The Burden of Severe Hypoglycemia on Quality of Life among Diabetes Mellitus Patients in a Tertiary Level Hospital of Bangladesh

Afsar Ahammed, Faruque Pathan[1], Faria Afsana[1], Imran Ahammed[2], Ahmed Salam Mir[3], Abdullah Yusuf[4]

Department of Physiotherapy, National Institute of Traumatology and Orthopedic Rehabilitation, [1]Department of Endocrinology, Bangladesh Institute of Research and Rehabilitation in Diabetes Endocrine and Metabolic Disorders, [2]Officer on Special Duty, Ministry of Health and Family Welfare, [3]Department of Endocrinology, Dhaka Central International Medical College and Hospital, [4]Department of Microbiology, National Institute of Neurosciences and Hospital, Dhaka, Bangladesh

Abstract

Objective: This study aimed to determine the impact of hypoglycemia on health-related quality of life from a patient perspective. **Materials and Methods:** A cross-sectional study was conducted in 164 type 2 diabetes patients admitted due to severe hypoglycemia from August 2015 to October 2016 at Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders, in Dhaka. Impact of severe hypoglycemia on health-related quality of life in diabetic patients was evaluated using the disease-specific questionnaire audit of diabetes-dependent quality of life-19 (ADDQOL-19). **Results:** The median ADDQOL score was calculated at −3.31. Totally, 88 (53.7%) patients reported an ADDQOL score of −3.31 or more, and 76 (46.3%) patients had an ADDQOL score of less than −3.31 (lower quality of life [QoL]). After considering weighting, "Freedom to eat" (mean Weighted Impact Score-6.32 ± 1.94) was the most and "Holidays" (mean Weighted Impact Score-0.96 ± 0.19) was the least affected QoL domains, respectively. In multivariate logistic regression analysis, severe hypoglycemia impact on ADDQOL was related with age (odds ratio [OR] 0.932, 95% confidence intervals [CIs] 0.897–0.969, $P < 0.001$), sex (OR 0.088, 95% CIs 0.023–0.338, $P < 0.001$), glycated hemoglobin (%) (OR 0.613, 95% CIs 0.422–0.890, $P = 0.010$), and marital status (OR 9.264, 95% CIs 2.467–34.790, $P = 0.001$). **Conclusions:** The results of this analysis suggest hypoglycemia impacts heavily on the well-being and quality of life of people with diabetes, and every effort should be made to minimize hypoglycemia while aiming for good glycemic control.

Keywords: Audit of diabetes-dependent quality of life-19, quality of life, severe hypoglycemia, type 2 diabetes

INTRODUCTION

Diabetes mellitus is a metabolic disease of multiple etiologies, characterized by chronic hyperglycemia together with disturbance of carbohydrate, fat and protein metabolism resulting from defects of insulin secretion, insulin action or both.[1] The number of people with diabetes are exceptionally increasing worldwide due to population growth, aging, urbanization, unhealthy eating habits, increasing prevalence of obesity and physical inactivity.[2] According to International Diabetes Federation, people living with diabetes are expected to rise from 382 million in 2013 to 592 million by 2035. In the South Asian region, Bangladesh has the second largest number of adults with diabetes (5.1 million adults, 6.3%).[3] Severe hypoglycemia may result in hospitalization, the moderate forms may need emergency care and consultation by a physician, and a mild hypoglycemic event may only require others assistance at the place of the event to resolve the situation.

Severe hypoglycemia has a significant economic impact and impairs quality of life in patients with diabetes mellitus. Hsu *et al.*[4] found in their study that symptomatic hypoglycemia is associated with an increased risk of cardiovascular events, all-cause hospitalization, and all-cause mortality. Another

Address for correspondence: Dr. Afsar Ahammed, Department of Physiotherapy, National Institute of Traumatology and Orthopedic Rehabilitation, Dhaka, Bangladesh, India. E-mail: meraz_aarm@yahoo.com

