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Research Paper

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

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Abstract

Objectives The study aim was to identify key factors associated with the health-related quality of life (HRQOL) of patients with type 1 diabetes mellitus (T1DM) treated with neutral protamine Hagedorn (NPH) insulin or human insulin analog glargine (IGLA).

Methods We conducted two cross-sectional studies in Minas Gerais State, Brazil. One with 401 patients treated with IGLA, and the other with 179 T1DM patients treated with NPH. HRQOL was measured by Euroqol (EQ-5D-3L).

Key findings Most participants were male (51%), aged between 18 and 40 years (47%), non-black (58%) and from the highest economic strata (A1-B2) (74%). Participants perceived their health as good/very good (51%), had one to three medical consultations in the previous year (51%), were not hospitalized in the previous year (74%), did not report angina (96%), diabetic neuropathy (90%), hearing loss (94%) or kidney disease (89%). Non-severe hypoglycaemia episodes in the last 30 days were reported by 17% of participants.

Conclusions Higher HRQOL was associated with younger age (18–40 years), good/very good health self-perception, having had up to three medical consultations in the last year, not being hospitalized in the last year, having none to three comorbidities, not reporting angina, diabetic neuropathy, hearing loss or kidney disease and having had episodes of non-severe hypoglycaemia. In addition, the findings of our study demonstrated inequalities in access to treatment, which will be the subject of future research projects.

Keywords: Brazil, type 1 diabetes mellitus; human insulin; human insulin analogue; quality of life; EQ-5D-3L

Introduction

Diabetes mellitus (DM) is a highly prevalent and costly chronic disease that requires continuous care including medicines to prevent the complications of diabetes, which include cardiovascular diseases, neuropathy and nephropathy as well as premature death.[1–8] According to the International Diabetes Federation, approximately 463 million adults were living with DM worldwide in 2019, and this figure is likely to grow to 700 million by 2045.[9] Among DM subtypes, type 1 diabetes mellitus (T1DM) represents 5–10% of the cases.[1]

Various types of insulin are available for the treatment of T1DM, which differ mainly by their pharmacokinetic parameters. Fast-acting insulins, such as regular and lispro insulins, are indicated for the glycaemic load associated with the main meal of the day. To maintain glycaemic levels throughout the day and between meals, intermediate or long-acting insulins, such as neutral protamine Hagedorn (NPH) insulin and insulin analogue glargine (IGLA), detemir (IDET) and insulin degludec (IDEG), are indicated. NPH or insulin recombinant DNA (DNA-r) has been among the first choice of basal insulin[10, 11] as typically they are considerably less expensive than analogue insulins – an especially important decision factor for lower- and middle-income countries where availability of insulins is a major concern especially in patients with T1DM.[12–15]

The Brazilian Network of Health Technology Assessment (*Rede Brasileira de Avaliação de Tecnologias em Saúde* [REBRATS]) systematic review of 2010 showed that because of the methodological biases identified in randomized controlled trials (RCTs) it was not possible to identify clear differences between IGLA and NPH insulin with respect to glycaemic control and safety.[16] In addition in 2014, the National Commission for Technology Incorporation in the Unified Health System (*Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde* [SUS] – Conitec), which makes recommendations to the Ministry of Health of Brazil regarding the potential funding of technologies within the public health system of Brazil – the SUS, did not recommend the incorporation of IGLA for the treatment of people with T1DM.[17] Although the available evidence does not prove the superiority of IGLA versus NPH insulin, especially in relation to glycated haemoglobin (HbA1c),[18–25] the Committee received a new request for incorporation of long-acting insulin analogs (IGLA, IDET and IDEG), this time from the health authority of Minas Gerais State. In this new decision, Conitec recommended the incorporation of human insulin analogs in SUS for patients with T1DM provided that their cost is not greater than that of NPH insulin (US$ 5.41 per vial). This limitation was imposed due to the estimated incremental budget impact ranging from US$ 168 million to US$ 3.7 billion over 5 years with the usual prices.[26] It is worth mentioning that in 2005, Minas Gerais State listed IGLA in response to a large number of lawsuits against the state for the provision of this insulin analogue, as lawsuits requesting high-cost medicines outside the list SUS are common in Brazil.[18, 27]

