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Original Article

The relationship of health-related quality of life to fear of hypoglycemia among Iranian patients with type 2 diabetes treated with oral antihyperglycemic agents

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Abstract

Fear of hypoglycemia is an additional psychological burden imposed on patients with type 2 diabetes mellitus (T2DM) and may reduce their health-related quality of life (HRQoL). The present study aimed to investigate the relationship between HRQoL and fear of hypoglycemia in patients with T2DM who have been taking oral antihyperglycemic agents in Iran. In this cross-sectional study, 357 patients with T2DM who were using oral anti-diabetic drugs were selected by convenient sampling. Data was collected using a three-part questionnaire [*i.e.*, socio-demographic, the EuroQoL (EQ-5D-3L) and the worry subscale of the hypoglycemia fear survey II (HSF-II)]. Hypoglycemic severity was categorized by the recommendations of the American Diabetes Association Workgroup on Hypoglycemia. Logistic and OLS regression models were used to investigate fear of hypoglycemia and other factors associated with EQ-5D score. The mean age of patients was 54.1±11.5 years and 56.6% were male. The mean EQ-5D and VAS scores were 0.579±0.313 and 48.76±20.09, respectively. In OLS regression models, EQ-5D score was greater in males (B=0.076, P<0.01) and patients with education level >12 years (B=0.118, P<0.015). At the same time, it was lower in patients with fear of hypoglycemia (B=-0.004, P<0.001), selected cardiovascular conditions (B=-0.151, P<0.001) and lower extremity lesions (B=-0.075, P<0.042). Fear of hypoglycemia levels should be evaluated and patients with higher levels of fear of hypoglycemia should be monitored closely. Therefore, clinicians and health systems should incorporate screening for fear of hypoglycemia into the routine health assessment of all patients with T2DM.

Keywords: health-related quality of life, hypoglycemia, type 2 diabetes, oral antihyperglycemic agents.

Introduction

Diabetes is a common chronic disease throughout the world [1]. In Iran, evidence shows a considerable progressive prevalence of diabetes in the age range of 25–64 years [2]. Anti-diabetic drugs are essential for managing patients with type 2 diabetes [3]. Biguanides and sulfonylureas were two of the most widely used anti-diabetes oral drugs in Iranian patients with type 2 diabetes of all ages [4]. All medications have side effects. One of the most common adverse events experienced by patients with diabetes during treatment is hypoglycemia [3, 5]. Hypoglycemic events are a limiting factor in glycemic control and can have devastating effects on psychosocial outcomes such as reduced well-being and health-related quality of life (HRQoL) [6, 7]. HRQoL might be influenced due to the effects and/or complications of hypoglycemia or as a result of avoidant actions

done from the fear of experiencing a hypoglycemia episode [8]. Following hypoglycemic events, patients often experience fear of hypoglycemia, which not only reduces their quality of life but also impairs the quality of life of family members [9]. Fear of hypoglycemia, in turn, is annoying and may lead to avoidant behaviors that increase blood sugar levels and increase the risk of long-term complications [10]. It is possible that fear of hypoglycemia and the experience of hypoglycemia would directly and negatively have an effect on different aspects of life, such as recreational activities, personal relationships, travel (including holidays), spontaneity and independence [11]. Patients with a high level of fear of hypoglycemia might display behaviors including overeating, taking less insulin than required or setting a limit on daily-life activities and routines (*e.g.*, exercising, driving, shopping, visiting friends) to avoid hypoglycemia [12]. These dysfunctional behaviors may lead to recurrent or persistent hyperglycemia and increase the risk of micro and macrovascular complications [7]. There can be some differences between a patient's level of hypoglycemic risk and their level of fear of hypoglycemia [13]. Earlier results yielded that many patients indicated high fear of hypoglycemia levels even when they had not had an episode of severe hypoglycemia in the previous year [14].

HRQoL is one of the most important therapeutic outcomes measured to evaluate the effects of chronic disease management [15]. Improving the HRQoL is the main goal of all healthcare interventions, including diabetes management programs. Therefore, identifying factors associated with poor HRQoL may help healthcare providers make interventions to improve the quality of life of these patients. It seems that no Iranian study has so far been conducted to identify the fear of hypoglycemia and its effects on the quality of life in patients suffering from diabetes. Hence, the current study aims to explore the relationship between HRQoL and fear of hypoglycemia in patients suffering from T2DM who are under the treatment of oral antihyperglycemic agents in Iran.