study done by McCoy *et al.*[5] found that self-report of severe hypoglycemia is associated with 3.4-fold increased risk of death. Hypoglycemia also has significant economic impacts. In the study by Ha *et al.*[6] done on a Korean population, the largest average medical cost per severely hypoglycemic event was $1,385, which was approximately 1.35 times the annual treatment cost ($1,027) for a diabetic patient without complications in Korea. Although the impact of hypoglycemia on quality of life (QoL) is unclear, in the United Kingdom Prospective Diabetes Study (1998) shows that patients experiencing several episodes of hypoglycemia have reported lower QoL. Whether patients with low QoL experience many hypoglycemic events, or whether many hypoglycemic events lead to low QoL is, however, not known. Apart from the distressing acute symptoms, hypoglycemia may also have a negative impact on the health of a patient with diabetes in the long term.[7] Another important aspect is the constant fear of developing hypoglycemia that some patients experience.[8] Therefore, it is evident that both diabetes and hypoglycemia negatively affect the patients' well-being as well as their QoL.[9-12] QoL is a multidimensional phenomenon. However, there is no concrete conceptual approach incorporating all the possible social, economic, psychological, and health dimensions into a single indicator. In the literature, different instruments for assessing the general health of a population (generic instruments) as well as the clinical implications of several treatment therapies (disease-specific instruments) have been used. Specifically designed questionnaires are used for the measurement of subjective evaluation of health.[12] The relation between diabetes and socioeconomic status and its impact on the lower income classes has been recently investigated by clinicians and health economists.[13] Cost-effectiveness analysis has been used to evaluate the impact on an individual's budget and the expenses involved for the improvement of QoL. To the best of our knowledge, this is the first study, conducted in our country, to assess the impact of severe hypoglycemia on patients' QoL. Hypoglycemia is an important element affecting the QoL of diabetic patients.

MATERIALS AND METHODS

Study procedure

A cross-sectional study was conducted in 164 Bangladeshi Type 2 diabetes mellitus patients admitted due to severe hypoglycemia within a 15-month time period to find out the burden of severe hypoglycemia on quality of life. Study participants were selected purposively from a specialized hospital, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), Shahbag, Dhaka. The inclusion criteria include diabetic patients aged >18 years of all socioeconomic strata admitted due to severe hypoglycemia in BIRDEM General Hospital, Dhaka. Patients unwilling to participate in this study, hypoglycemia in non diabetic patients, pregnant women, and age <18 years were excluded. Impact of severe hypoglycemia on health-related quality of life in diabetic patients was evaluated using the disease-specific questionnaire audit of diabetes-dependent quality of life-19 (ADDQOL-19). The ADDQOL measures 19 items which were concerned with the impact of diabetes on specific aspects of life. These 19 domains ask the respondents to evaluate how their life would be if they did not have diabetes. The scales range from −3 to +1 for 19 life domains (impact rating) and from 0 to 3 in attributed importance (importance rating). A weighted score for each domain is calculated as a multiplier of impact rating and importance rating (ranging from −9 to +3). Lower scores reflect poorer QOL. Finally, a mean weighted impact score (ADDQOL score) was calculated for the entire scale across all applicable domains. Ethical clearance for the study was taken from the Institutional Review Board of BIRDEM. Statistical analysis: After collection all the data were checked and edited. Then, data were entered into computer with the help of software SPSS for windows programmed version 17. The ADDQOL score was calculated in a range from −9 to +3 and a median score is calculated from the study population. The respondents whose score was below the median value were classified as "lower QoL" and those with score equal to or above the median value were classified as "above lower QoL. Cross-tabulation was prepared and a comparison had been made. Chi-square, t-test were done where and whenever required. $P < 0.05$ was considered statistically significant, and 95% confidence interval was calculated.

RESULT

A total of 182 patients were enrolled in the study. Of them, 7 patients had spontaneous hypoglycemia that was not proven as diabetic and 11 patients refused to be included in the study. Data from the remaining 164 patients were collected and analyzed for the study. Among them, 78 were male (47.6%) and 86 were female (52.4%). Highest percentage (30.5%) of patients belonged to the age group of 51–60 years and male (47.6%) is found lower than female (52.4%) which is not significant. In the distribution of the patients by occupational status, most of the respondents were homemakers 66 (40.2%), self-employed 37 (22.60%), number of patients. Government employee was 13 (7.9%), nongovernment employee was 14 (8.5%), retired 11 (6.7%), and 23 (14%) was unemployed. This study found no statistically significant difference between incidence of hypoglycemia in between demographic distribution, however the incidence was much higher (58.5%) in less educated persons than who are highly educated. Relationship of BMI with severe hypoglycemia was evaluated.