Consequently, concerns regarding the sustainability of SUS following the incorporation of long-acting insulin analogs in 2019 are legitimate; however, eased by the entry of biosimilars at lower prices across countries.[28] In 2017, the Brazilian National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, Anvisa) gave market authorization to biosimilar of IGLA (Abasaglar, Lilly) at a retail price 70% lower than IGLA and 45% lower than IDET.[21] In July 2018, a second biosimilar was approved by Anvisa, which is Biomm's Glargilin.[29]

Desirable glycaemic control while also minimizing episodes of hypoglycaemia is a fundamental aspect to improving health-related quality of life (HRQOL) among patients with T1DM especially considering that approximately 10% of the deaths of T1DM patients, especially of young people, are due to hypoglycaemia.[30] It is important to stress that the psychosocial burden of living with DM is considerable since it affects self-care behaviour leading to non-glycaemic control, as well as increasing both macro and microvascular complications, all contributing to lower HRQOL unless addressed.[31, 32] Consequently, it is important to understand which factors are associated with a lower HRQOL in patients with T1DM to be able to act on them to alleviate the physical and psychosocial burden related to DM, which if addressed can potentially reduce morbidity, mortality and costs associated with DM.[33]

Currently, there no consensus about which factors influence the QOL of patients with DM. However, the following have been highlighted in various studies: insulin therapy and compliance to it, hypoglycaemia episodes, glycaemic control, age, ethnicity, social level, education level, employment, complications of the disease, psychological and family factors, as well as knowledge about the disease and self-health care.[33–36] A range of instruments are currently available to assess the HRQOL of patients with T1DM.[37] The generic instrument EuroQol (EQ-5D-3L)[38] can be used both in healthy individuals and in groups of patients with different types of diseases, such as DM, and is widely used in economic analyses.[34, 36, 38]

We have previously shown in a systematic review that there are only a limited number of robust studies evaluating the QOL of individuals treated with IGLA versus NPH insulin, and that these studies are heterogeneous in terms of the QOL instrument used.[31] In addition, there is also a scarcity of such studies in Brazil, since no study in the systematic review used EQ-5D-3L to assess QOL.[31] Consequently, we sought to assess the HRQOL of people living with T1DM using IGLA or NPH insulin and to identify which key factors are associated with it with data from two independent cross-sectional studies. We believe our findings can potentially be used to guide future treatment approaches.

Methods

Study design, setting and participants

This is a non-comparative analysis of data from two cross-sectional studies that assessed the HRQOL of people living with T1DM, one with patients treated with IGLA and the other with patients treated with NPH insulin. The first study was conducted in March 2017 with 401 patients treated with IGLA identified in the SUS database across the state of Minas Gerais, Brazil. The second study was conducted between January and February 2014 with 179 patients treated with NPH insulin conducted in 63 municipalities in Minas Gerais, Brazil.[39] It should be noted that we could not undertake a comparative study as we used different populations at different time points with a different number of patients, however, with the same inclusion and exclusion criteria. We sought though to combine the data to provide an assessment of the QOL of individuals living with T1DM and key factors of interest.

We used the same inclusion and exclusion criteria in both cross-sectional studies.[39] The following inclusion criteria were applied: patients with T1DM, aged 18 years or more, treated with IGLA for a period equal to or superior to 6 months, with or without other insulins. The following exclusion criteria were applied: patients with a diagnosis of mental disorders (except for depression and bipolar disorder), bedridden, patients with the cognitive deficit, pregnant or lactating women and patients diagnosed with adult latent autoimmune diabetes. Data from these different studies were used because patients with T1DM prescribed IGLA can only obtain this in pharmacies of the Government of the State of Minas Gerais due to current restrictions. This means access to IGLA insulin within the public system can only be authorized once an assessment has been performed against an agreed clinical protocol specific to IGLA within the state of Minas Gerais.[40] However, the dispensing of NPH insulin is performed by multiple pharmacies of the municipal government, which are different from the pharmacies dispensing IGLA, and no such restrictions apply. Consequently, it can be difficult to obtain reliable utilization data. As a result, we necessarily adopted this pragmatic approach.

Patients were selected from IGLA requests submitted to Minas Gerais Health Authority. We interviewed patients through telephone calls. Up to five attempts were made at different times. In case of no response, the patient was excluded from the study. It is worth mentioning that the administrative processes of the patients were chosen at random, as they were available in the database of the Minas Gerais Health Authority.