Material and methods

In this cross-sectional study, 357 patients suffering from T2DM who were under the treatment of oral anti-diabetic drugs were chosen by convenience sampling. Patients referred to a specialized diabetes clinic in Qazvin were selected if they had the inclusion criteria for participation in the study. To fulfill the goals of this study, the researchers determined inclusion criteria which were as follows: to have the age of 18 years or older, received a diagnosis for at least one year and finally have T2DM that had been under the treatment of antihyperglycemic drugs for at least six months. Patients were excluded if they suffered from type 1 diabetes disorder, were pregnant or treated with insulin, or could not fill out the questionnaire but consented to participate in the study.

A skilled interviewer helped to collect the required data through face-to-face interviews. Patients were free to participate and all subjects gave their written informed consent. The research was approved by the ethics committee of the Qazvin University of Medical Sciences (IR.QUMS.REC.1394.818).

The questionnaire used for socio-demographic characteristics included questions about gender, age, education and clinical history, such as diabetes duration, body mass index (BMI), glucometer use frequency, co-morbidity and diabetes complications, type, number and duration of oral antihyperglycemic agents. All respondents self-reported height and weight, which were used to calculate body mass index (BMI).

In order to determine the severity of hypoglycemia, patients were asked if they had felt symptoms of hypoglycemia in the past six months prior to study enrollment, based on a list of symptoms (sweating, confusion/feeling disoriented, shakiness, clumsy or jerky movements, dizziness, sudden moodiness or behavior changes, hunger, tingling sensations around the mouth, difficulty concentrating, headache and pale skin color) [16]. Patients who recorded a positive response were further asked to rate the severity of their episodes according to the clear recommendations of the American Diabetes Association Workgroup on Hypoglycemia. The hypoglycemic severity was classified into three categories as follows: 1) mild (little or no interruption of activities and no assistance needed to manage symptoms); 2) moderate (some interruption of activities and no assistance needed to manage symptoms); 3) severe (needed the assistance of others to manage symptoms). In addition, a fourth category which shows a very severe level of hypoglycemia, was thoughtfully added to record episodes needed for medical assistance [17].

The European Quality of Life scale (EQ-5D-3L) was applied to quantify the level of HRQoL. This questionnaire included five questions that each assessed one of the five dimensions of the HRQOoL, including mobility, usual activities, self-care, pain/discomfort and anxiety/depression. Each dimension was responded to on a

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three scale (as no problem, some or moderate problems and extreme problems). The scales were scored from 1 (*i.e.*, no problem) to 3 (*i.e.*, severe problem) and lastly, the score digits were placed together to present a 5-digit code for the HRQoL of each patient. By application of this method, there could be 243 (3 in the power of 5) different codes. Members of the EuroQol Group have conducted studies that are mostly concerned with statistical modeling methods in order to generate numerical values for each one of 243 possible health conditions defined by EQ-5D. Value sets are normally estimated by valuing a selection from EQ-5D conditions to generalize to the full set of conditions. We used a national value set to convert the five digit codes to EQ-5D scores [18].

Furthermore, the EQ-5D includes a visual analog scale (VAS), which measures the subjects' standpoints of their quality of life level on a 100-point scale. A score of 100 meant the "best health condition" at the top and 0 meant the "worst health condition" at the bottom. This information has presented a quantitative measure of overall health outcomes which is evaluated by the individual respondents.

The degree of fear of hypoglycemia was measured by employing the worry subscale in the hypoglycemia fear survey II (HSF-II) [19]. One of the two sub-scales of the Hypoglycemic Fear Survey was considered to present this factor. The worry subscale had 18 questions that quantified the degree of fear felt by the patients in the last six months and scored on a range of 0 to 72 (most worry). It was found that the worry scale was often utilized alone [20]. Although these two subscales demonstrated adequate statistical reliability and validity, the worry subscale had a better performance compared to the behavior subscale [21]. The Worry Scale indicated high internal consistency estimates (Cronbach's alpha coefficient) ranging from 0.89 to 0.96 and also a satisfactory and acceptable test-retest reliability of r=50.64–0.76 [22].