This study found majority 81 (49.4%) of hypoglycemia patients had BMI between 18 and 22.9 kg/m², i.e., normal weight according to Asian category. 29 (17.7%) of patients were in overweight group (BMI of 23–24.9 (kg/m²). This study shows highest incidence of hypoglycemia (31.1%) in patients who had a duration of diabetes >10–20 years. Patients who used insulin with syringe had a higher rate (69.4%) of hypoglycemic events than those who used pen (30.6%). Mixed insulin users (both premixed and split mixed) had highest incidence (79.3%) while only long-acting insulin users had

the lowest rate (5%) of hypoglycemic events. This study has also shown variation in presentation of severe hypoglycemia. All episodes were resuscitated by the assistance of another person. Documented symptomatic hypoglycemia was 54.90% Symptomatic hypoglycemia without documentation of blood sugar were 44.5%, asymptomatic group were 0.6%. Among the severe hypoglycemia significantly, 102 (62.2%) recovered from hypoglycemia by IV glucose and 62 (37.8%) recovered by oral glucose [Tables 1 and 2].

The distribution of responses and the weights assigned to the impact ratings are shown in Table 3. Severe hypoglycemia had the three most greatest impact on "Freedom to eat" (mean impact rating 2.73 ± 0.44), "Dependence on others" (mean impact rating 2.72 ± 0.46), "Financial situation" (mean impact rating 2.59 ± 0.51) and the three least impact on "Leisure activities" (mean impact rating 0.99 ± 0.11), "Holidays" (mean impact rating 0.99 ± 0.11), "Personal relationship" (mean impact rating 1.00 ± 0.00), respectively. "Freedom to eat" (mean important rating 2.28 ± 0.48) and "Physical health" (mean important rating 2.04 ± 0.50) were rated as the two most important while "Holidays" (mean important rating 0.96 ± 0.19) and "Leisure activities" (mean important rating 0.97 ± 0.17) were rated as the least important QoL domains, respectively, for the study participants. After considering weighting, "Freedom to eat" (mean Weighted Impact Score-6.32 ± 1.94) was the most and "Holidays" (mean Weighted Impact Score-0.96 ± 0.19) was the least affected QoL domains, respectively.

The ADDQOL score was calculated in a range of −9.0 to 0 on a defined range from −9 to +3. The median ADDQOL score was calculated at − 3.31. Then lower quartile cutoff was calculated at <−3.31, upper quartile cutoff was calculated at ≥−3.31 88 (53.7%) patients with severe hypoglycemic patient reported an ADDQOL score of − 3.31or more (upper QoL), and 76 (46.3%) patients had an ADDQOL score of less than −3.31 (lower QoL).

In our study, according to the results of the Univariate analysis [Table 4], QoL was significantly related with age ($P = 0.008$), sex ($P = 0.002$), marital Status ($P = 0.001$), education level ($P = 0.017$), treatment modalities ($P < 0.001$), glycated hemoglobin (HbA1c) (%) ($P < 0.001$), and BMI ($P = 0.048$). In multivariate logistic regression analysis [Table 5], severe hypoglycemia impact on ADDQoL were related with age (odds ratio [OR] 0.932, 95% confidence intervals [CIs] 0.897–0.969, $P < 0.001$), sex (OR 0.088, 95% CIs 0.023–0.338, $P < 0.001$), HbA1c (%) (OR 0.613, 95% CIs 0.422–0.890, $P = 0.010$), and marital status (OR 9.264, 95% CIs 2.467–34.790, $P = 0.001$). No statistical significant relations were observed between severe hypoglycemia impact on ADDQoL and duration of diabetes, BMI, smoking habits, education level, monthly income, and antidiabetic treatment. In our study, logistic regression analysis among the predictors of severity of hypoglycemia did not found any significant association on ADDQoL-19 Score through demographic distribution.

Table 1: Demographic characteristics

Variables	Domain	n (%)
Age group (years)	>18-40	15 (9.15)
	41-60	72 (43.90)
	61-80	66 (40.24)
	>80	11 (6.71)
Gender	Male	78 (47.60)
	Female	86 (52.40)
Occupation	Government employee	13 (7.90)
	Nongovernment employee	14 (8.50)
	Self-employed	37 (22.60)
	Unemployed (able to work)	13 (7.90)
	Unemployed (unable to work)	10 (6.10)
	Homemaker	66 (40.20)
	Retired	11 (6.70)
Area of residence	Urban	84 (51.20)
	Rural	80 (48.80)
Education	<HSC	96 (58.50)
	≥HSC	68 (41.50)
BMI (kg/m^2)	<18	10 (6.1)
	18-22.9	81 (49.4)
	23-24.9	29 (17.7)
	≥25	44 (26.8)