Study instrument

We used the same instrument for both cross-sectional studies.[39] The instrument comprised a questionnaire addressing the following aspects: (1) socio-demographic characteristics (age, gender, race, marital status, school years, type of dwelling, presence of other residents in the household and economic class based on criteria used by the Brazilian Economic Classification methodology of the Brazilian Association of Research Companies [*Associação Brasileira de Empresas de Pesquisa*, ABEP])[41]; (2) clinical parameters and access to health services (self-perception of health, medical consultations, hospitalizations in the last year, private health insurance, self-reported comorbidities, time of T1DM diagnosis, consumption of alcohol and tobacco, problems to access health services, extent of physical exercise, self-reported episodes of hypoglycaemia and types, i.e. severe or non-severe, in the last 30 days, other insulins used); (3) the patient's QOL – measured by the validated version for the Brazilian population of the EQ-5D-3L.[42] The EQ-5D-3L is composed of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and three levels of severity (no problem, moderate problem or problem and more serious problems).[38] The combination of these dimensions and severity levels identify 243 health states with respective utility values.[42]

Statistical analysis

Categorical variables were presented as absolute and relative frequencies and the continuous variables as means and standard deviations. We performed the following tests to check the differences between the groups treated with either IGLA or NPH insulin: we used Fisher's exact test or Pearson's chi-square test for categorical variables, and for comparison of continuous variables, independent samples Student's *t*-test or analysis of variance was used. For the utilities of EQ-5D-3L, we verified normality parameters using the Kolmogorov–Smirnov test.

We performed multiple linear regression analysis using the forward stepwise method with the utilities of the EQ-5D-3L as the dependent variable and all other variables as explanatory variables. The explanatory variables that obtained P values <0.05 remained in the final model. The suitability of the model was assessed by residue analysis.

The analyses were performed using the IBM Statistical Package for the Social Sciences software, version 26.0, 2019 (IBM Corp., Armonk, USA) and we adopted 95% confidence intervals (95% CIs).

Compliance with ethical standards

The research followed all current ethical principles and was approved by the Ethics and Research Committee of the Federal University of Minas Gerais under the protocol n. 55876816.0.0000.519, observing the principles of patient confidentiality according to the declaration of Helsinki.

The date of approval of the ethical committee was 2 June 2016 (head of the ethical committee). The approval number was 1.572.257. We also obtained informed consent from the patients before initiating the interviews.

Results

Of the 580 patients evaluated, most were women (54%), aged between 18 and 40 years (47%) with a mean age of 44.13 years (18.507), self-declared as non-black (53%), without a partner (54%), studied for 9 years or more (60%), owned their own homes (81%), did not live alone (93%) and were between the economic classes A1 and B2 (Table 1).

51% of the patients reported having a self-perception of good/very good health. In the previous year, 51% had one to three consultations and 74% were not hospitalized. Fifty-three percent did not have private health insurance, 58% practiced physical activities and 87% had not been bedridden in the last 15 days. Direct access to physicians and difficulties in scheduling medical consultations accounted for 35% of the most recurring problems in accessing health services (Table 2).

Most participants reported having between one and three comorbidities, with a mean of 2.44 (2.406) comorbidities per person. The most self-reported comorbidities were systemic arterial hypertension (30%), hyperthyroidism (16%), diabetic retinopathy (15%), cardiovascular disease (13%), dyslipidaemia (12%), depression (12%), kidney disease (11%) and diabetic neuropathy

Table 1 Socio-demographic characteristics of patients with type 1 diabetes mellitus (n = 580), Minas Gerais, Brazil, 2017 (IGLA users = 401) and 2014 (NPH insulin users = 179)