In the final phase, all the instruments above were accurately translated into Persian and then back-translated into English. This process was repeated until the instruments demonstrated a high degree of readability and were tested on 20 patients suffering from T2DM before the final versions of these instruments were ready to be used. Persian version of the worry subscale indicated internal consistency reliability (Cronbach's alpha) of 0.96.

Statistical analysis

The continuous variables were expressed as mean, standard deviation and categorical variables as absolute numbers and percentages. Between-group comparisons on continuous variables were performed using a t-test (or ANOVA of more than two groups). For categorical variables, the comparisons between groups were performed using a Chi-squared test or a Fisher exact test if the requirements for the Chi-squared test were not met. The mean values were adjusted using an analysis of covariance (ANCOVA). All dimensions in levels 2 and 3 on the EQ-5D were combined and consequently dichotomized to "no problem" and "some or extreme problem". The logistic regression was used to achieve odds ratios (ORs) and 95% confidence intervals (95% CIs) for determinants of EQ-5D dimensions after adjusting for the covariates. Lastly, the ordinary

Table 1: Characteristics of the patients (N=357).

Variable	Subgroup	All patients (N=357) N (%)	With Hypoglycemic Symptoms (n=273) N (%)	Without Hypoglycemic Symptoms (n=84) N (%)	P-value
Age		54.09 (11.5)	55.89 (10.83)	48.36 (11.97)	0.001
Gender	Male	155 (43.42)	115 (42.1)	40 (47.6)	0.381
	Female	202 (56.58)	158 (57.9)	44 (52.4)	
Education (years)	Primary	119 (33.3)	99 (35.9)	20 (23.8)	0.001
	Secondary	178 (49.8)	140 (51.5)	38 (45.2)	
	Collegial	60 (16.9)	34 (12.6)	26 (31)	
Diabetes duration (years), mean (SD)		8.71 (6.8)	10.07 (6.8)	4.3 (4.15)	0.001

Table 1: Continued.

Variable	Subgroup	All patients (N=357) N (%)	With Hypoglycemic Symptoms (n=273) N (%)	Without Hypoglycemic Symptoms (n=84) N (%)	P-value
Body mass index (kg/m²)	Normal (<25)	210 (58.9)	154 (56.42)	56 (66.7)	
	Overweight (25–29.9)	100 (28)	83 (30.4)	17 (20.2)	0.233
	Obese (≥30)	47 (13.1)	36 (13.18)	11 (13.1)	
Glucometer use frequency (in last month)	Never	98 (27.5)	62 (22.71)	36 (42.85)	
	≤4	66 (18.5)	51 (18.68)	15 (17.86)	0.001
	>4	193 (54)	160 (58.61)	33 (39.29)	
Selected cardiovascular diseases	Hypertension (Yes)	153 (42.9)	135 (49.5)	18 (22)	0.001
	Hyperlipidemia (Yes)	148 (41.5)	128 (46.3)	20 (24.7)	0.001
	Coronary artery disease (Yes)	32 (9)	31 (11.4)	1 (3.1)	0.002
	Heart failure (Yes)	27 (7.6)	23 (8.4)	4 (4.8)	0.349
	Arrhythmia (Yes)	17 (4.8)	16 (5.9)	1 (1.2)	0.137
	Cerebrovascular accident (CVA) (Yes)	17 (4.8)	17 (6.2)	0	0.016
	Peripheral vessel disease (Yes)	5 (1.4)	5 (1.8)	0	0.595
Selected nephropathy conditions	Nephropathy (Yes)	34 (9.5)	32 (11.7)	2 (2.4)	0.01
	Dialysis (Yes)	10 (2.8)	10 (3.7)	0	0.125
	Retinopathy (Yes)	46 (12.9)	44 (16.1)	2 (2.4)	0.001
	Lower extremity lesions (Yes)	64 (17.9)	62 (22.7)	2 (2.4)	0.001
	Neuropathy (Yes)	16 (4.5)	16 (5.9)	0	0.016
Type of oral antihyperglycemic agents	Sulfonylurea (Yes)	290 (81.2)	234 (85.7)	56 (66.7)	0.001
	Biguanide (Yes)	331 (92.7)	51 (18.7)	32 (38.1)	0.001
	Thiazolidindiones (Yes)	15 (4.2)	15 (5.5)	4 (4.8)	0.525
	Dipeptidase (Yes)	22 (6.2)	20 (7.3)	2 (2.4)	0.075
Number of oral antihyperglycemic agents	1	76 (21.3)	44 (16.1)	32 (38.1)	
	2	261 (73.1)	211 (77.3)	50 (19.2)	0.001
	3	20 (5.6)	18 (76.5)	2 (10)	
Fear of Hypoglycemia (HSF score), mean (SD)		16.8 (16.33)	20.87 (16.16)	3.45 (7.26)	0.001
Duration of oral anti-hyperglycemic agents use(year), mean (SD)		6.7 (5.2)	7.59 (5.37)	3.8 (3.25)	0.001

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least-squares (OLS) model was used to identify any factors associated with the EQ-5D scores. STATA/SE 10.0 for Windows was used to perform all the analyses.