HSC: Higher secondary certificate, BMI: Body mass index

Table 2: Clinical characteristics

Variables	Domain	n (%)
Duration of T2DM (years)	<5	39 (23.80)
	5-10	47 (28.70)
	11-20	51 (31.10)
	>20	27 (16.50)
HbA1c	Controlled (<7%)	62 (37.80)
	Uncontrolled (≥7%)	102 (62.20)
Presentation	Symptoms with low blood glucose	90 (54.90)
	Only symptoms	73 (44.50)
	No symptoms only low blood glucose	1 (0.60)
Treatment modalities	Only OAD	43 (26.20)
	Only insulin	90 (54.90)
	OAD+insulin	31 (18.90)
Insulin regime	Only short-acting	14 (11.60)
	Only long-acting	6 (5.00)
	Premixed	64 (52.90)
	Split mixed	32 (26.40)
	Basal-bolus	5 (4.10)
Injection device	Syringe	84 (69.40)
	Pen	37 (30.60)
Recovery method	Intravenous glucose	102 (62.20)
	Oral glucose	62 (37.80)

T2DM: Type 2 diabetes mellitus, HbA1c: Glycated hemoglobin, OAD: Oral antidiabetes drug

DISCUSSION

In accordance with our results, various studies, in different countries, have reported a negative impact of T2D on QoL.[14-17] QoL in T2D is somewhat lower than in patients with other

Table 3: Distribution of response by impact and importance rating together with weighted impact score (*n*=164)

Domain	Mean±SD		Weighted impact score
	Impact rating	Importance rating	
Leisure activities	−0.99±0.11	0.97±0.17	−0.97±0.17
Working life	−2.28±0.59	1.54±0.51	−3.65±1.75
Journey	−2.46±0.59	1.84±0.59	−4.63±2.09
Holidays	−0.99±0.11	0.96±0.19	−0.96±0.19
Physical health	−2.52±0.50	2.04±0.50	−5.18±2.16
Family life	−1.51±0.50	0.99±0.18	−1.51±0.54
Friendship and social life	−1.00±0.19	0.98±0.17	−1.00±0.29
Personal relationship	−1.00±0.00	1.00±0.00	−1.00±0.00
Sex life	−2.24±0.84	1.69±0.75	−4.16±2.63
Physical appearance	−1.67±0.88	1.03±0.42	−1.80±1.44
Self confidence	−2.43±0.51	1.90±0.54	−4.73±1.98
Motivation	−2.08±0.40	1.19±0.39	−2.46±0.85
People's reaction	−1.02±0.13	1.01±0.11	−1.04±0.27
Feeling about future	−2.08±0.64	1.77±0.42	−3.82±1.62
Financial situation	−2.59±0.51	1.96±0.69	−5.31±2.42
Living condition	−1.41±0.49	1.42±0.50	−2.14±1.31
Dependence on others	−2.72±0.46	1.99±0.53	−5.55±1.70
Freedom to eat	−2.73±0.44	2.28±0.48	−6.32±1.94
Freedom to drink	−1.99±0.08	1.34±0.47	−2.65±0.95

SD: Standard deviation

Table 4: Association of factors with quality of life

Variables	Domain	QoL (score)		P
		≥−3.31 (%)	<−3.31 (%)	
Age (years)	>60	50 (64.9)	27 (35.1)	0.006
	≤60	38 (43.6)	49 (56.4)	
Gender	Female	56 (65.1)	30 (34.9)	0.002
	Male	32 (41.0)	46 (59.0)	
Educational status	<HSC	59 (61.5)	37 (38.5)	0.017
	≥HSC	29 (42.6)	39 (57.4)	
HbA1c	≥7.0%	71 (69.6)	31 (30.4)	<0.001
	<7.0%	17 (32.7)	45 (67.3)	
BMI	Over weight	46 (62.2)	28 (37.8)	0.048
	Normal weight	42 (46.7)	48 (53.3)	
Marital status	Unmarried	7 (24.14)	22 (75.86)	0.001
	Married	81 (60.0)	54 (40.0)	
Smoking status	Smoker	9 (52.9)	8 (47.1)	0.118
	Nonsmoker	66 (58.4)	47 (41.6)	
	Quited	13 (38.2)	21 (61.8)	

QoL: Quality of life, BMI: Body mass index, HbA1c: Glycated hemoglobin, HSC: Higher secondary certificate