Variables		Total = 580		NPH = 179		IGLA = 401	
		n	%	*n*	%	*n*	%
Gender							
	Female	313	54	114	64	199	49
	Male	267	46	65	36	202	51
Age							
		44.13 ± 18.507		51.69 ± 19.858		40.76 ± 16.831	
	18–40	275	47	52	29	223	56
	41–60	174	30	57	32	117	30
	61–90	131	23	70	39	61	14
Ethnicity							
	Black	270	47	102	57	168	42
	Non-black	310	53	77	43	233	58
Marital status							
	With partner	265	46	78	44	187	47
	Without partner	315	54	101	56	214	53
School years							
	<9 years	231	40	154	86	77	19
	≥9 years	349	60	25	14	324	81
Type of dwelling							
	Ownership	109	19	34	19	75	19
	No ownership	471	81	145	81	326	81
Residents in dwelling							
	Only the interviewee	40	7	13	7	27	8
	Other people	540	93	166	93	374	92
Economic classes							
	A1–A2	200	34	1	0.5	199	50
	B1	201	35	7	4	194	48
	B2	27	5	19	11	8	2
	C1	45	7	45	25	0	0
	C2	48	8	48	27	0	0
	D–E	59	11	59	33	0	0

A1–A2 = richest and D–E = poorest.[41]

(10%). The other comorbidities self-reported presented less than 10% of the observations and are available in Table 2. The time since the diagnosis of T1DM ranged from 1 to 65 years, with a mean of 17.05 years (10.970). 74% of the patients did not consume alcohol, 98% did not smoke and 43% did not use other insulins (Table 2).

Of those who used other insulins, lispro was the most used (25%). Of the 580 patients who participated in the study, 65% reported they did not experience episodes of hypoglycaemia in the last 30 days. In addition, 191 patients described the severity of their episodes of hypoglycaemia. Non-severe hypoglycaemic episodes prevailed in 18% of the reports. With respect to episodes of hypoglycaemia among the treatment groups (n = 191), patients treated with IGLA reported a higher number of episodes compared with those treated with NPH insulin (66% versus 34%, respectively; Table 2).

Regarding HRQOL, EQ-5D-3L analysis showed that 29% of patients with T1DM had a perfect health state (11111), followed by 11112 (13%), 11122 (10%) and 11121. Other health states are given in Table 3.

Moderate problems that had an impact on HRQOL were reported in the dimensions of anxiety/depression and pain/discomfort with the same value (35%), mobility (19%) and usual activities (e.g. work, study, housework, family or leisure activities; 17%) and self-care, i.e. moderate problems in carrying out usual activities such as work, family or leisure activities and having moderate self-care problems such as having difficulty to preserve or improve one's health (7%). For the group treated with IGLA, these values were 36% for anxiety/depression, 31% for pain/discomfort, 13.8% for mobility, 13% for usual activities and 5.8% for personal care. Moderate problems in NPH insulin-treated patients were 44% for pain/discomfort, 35% for mobility, 34% for anxiety/depression, 25% for usual activities and 9% for self-care (Table 3).

Regarding utilities, the total population (n = 580) presented a mean utility of 0.731 (0.202, 95% CI, 0.744 to 0.777). Patients with T1DM treated with IGLA (n = 401) had a mean utility of 0.796 (0.181, 95% CI, 0.778 to 0.813) and NPH insulin-treated patients (n = 179) had a mean utility of 0.683 (0.224, 95% CI, 0.650 to 0.716). The mean utilities of all variables are given in Supplementary Tables 1 and 2.

Multiple regression analysis showed that higher HRQOL was associated with younger age; a self-perception of health as very good/good; a maximum of three medical consultations in the previous year; no hospitalization in the previous year; reporting up to three comorbidities; not reporting angina, diabetic neuropathy, hearing problems and kidney disease and having had episodes of non-severe hypoglycaemia (Table 4). The variables that remained in the final model explained 23.8% of the EQ-5D-3L utility variability.

Table 2 Clinical information, life style and access to health services of patients with diabetes mellitus type 1 ($n = 580$), Minas Gerais, Brazil, 2017 (IGLA users = 401) and 2014 (NPH insulin users = 179)