Results

The mean age of patients was 54.1 (SD=11.5) years and 56.58% were females. The mean duration of diabetes was 8.7 years (SD=6.8). Characteristics of patients with hypoglycemic symptoms (76.48%) were compared to those without hypoglycemic symptoms (23.52%). In general, older patients (P<0.001) with a secondary education (P<0.001), a longer duration of diabetes (P<0.001), a higher frequency of glucometer use (P<0.001), a history of conditions such as coronary artery disease (P<0.002), cerebrovascular accident (P<0.016), nephropathy (P<0.01), retinopathy (P<0.001), neuropathy (P<0.016), lower extremity lesions (P<0.001), treated with sulfonylurea (P<0.001) and biguanide (P<0.001), the simultaneous use of two oral antihyperglycemic agents (P<0.001) and the longer duration of oral antihyperglycemic agents (P<0.001) were more likely to experience symptoms of hypoglycemia over the previous six months (Table 1).

Health-related quality of life

The mean EQ-5D and VAS scores were 0.579 (SD=0.313) and 48.76 (SD=20.09), respectively and are reported in Table 2. The lowest EQ-5D and VAS scores were found in patients who suffered from a severe level of hypoglycemia; the mean EQ-5D and VAS scores were 0.329 and 34.43, respectively.

Fear of hypoglycemia

The mean HSF-II score was 16.8 (SD=16.336). As indicated in Table 2, there was a lower mean score for the group with severe hypoglycemia, 34.45 (SD=17.07), compared with patients without hypoglycemia, who experienced 3.456 (SD=7.364).

Multivariate logistic regression models

Table 3 summarizes the results of the OLS regression model for the EQ-5D score. The EQ-5D score was found to be greater in males (B=0.076, 95% CI: 0.018–0.133, P<0.01) and also those patients with education experience of more than 12 years (B=0.118, 95% CI: 0.023–0.213, P<0.015). In contrast, it was lower in patients with fear of hypoglycemia (B=-0.004, 95% CI: -0.006– -0.002, P<0.001), patients with lower extremity lesions (B=-0.075, 95% CI: -0.147– -0.003, P<0.042) and selected cardiovascular conditions (B=-0.151, 95% CI: -0.224– -0.078, P<0.001).

As presented in Table 4, the findings indicated that significant relationship between fear of hypoglycemia with self-care (OR=1.035, P<0.005), usual activities (OR=1.036, P<0.003), pain/discomfort (OR=1.023, P<0.049) and anxiety and depression (OR=1.066, P<0.001). Also, the quality of life score on pain/discomfort was associated with all degrees of severity of the symptoms of hypoglycemia. Increasing the severity of the symptoms of hypoglycemia worsened the pain and discomfort.

Discussion

The current study assessed the relationship between HRQoL and fear of hypoglycemia in T2DM patients taking oral antihyperglycemic agents in Qazvin, Iran.

The results indicated that hypoglycemia symptoms were prevalent among the patients in the present study, 76.48%. In an American study on patients suffering from T2DM who were taking oral antihyperglycemic agents, symptoms of hypoglycemia were found

Table 2: Mean EQ-5D, HFS and VAS score and severity of hypoglycemic symptoms.

The severity of hypoglycemic symptoms (mean±SD)	N (%)	EQ-5D score	VAS score	HFS score
Very severe	62 (17.37)	0.32±0.3	34.43±19.64	34.45±17.07
Severe	60 (16.81)	0.42±0.27	42.48±16.29	25.25±12.53
Moderate	73 (20.45)	0.58±0.29	48.35±17.39	16.53±13.1
Mild	78 (21.85)	0.66±0.27	55.11±17.23	10.56±10.94
No hypoglycemia	84 (23.52)	0.78±0.21	58.45±20.18	3.45±7.36
P-value	-	0.001	0.001	0.001

Table 3: Results of the OLS regression model.

