, September 28, 2017. Available from https://bvsms.saude.gov.br/bvs/saudelegis/gm/2017/prc0002_03_10_2017.html. Accessed 8 June 2021 [in Portuguese]

54. Oliveira LCF, Nascimento MAA, Lima IMSO. Access to medication in universal health systems: perspectives and challenges. Saúde Debate 2019;43(Suppl. 5):286–298 [in Portuguese]

55. Gomes MB, Rodacki M, Pavin EJ, et al. The impact of ethnicity, educational and economic status on the prescription of insulin therapeutic regimens and on glycemic control in patients with type 1 diabetes: a nationwide study in Brazil. Diabetes Res Clin Pract 2017;134:44–52

56. Lemos LLP, Carvalho de Souza M, Pena Moreira D, et al. Stage at diagnosis and stage-specific survival of breast cancer in Latin America and the Caribbean: a systematic review and meta-analysis. PLoS One 2019;14:e0224012

57. Silva WC, Araujo VE, Lima EMEA, et al. Comparative effectiveness and safety of monoclonal antibodies (bevacizumab, cetuximab, and panitumumab) in combination with chemotherapy for metastatic colorectal cancer: a systematic review and meta-analysis. BioDrugs 2018;32:585–606

58. Silva MRR, Santos JBR, Almeida AM, Alvares-Teodoro J, Kakehasi AM, Acurcio FA. Access to high-cost medications for psoriatic arthritis in the National Health System in Brazil: the long path up to dispensation. Adv Rheumatol 2019;59:48

59. Nielsen HB, Ovesen LL, Mortensen LH, Lau CJ, Joensen LE. Type 1 diabetes, quality of life, occupational status and education level: a comparative population-based study. Diabetes Res Clin Pract 2016;121:62–68

60. Hilliard ME, Yi-Frazier JP, Hessler D, Butler AM, Anderson BJ, Jaser S. Stress and A1c among people with diabetes across the lifespan. Curr Diab Rep 2016;16:67

61. Esteban y Peña MM, Hernandez Barrera V, Fernández Cordero X, et al. Self-perception of health status, mental health and quality of life among adults with diabetes residing in a metropolitan area. Diabetes Metab 2010;36:305–311

62. Goh CSY, Mohamed A, Lee YS, et al. The associations of self-care, illness perceptions and psychological distress with metabolic control in Singaporean adolescents with type 1 diabetes mellitus. Health Psychol Behav Med 2016;4:1–14

63. Melo LGN, Morales PH, Drummond KRG, et al. Current epidemiology of diabetic retinopathy in patients with type 1 diabetes: a national multicenter study in Brazil. BMC Public Health 2018;18:989

64. Smith-Palmer J, Bae JP, Boye KS, Norrbacka K, Hunt B, Valentine WJ. Evaluating health-related quality of life in type 1 diabetes: a systematic literature review of utilities for adults with type 1 diabetes. Clinicoecon Outcomes Res 2016;8:559–571

65. Piette JD, Kerr EA. The impact of comorbid chronic conditions on diabetes care. Diabetes Care 2006;29:725–731

66. Rys P, Wojciechowski P, Rogoz-Sitek A, et al. Systematic review and meta-analysis of randomized clinical trials comparing efficacy and safety outcomes of insulin glargine with NPH insulin, premixed insulin preparations or with insulin detemir in type 2 diabetes mellitus. Acta Diabetol 2015;52:649–662

67. Fiesselmann A, Wiesner T, Fleischmann H, Bramlage P. Real-world therapeutic benefits of patients on insulin glargine versus NPH insulin. Acta Diabetol 2016;53:717–726

68. Raskin P, Klaff L, Bergenstal R, Hallé JP, Donley D, Mecca T. A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. Diabetes Care 2000;23:1666–1671

69. Yamamoto-Honda R, Takahashi Y, Yoshida Y, et al. Use of insulin glargine in Japanese patients with type 1 diabetes. Intern Med 2007;46:937–943

70. Melo KFS, Bahia LR, Pasinato B, et al. Short-acting insulin analogues versus regular human insulin on postprandial glucose and hypoglycemia in type 1 diabetes mellitus: a systematic review and meta-analysis. Diabetol Metab Syndr 2019;11:2

71. Fidler C, Elmelund Christensen T, Gillard S. Hypoglycemia: an overview of fear of hypoglycemia, quality-of-life, and impact on costs. J Med Econ 2011;14:646–655

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72. Marra LP, Araújo VE, Oliveira GC, et al. The clinical effectiveness of insulin glargine in patients with type I diabetes in Brazil: findings and implications. J Comp Eff Res 2017;6:519–527

73. Viana LV, Leitão CB, Kramer CK, et al. Poor glycaemic control in Brazilian patients with type 2 diabetes attending the public healthcare system: a cross-sectional study. BMJ Open 2013;3:e003336

74. Mendes ABV, Fittipaldi JAS, Neves RCS, Chacra AR, Moreira ED Jr. Prevalence and correlates of inadequate glycaemic control: results from a nationwide survey in 6,671 adults with diabetes in Brazil. Acta Diabetol 2010;47:137–145

75. Caires de Souza AL, Assis Acurcio F, Guerra Júnior AA, Rezende Macedo do Nascimento RC, Godman B, Diniz LM. Insulin glargine in a Brazilian state: should the government disinvest? An assessment based on a systematic review. Appl Health Econ Health Policy 2014;12:19–32

76. Marra LP, Araújo VE, Silva TBC, et al. Clinical effectiveness and safety of analog glargine in type 1 diabetes: a systematic review and meta-analysis. Diabetes Ther 2016;7:241–258

77. Silva TBC, Almeida PHRF, Araújo VE, et al. Effectiveness and safety of insulin glargine versus detemir analysis in patients with type 1 diabetes: systematic review and meta-analysis. Ther Adv Endocrinol Metab 2018;9:241–254

78. Cefalu WT, Dawes DE, Gavlak G, et al. Insulin Access and Affordability Working Group: conclusions and recommendations. Diabetes Care 2018;41:1299–1311

79. Bahia L, Kupfer R, Momesso D, et al. Health-related quality of life and utility values associated to hypoglycemia in patients with type 1 diabetes mellitus treated in the Brazilian Public Health System: a multicenter study. Diabetol Metab Syndr 2017;9:9

80. Strandberg RB, Graue M, Wentzel-Larsen T, Peyrot M, Wahl AK, Rokne B. The relationships among fear of hypoglycaemia, diabetes-related quality of life and psychological well-being in Norwegian adults with type 1 diabetes. Diabetes Res Clin Pract 2017;124:11–19

81. Zhang Y, Wu J, Chen Y, Shi L. EQ-5D-3L decrements by diabetes complications and comorbidities in China. Diabetes Ther 2020;11:939–950

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