Variables		Total = 580		NPH = 179		IGLA = 401	
		n	%	*n*	%	*n*	%
Self-perception of health							
	Good/Very good	296	51	69	39	227	57
	Regular	229	39	74	41	155	39
	Bad/Very bad	55	10	36	20	19	4
Bedridden in the last 15 days							
	Yes	79	13	39	22	40	10
	No	501	87	140	78	361	90
Number of medical consultations on the last year							
	0–3	315	54	65	36	250	63
	4 or more	255	44	112	63	143	35
	DK/DR	10	2	2	1	8	2
Number of hospitalizations on the last year							
	None	430	74	118	66	312	78
	1	112	20	40	22	72	18
	2 or more	38	6	21	12	17	4
Private health insurance							
	Yes	270	47	46	26	224	56
	No	310	53	133	74	177	44
Physical activity in the last 15 days							
	Yes	335	58	78	44	257	64
	No	245	42	101	56	144	36
Problems to access health services							
	Schedule an appointment	196	35	53	30	143	36
	None	189	31	80	45	110	28
	Access to medicines	132	22	22	13	109	26
	Other	63	12	24	12	39	10
Number of comorbidities							
		2.44 ± 2.406		4.44 ± 3.054		1.55 ± 1.289	
	0–3	446	77	73	41	373	93
	4–6	83	14	61	34	22	5
	7 or more	51	9	45	25	6	2
Systemic arterial hypertension							
	Yes	176	30	114	64	62	15
	No	404	70	65	36	339	85
Cardiovascular disease							
	Yes	75	13	51	28	24	6
	No	505	87	128	72	377	94
Stroke							
	Yes	20	3	15	8	5	1
	No	560	96	164	92	396	99
Kidney disease							
	Yes	66	11	42	23	24	6
	No	514	89	137	77	377	94
Diabetic retinopathy							
	Yes	88	15	47	26	41	10
	No	492	85	132	74	360	90
Dyslipidaemia							
	Yes	73	12	63	35	10	2
	No	507	88	116	65	391	98
Obesity							
	Yes	47	8	40	22	7	2
	No	533	92	139	78	394	98
Diabetic foot							
	Yes	36	6	32	18	4	1
	No	544	94	147	82	397	99
Diabetic neuropathy							
	Yes	62	10	35	20	27	7
	No	518	90	144	80	374	93

Table 2 Continued

Variables		Total = 580		NPH = 179		IGLA = 401	
		n	%	*n*	%	*n*	%
Chronic lung disease (e.g. emphysema, asthma and bronchitis)							
	Yes	41	7	30	17	11	3
	No	539	93	149	83	390	97
Hearing loss							
	Yes	35	6	28	7	7	2
	No	545	94	151	93	394	98
Depression							
	Yes	71	12	48	27	23	6
	No	509	88	131	73	378	94
Hyperthyroidism							
	Yes	94	16	26	14	68	17
	No	486	84	153	86	333	83
Any type of cancer							
	Yes	12	2	9	5	3	1
	No	568	98	170	95	398	99
Spondylarthritis							
	Yes	51	9	40	22	11	3
	No	529	91	139	78	390	97
Thrombosis or cerebral ischaemia							
	Yes	13	2	12	7	1	0.2
	No	567	98	167	93	400	99.8
Any type of angina							
	Yes	24	4	23	13	1	0.2
	No	556	96	156	87	400	99.8
Time since diagnosis of T1DM (years)							
		17.05 ± 10.970		15.07 ± 11.950		17.93 ± 10.400	
	1–10	199	34	80	44	119	30
	11–20	209	36	62	35	147	35
	21–30	105	18	22	12	83	21
	31–40	52	9	10	6	42	11
	41 or more	15	3	5	3	10	3
Hypoglycaemia episodes in the last 30 days							
	Yes	191	33	64	36	127	32
	No	379	65	115	64	264	66
	DK/DR	10	2	0	0	10	2
Type of episodes hypoglycaemia							
	Severe	93	16	46	26	47	12
	Non-severe	98	17	18	10	80	20
	None/DK/DR	389	67	115	64	274	68
Alcohol consumption							
	No	429	74	32	18	282	70
	Yes	151	26	147	82	119	30
Tobacco consumption							
	Yes	58	10	30	17	28	7
	No	522	90	149	83	373	93
Use of other insulins							
	None	249	43	136	76	113	28
	Lispro	147	25	7	4	140	35
	Asparte	88	15	2	1	86	21
	Glulisin	60	10	0	0	60	15
	Other	36	7	34	19	2	1

DK, did not know; DR, did not respond; T1DM, type 1 diabetes mellitus.