Variables	EQ-5D score			
	B	95% CI		P-value
		Lower	Upper	
Age	-0.001	-0.004	0.002	0.541
Sex (female=0, male=1)	0.076	0.018	0.133	0.01
Education (years)				
Primary	1.0 (ref)			
Secondary	0.070	0.001	0.140	0.051
Collegial	0.118	0.023	0.213	0.015
Fear of Hypoglycemia (HSF score)	-0.004	-0.006	-0.002	0.001
Diabetes duration (years)	-0.004	-0.010	0.001	0.125
Body mass index (kg/m^2)				
Normal (<25)	1.0 (ref)			
Overweight (25-29.9)	-0.022	-0.088	0.044	0.510
Obese (≥30)	-0.048	-0.136	0.041	0.289
Glucometer use frequency (in last month)				
Never	1.0 (ref)			
≤4	0.004	-0.081	0.088	0.931
>4	-0.003	-0.068	0.062	0.935
Selected cardiovascular conditions (no=0, yes=1)	-0.151	-0.224	-0.078	0.001
Retinopathy (no=0, yes=1)	0.021	-0.064	0.106	0.628
Selected nephropathy conditions (no=0, yes=1)	-0.095	-0.191	0.001	0.053
Lower extremity lesions (no=0, yes=1)	-0.075	-0.147	-0.003	0.042
Neuropathy (no=0, yes=1)	0.039	-0.091	0.170	0.553
Number of oral antihyperglycemic agents				
1	1.0 (ref)			
2	-0.002	-0.072	0.069	0.961
3	-0.101	-0.230	0.029	0.127
The severity of hypoglycemic symptoms				
No hypoglycemia	1.0 (ref)			
Very severe	-0.097	-0.226	0.033	0.144
Severe	-0.102	-0.211	0.007	0.067
Moderate	-0.044	-0.137	0.048	0.344
Mild	-0.036	-0.121	0.049	0.406
F	0.001			
Adjusted R-squared	0.4354			

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Table 4: Results of multivariate logistic regression models.

	Mobility			Self-care			Usual activities			Pain/discomfort			Anxiety/depression		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Age	1.065	1.03, 1.1	0	1.042	1.01, 1.08	0.022	1.068	1.03, 1.11	0	1.033	1, 1.07	0.039	0.995	0.97, 1.02	0.743
Education (years)															
Primary (ref)	1			1			1			1			1		
Secondary	0.713	0.36, 1.4	0.324	0.535	0.26, 1.11	0.091	0.497	0.24, 1.01	0.054	1.056	0.51, 2.17	0.88	0.823	0.39, 1.73	0.608
Collegial	0.423	0.13, 1.39	0.157	1	-	-	0.076	0.02, 0.39	0.002	1.102	0.39, 3.11	0.854	0.658	0.24, 1.78	0.411
Hypoglycemia fear (HSF score)	1.002	0.98, 1.03	0.812	1.035	1.01, 1.06	0.005	1.036	1.01, 1.06	0.003	1.023	1, 1.05	0.049	1.066	1.04, 1.1	0.001
Diabetes duration (years)	1.071	1.02, 1.13	0.012	1.03	0.98, 1.09	0.27	1.029	0.98, 1.09	0.296	1.014	0.96, 1.02	0.611	1.002	0.95, 1.06	0.932
Body mass index (kg/m^2)															
Normal (<25)	1			1			1			1			1		
Overweight (25–29.9)	1.648	0.83, 3.28	0.154	1.535	0.76, 3.11	0.233	1.399	0.69, 2.85	0.354	0.599	0.3, 1.21	0.155	0.707	0.35, 1.42	0.33
Obese (≥30)	2.531	1.12, 5.75	0.026	1.779	0.74, 4.3	0.2	1.383	0.58, 3.3	0.465	0.998	0.42, 2.35	0.997	0.464	0.2, 1.08	0.074
Severity of hypoglycemic symptoms															
No hypoglycemia	1			1			1			1			1		
Very severe	3.269	0.86, 12.44	0.082	1.296	0.27, 6.3	0.747	1.564	0.38, 6.43	0.535	12.417	3.04, 50.65	0.001	0.62	0.16, 3	0.496
Severe	2.508	0.76, 8.29	0.131	1.987	0.48, 8.27	0.345	2.723	0.77, 9.69	0.122	7.636	2.39, 24.4	0.001	1.179	0.34, 4.05	0.793
Moderate	1.544	0.51, 4.64	0.438	2.275	0.61, 8.53	0.223	1.875	0.57, 6.13	0.298	5.821	2.2, 15.43	0.001	0.949	0.39, 2.29	0.908
Mild	2.15	0.77, 6.02	0.145	1.909	0.52, 7	0.329	1.629	0.51, 5.19	0.409	6.003	2.37, 15.2	0.001	1.097	0.5, 2.39	0.814