Discussion

Patients with T1DM treated with IGLA in this study were mostly white, with a high educational level and of the higher social strata. This result is not surprising, as in Brazil there is a major barrier to access to medicines the Specialized Component of Pharmaceutical Assistance of the SUS (CEAF/SUS). Access to the high-cost medicines, CEAF/SUS, such as IGLA, requires the opening of an administrative claim which has to be updated every 6 months with a new medical prescription. This access barrier is more easily overcome by those from

Table 3 EQ-5D-3L score of patients with diabetes mellitus type 1 (*n* = 580), Minas Gerais, Brazil, 2017 (IGLA users = 401) and 2014 (NPH insulin users = 179)

Variable		Total = 580		NPH = 179		IGLA = 401	
	Severity*	*n*	%	*n*	%	*n*	%
Mobility	1	459	80	109	61	350	86
	2	112	19	62	35	50	13.8
	3	9	1	8	4	1	0.2
Self-care	1	529	91	154	86	375	94
	2	41	7	16	9	25	5.8
	3	10	2	9	5	1	0.2
Usual activities	1	466	80	122	68	344	86
	2	96	17	44	25	52	13
	3	18	3	13	7	5	1
Pain/discomfort	1	311	54	67	37	244	61
	2	202	35	78	44	124	31
	3	67	11	34	19	33	8
Anxiety/depression	1	285	49	85	47	200	50
	2	203	35	60	34	143	36
	3	92	16	34	19	58	14

*Severity: Level 1, indicating no problem; Level 2, indicating some problems; Level 3, indicating extreme problems.[38, 42]

Table 4 Forward stepwise multiple regression analysis of factors associated with quality of life of patients with type 1 diabetes mellitus (*n* = 580)

Variable		Utility		
		Coeficient	SE±	*P* value*
Age (years)	41–60	−0.040	0.018	0.027
	61–90	−0.055	0.020	0.006
	18–40	0		
Self-perception of health	Regular	−0.085	0.017	<0.001
	Bad/Very bad	−0.372	0.026	<0.001
	Good/Very good	0		
Number of consultations on the last year	DK/DR	−0.085	0.050	0.087
	4 or more	−0.148	0.018	<0.001
	0–3	0		
Number of hospitalizations on the last year	1	−0.054	0.021	0.010
	2 or more	−0.119	0.034	<0.001
	None	0		
Number of comorbidities	4–6	−0.055	0.030	0.063
	7 or more	−0.136	0.023	<0.001
	0–3	0		
Any type of angina				
	Yes	−0.147	0.039	<0.001
	No	0		
Diabetic neuropathy				
	Yes	−0.064	0.028	0.022
	No	0		
Hearing loss				
	Yes	−0.089	0.035	0.012
	No	0		
Kidney disease				
	Yes	−0.101	0.026	<0.001
	No	0		
Type of episodes of hypoglycaemia	Severe	−0.043	0.017	0.012
	Non-severe	0		

DK, did not know; DR, did not respond; SE, standard error.
*$P < 0.05$.

the higher socio-economic strata. In the multicenter cross-sectional study of the Brazilian Type 1 Diabetes Study Group similar results were found, as patients with T1DM treated with insulin analogues (among them, IGLA) had higher education, better economic conditions and were white.[43] Another study, focussing on psoriatic arthritis, also showed that patients with access to medicines from CEAF/

SUS are from the higher socio-economic strata and that the prescriptions came from private medical offices.[44] Furthermore, medicines access barriers are seen in other chronic diseases in Brazil (e.g. cancer),[45, 46] in the technical report of the Pan American Health Organization[47] and data from the National Survey on Access, Use and Promotion of Rational Use of Medicines.[48] These studies all indicated greater access to medicines from higher economic classes to the detriment of the lower classes. This can be explained, in part, by the greater access to health services, such as private medical offices, private clinics and diagnostic tests by patients belonging to the highest socio-economic strata.[49, 50] It is noteworthy that continuous access to IGLA requires the presentation of HbA1c results every 6 months[51]; however, access to this exam is considerably unequal.[49, 52–54] Although this study did not specifically investigate access to CEAF/SUS medicines, the findings reinforce the evidence of a considerable access barrier to medicines from CEAF/SUS. This difference in equity needs to be addressed and will be the subject of future research projects, as it occurs for instance in accessing the diagnosis of breast cancer in Brazil.[55]

The number of self-reported comorbidities in this study was similar to those found in other studies with patients with DM in Brazil, that is a higher prevalence of individuals with systemic arterial hypertension, hyperthyroidism, diabetic retinopathy, cardiovascular disease, dyslipidaemia, depression, kidney disease and diabetic neuropathy.[34, 43, 56] This raises concern since most of the study participants were women. It is known that women with DM have a lower number of microvascular complications compared with men with DM, but they present a greater number of macrovascular complications in general such as coronary artery disease and stroke.[57] As complications related to DM are related to a poorer HRQOL,[32, 35] it is important to promote public policies to address both the early diagnosis of micro and macrovascular problems and the treatment corrections needed for their control.

The treatment groups IGLA and NPH insulin showed appreciable differences in relation to clinical profiles and access to health services. Overall, patients treated with IGLA had better self-perceived health, were less bedridden in the last 15 days, attended one to three medical consultations in the last year, were not hospitalized in the last year, exercised regularly in the last 15 days and reported fewer comorbidities. In addition, they reported fewer comorbidities compared with patients treated with NPH insulin. However, these patients were of a higher economic class and had higher schooling. This again may be related to greater access to health services through a double public–private doorway for individuals with a better socio-economic status,[58] as well as greater access to information on the disease and T1DM care and to medicines.[50] These are important considerations because initially IGLA was only provided free of charge following a successful collective lawsuit[18] which may have increased access barriers especially for patients from lower economic classes who can be less confident using the judiciary to obtain high-cost medicines.[27, 59]

With respect to the type of hypoglycaemic episode, individuals treated with NPH insulin self-reported more episodes of severe hypoglycaemia in relative numbers compared with individuals treated with IGLA. However, in terms of absolute number, IGLA patients presented one episode of severe hypoglycaemia more than the NPH insulin. This compares with the study conducted by Ratner *et al.*[60] where the authors found a lower number of episodes of severe hypoglycaemia in IGLA-treated individuals when compared with NPH insulin-treated group. In addition, two other retrospective cohort studies showed a reduction in the number of hypoglycaemic episodes in the groups treated with IGLA versus NPH insulin, but without statistically significant differences in glycaemic control.[61, 62] The results of an RCT showed that, in general, there were no differences in the number of episodes of hypoglycaemia between patients treated with IGLA versus NPH insulin.[63] In general, the findings are conflicting in the literature in terms of hypoglycaemic episodes, as some studies show that the episodes are more frequent in patients treated with IGLA when compared with patients treated with NPH insulin and other studies show the opposite. It should be noted that in some articles there was no statistically significant difference in the number of hypoglycaemic episodes between the two treatments (IGLA versus NPH insulin), consequently there are many uncertainties in the literature.[60–63]

Interestingly as well, the meta-analysis of observational studies conducted by Marra *et al.*[19] also found discrete favourable effectiveness and safety results with IGLA. This was also reported in the recommendations of the Conitec.[17, 26] Overall, the evidence suggests that IGLA is associated with better safety outcomes in controlled settings; however, when subjected to real-world scenarios, as in the study by Marra *et al.*,[20] the results can be conflicting, sometimes similar to, or lower than, those achieved by NPH-treated patients.[16, 18–21, 31] This may be one of the reasons, along with cost differences, why long-acting insulins were not within the 2019 World Health Organization Essential Medicines List[64]; however, this is changing for those patients allergic to conventional insulins or no longer responding to them,[15] and it is likely we will see a growth in the use for long-acting insulin analogues especially with the increasing availability of lower-cost biosimilars.

The HRQOL results of this study were similar to those found in people living with T1DM by two other studies.[34, 36] In general, patients reported good health states, with the worst health state being rarely reported, as well as the predominance of moderate-level problems. In addition, the results indicated better HRQOL in patients treated with IGLA compared with those treated with NPH insulin. In general, systematic review studies[23, 31] point to no differences in HRQOL, measured by the most diverse instruments, in patients treated with IGLA or NPH insulin. However, studies that use a therapeutic preference tool, such as Diabetes Treatment Satisfaction Questionnaire, show that patients prefer treatment with long-acting insulin analogues, such as IGLA, over treatment with human insulin, as there can be benefit in human insulin analogue dosage regimens compared with human insulin treatment. It should be noted, however, that these studies of satisfaction with treatment with insulin analogues mostly have a moderate methodological quality.[31] These findings were expected as our treatment groups had significant sociodemographic and clinical differences including, for example less comorbidities in the IGLA treatment group. Many variables are important for improved HRQOL, with our findings indicating which are the predictors that influence a better perception of HRQOL in people living with T1DM. Consequently, the combined studies[33, 36, 43, 65] can influence policies when deciding and funding treatment approaches to enhance the HRQOL of patients with T1DM.