Table 4: Continued.

	Mobility			Self-care			Usual activities			Pain/discomfort			Anxiety/depression		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Glucometer use frequency (in last month)															
Never (Ref)	1			1			1			1			1		
≤4	1.457	0.56, 3.77	0.436	2.036	0.71, 5.85	0.187	1.873	0.68, 5.18	0.226	0.758	0.32, 1.81	0.534	1.288	0.55, 3	0.556
>4	0.346	0.65, 2.8	0.426	2.64	1.16, 6.04	0.021	2.205	1.01, 4.84	0.048	0.925	0.46, 1.85	0.827	1.151	0.59, 2.25	0.679
Selected cardiovascular conditions (no=0, yes=1)	2.555	1262, 5.17	0.009	1.1	0.54, 2.26	0.793	2.07	1.01, 4.26	0.048	4.934	2.02, 12.05	0	2.159	0.85, 5.46	0.104
Retinopathy (no=0, yes=1)	0.88	0.39, 2.01	0.762	2.101	0.91, 4.83	0.08	1.641	0.7, 3.85	0.253	1.072	0.41, 2.82	0.886	0.438	0.17, 1.15	0.095
Selected nephropathy conditions (no=0, yes=1)	1.166	0.48, 2.85	0.736	0.612	0.23, 1.61	0.319	1.303	0.51, 3.35	0.581	15.777	1.93, 129.23	0.01	12.502	1.44, 108.76	0.022
Lower extremity lesions (no=0, yes=1)	1.782	0.51, 6.29	0.369	1.097	0.27, 4.4	0.896	0.868	0.2, 3.72	0.849	0.484	0.15, 1.58	0.229	0.446	0.14, 1.38	0.162
Neuropathy (no=0, yes=1)	0.996	0.29, 3.44	0.995	1.218	0.36, 4.1	0.749	0.748	0.21, 2.64	0.653	1.524	0.27, 8.64	0.634	2.289	0.33, 15.87	0.402
Number of oral antihyperglycemic agents															
1 (ref.)	1			1			1			1			1		
2	0.629	0.27, 1.46	0.281	0.806	0.33, 2	0.643	0.858	0.35, 2.1	0.737	1.211	0.54, 2.52	0.606	1.095	0.54, 2.21	0.804
3	1.318	0.23, 7.63	0.757	1.21	0.21, 6.89	0.829	5.242	0.67, 41.28	0.116	49.693	2.83, 872.6	0.008	3.346	0.44, 25.33	0.242

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common and reported by 63% of patients, 17% of whom reported severe or very severe events [23].

On the other hand, in a study in the Asia-pacific region, 35.8% of the patients with T2DM reported hypoglycemia symptoms in the last six months [16]. However, it is problematic to compare the occurrence and frequency of hypoglycemia across studies due to differences in study designs and populations, definitions of hypoglycemia and medication regimens [23].

In line with the findings of previous studies [24–27], the present study indicated that the severity of hypoglycemia symptoms was associated with HRQoL. This relationship was shown in the pain/discomfort dimension of EQ-5D. As the severity of the hypoglycemia increased, patients experienced more pain/discomfort. Barendse *et al*. indicated the possible adverse impact of hypoglycemia on people suffering from T2DM, such as the impairment of the ability to work, drive, and function in ways that are important for a better quality of life [11]. Also, hypoglycemia reduced overall work productivity and interfered with social activities compared to patients who had never suffered from hypoglycemia; hypoglycemia can exert a negative impact on various aspects of life [8].