Multiple regression analysis in our study showed a better HRQOL in younger people (18–40 years) with good or very good self-perception of health, between zero and three medical consultations and without hospitalization in the last year, and few comorbidities other than self-reporting angina, diabetic neuropathy, hearing loss and kidney disease and non-severe hypoglycaemia. However, the type of insulin therapy, IGLA or NPH insulin, did not explain the differences in HRQOL in the multiple regression analysis although this was not a comparative analysis. Overall, our results suggest that many factors are important for a better HRQOL in patients with T1DM, and that clinical variables, especially comorbidities, are very important for people

living with T1DM.[66, 67] Similar results are reported by Braga de Souza *et al*.[43] in which HbA1c, regular physical activity, duration of DM, age and microvascular and macrovascular complications were identified as predictors of HRQOL. However, together, they managed to explain only 7.1% of the HRQOL of patients with T1DM.[43] It is worth mentioning that we did not evaluate HbA1c in our study, which is an important limitation in our findings.

Limitations

Overall, we believe that the strengths of the present study are, firstly, the use of a validated and well-tested instrument, i.e. the EQ-5D-3L. Second, the study was carried out in one of the few states in Brazil that incorporated IGLA into its list of publicly funded medicines; finally, the study provides useful values for carrying out economic studies (Supplementary Material). However, we are aware of a number of limitations with this study, such as the data collection process was carried out in different periods of time (2017 for individuals with IGLA and 2014 for patients with NPH insulin); this is a cross-sectional study and cannot be used to analyse behaviour over a period of time; our results were based on the self-reporting of individuals from two cross-sectional studies; clinical data on treatment with other insulins and time of diagnosis were obtained by self-reporting without substantiation; it was not possible to verify whether changes in HbA1c could influence HRQOL since the project that evaluated patients treated with NPH insulin did not measure this variable; T1DM diagnostic data were obtained from SUS database across the state of Minas Gerais and confirmed by self-reports with patients, however there may be outliers, and it was not possible to perform propensity score matching as few individuals were evaluated. Furthermore, it was not the object of this study to make a comparative approach between the two groups of treatments. Alongside this, the patients showed considerable clinical and socio-demographic differences.

Conclusions

Our study showed that a higher HRQOL was associated with being young, having good or very good self-rated health, having had up to three medical consultations in the last year, not having been hospitalized in the last year, not having any or at the most three comorbidities, not having angina, diabetic neuropathy, hearing loss, kidney disease or episodes of non-severe hypoglycaemia to the detriment of serious episodes. In addition, our findings suggest an access barrier to medicines from CEAF/SUS, as patients treated with IGLA presented a higher socio-economic status when compared with NPH insulin patients. It is important to highlight that this perception should be interpreted with caution, as our study was not designed to evaluate access to medicines from CEAF/SUS. Nevertheless, this discovery is a concern that needs to be addressed and we will continue to monitor this.

In conclusion, many clinical and socio-demographic predictors are important for the HRQOL of patients living with T1DM. Our findings may assist with future public health policies in the treatment of patients with T1DM, and we will be monitoring this.

Supplementary Material

Supplementary data are available at *Journal of Pharmaceutical Health Services Research* online.

Author Contributions

P.H.R.F.A. contributed to the project design, collection, analysis and interpretation of data, article writing and final approval of the submitted article. L.L.P.L. and T.B.C.S. critiqued the content and approved the final version. B.G., F.A.A., A.A.G-J., V.E.A., A.M.A. and J.A-T. contributed to project design, article writing, critiqued the content and approved the final version. All authors state that they had complete access to the study data that support the publication.

Authors' Statement

We confirm that the manuscript has been read and approved by all named authors.

Ethical Statement

The study was approved by the Ethics and Research Committee of the Federal University of Minas Gerais (approval number 55876816.0.0000.519, 2 June 2016).

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Conflict of Interest

The authors declare that they have no conflicts of interest to disclose.

Data Availability

The data used for this study is available on reasonable request to the corresponding author.

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