This study's findings revealed that the relationship between HRQoL and fear of hypoglycemia is mainly in usual activities, self-care, pain/discomfort and anxiety/depression dimensions. Another study showed that self-reported hypoglycemic symptoms were associated with worry about hypoglycemia and also hypoglycemic symptoms among five domains of the EQ-5D were in relationship with increasing anxiety/depression, greater pain/discomfort and also more problems concerning usual activities (work, housework, study, leisure and family activities) [16]. McCoy *et al*. showed that fear of hypoglycemia was the highest in patients suffering from T2DM with severe hypoglycemia. Furthermore, the level of HRQoL was found to be lower in patients suffering from T2DM with severe hypoglycemia [28]. An American study indicated that fear of hypoglycemia was independently in relationship with mental and physical health and lower overall health condition [29]. Findings from another study showed a link between a previous history of severe and symptomatic hypoglycemia with fear of hypoglycemia and the development of distress and depression in patients with type 2 diabetes [9]. Fear of hypoglycemia affects health behaviors applied in diabetes self-management, such as physical activity and dietary patterns [30].

Moreover, it can lead to avoiding exercise and is related to reduced work hours and other lifestyle opportunities. Fear of hypoglycemia and the experience of hypoglycemia would directly and negatively have an effect on different aspects of life, such as recreational activities, personal relationships, travel (including holidays), spontaneity, and independence. Additionally, fear of hypoglycemia may link self-care activities with weight management, implications of glycemic control, and quality of life [11]. These can disrupt patients' usual activities and self-care and have adverse effects on HRQoL.

The main factors influencing fear of hypoglycemia included coping ability and the individual's emotional condition. Fear of hypoglycemia is associated with anxiety, anger, depression, stress, and impaired HRQoL [30]. Increasing depression symptoms reported in patients with a high level of fear of hypoglycemia might be secondary to a high level of anxiety. It is also worth mentioning that data also indicate that fear of hypoglycemia is related to reduced HRQoL, which can deepen the feeling of depression [13]. Green *et al*. presented evidence that hypoglycemia is associated with higher severity levels of depression and higher depression scores. Hypoglycemia and depression might likely have a common clinical pathway, including stimulation of the sympathetic nervous system; consequently, self-reported hypoglycemia might be applied as an instrument by physicians to become alert to the possibility of depression in patients suffering from diabetes [31]. The results of Shi *et al*. study highlights this issue that the participants who perceived themselves as alone with their worries and fears are of great concern because they found themselves getting insufficient emotional support from health professionals, such as nurses. Nurses should measure health needs regarding clients' real-life situations, particularly those who did not show any adherence to the treatment regimens or perform any educational activities [32].

Several limitations to the current study need to be acknowledged which are important for the interpretation of results. Firstly, this study's design was cross-sectional because it used a convenience sample of patients; therefore, survey participants may not represent all patients with T2DM. Second, the survey is based on recall of the events and thereby carries the limitations of a retrospective study. It is impossible to rule out any "responder bias" for such a questionnaire survey; however, the recall of severe hypoglycemia within one year is well preserved in both type 1 and type 2 diabetes [33]. Also, sulfonylureas are one of the most widely used drugs in treating patients with type 2 diabetes in Iran and most of our samples were treated with sulfonylureas. This

may have a very strong effect on hypoglycemia and fear of hypoglycemia. Therefore, it seems necessary to state it as one of the limitations of our study.

Conclusion

Regarding the importance of hypoglycemia's adverse effects and fear of hypoglycemia on HRQOL in patients with T2DM, the first step is to identify those patients for whom hypoglycemia and fear of hypoglycemia is a significant clinical issue. Fear of hypoglycemia levels should be evaluated and patients with higher levels of fear of hypoglycemia should be monitored closely; therefore, clinicians and health systems should incorporate screening for fear of hypoglycemia into the routine health assessment of all patients with T2DM. Fear of hypoglycemia places patients at risk for counterproductive behaviors, impairs HRQoL and should be considered in individualizing glycemic goals. Our findings suggest that experimental research can conduct to find appropriate screening measures for patients with hypoglycemia experience for early diagnosis and determine behavioral and psychological interventions which can reduce fear of hypoglycemia and improve diabetes management in patients with T2DM.

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Conflicts of interest

The authors declare no conflict of interest.

Ethics approval

The approval for this study was obtained from the Ethics Committee of the Qazvin University of Medical Sciences (approval ID: IR.QUMS.REC.1394.818).

Consent to participate

Written informed consent was obtained from the participants.

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