Table 5: Logistic regression analysis: Predictors of lower quality of life according to the audit of diabetes-dependent quality of life-19 score (*n*=164)

Variables	OR	95% CIs		P
		Lower	Upper	
Gender (males)	0.088	0.023	0.338	<0.001
Age (<60 years)	0.932	0.897	0.969	<0.001
DM duration (years)	0.956	0.602	1.519	0.849
HbA1c (<7%)	0.613	0.422	0.890	0.010
BMI (normal weight)	1.006	0.889	1.140	0.919
Monthly income	1.000	1.000	1.000	0.787
Education level (>HSC)	0.742	0.312	1.766	0.500
Marital status (married)	9.264	2.467	34.790	0.001
Smoking status (smoker)	3.097	0.801	11.976	0.101
OAD therapy (yes)	1.464	0.571	3.754	0.427

DM: Diabetes mellitus, HbA1c: Glycated hemoglobin, OAD: Oral antidiabetes drug, BMI: Body mass index, OR: Odds ratio, CIs: Confidence intervals, HSC: Higher secondary certificate

food."[20] The observation that QoL is impaired in patients with diabetes, especially for the "freedom to eat" domain, which is related to the individuals' perception about their eating ability indicates that an intervention to improve dietary freedom might be a good way of improving QoL in diabetics.[21] Interestingly, in contrast to our study, other international studies[22,23] shows that the dimensions leisure activities, holidays, friendship and social life, personal relationship had been more negatively influenced which is inconsistent with our study. In our study, holidays were the least affected QoL domains. There are several possible explanations of this finding. As the majority of our study population were female (52.4%) and most of the respondents were homemakers (40.2%), whole day of household activities, inconsistent eating pattern, missed meals, neglected self-care, lack of leisure opportunity, social prejudice, and economic condition, all may have been contributing factor for this.

In the present study, we observed that lower QoL was related to male, age below 60 years, unmarried and controlled (HbA1c<7%) patient. In contrast with our results, various studies have shown that QoL is better among people who are at younger age than the eldest ones.[9,19] However, two recent studies showed that younger age was associated with lower ADDQOL scores in Korean T2D patients[16] and that being younger was associated with a greater negative impact of diabetes on QoL.[21] A possible explanation for this discrepancy might be that diabetics at younger age are afraid in a larger degree for their future and the impact of T2D in their life than the eldest ones. Finally, as it has been showed by previous studies, living alone was significantly correlated with lower QoL. It is well known that QoL is better among married people.[24]

In our study, 62.2% of patients with hypoglycemia had HbA1c level ≥7%. In ACCORD, 2008 and ADVANCE, 2008 trial shows that severe hypoglycemia and major fatal outcome was more when Hba1c was <6.5%. In contrast, Leese *et al*.[25]

chronic disease entities.[18] The largest negative impact of severe hypoglycemia observed in the present study was on "freedom to eat," which is in line with previous studies.[9,19] Fear of weight gain, high blood glucose levels as well as fear of hypoglycemia affects patient's dietary behavior.[9,19] As it has been showed in a recent multicenter study, there is a relationship between diabetes-specific QoL and dietary behavior.[17] Similar results were found in another study where diabetes had the largest impact on "enjoyment of

reported higher incidence of hypoglycemia when HbA1c was >7% although finding was not statistically significant. Intensive glucose control strategies have been previously shown to increase the risk of hypoglycemia in clinical trials but did not find an inverse relationship between HbA1c level and hypoglycemia. Instead, hypoglycemia was common at all levels of glycemic control. Previously other study[26] also supported the findings of a strong association between severe hypoglycemia and high level of HbA1c. The 73rd Scientific Sessions of the American Diabetes Association, Chicago, June 2013, concluded that self-reported severe hypoglycemia was common among all patients with type 2 diabetes irrespective of glycemic status. Contrary to conventional wisdom, hypoglycemia occurred just as frequently among those with poor glycemic control as it does in those achieving near-normal glycaemia which was supported in our study. Interestingly, in our QoL study, although severe hypoglycemia occurred more in the uncontrolled group regarding quality of life the controlled had lower QoL compared to the uncontrolled group which was in contrast to international literature where hypoglycemic and uncontrolled patients have lower QoL than their controlled counterparts and patients without hypoglycemia. Whether good glycemic control is associated with increased QoL is controversial. The UK Prospective Diabetes Study Group in 1999 stated that quality of life in type 2 diabetes is affected by complications but not by intensive policies to improve blood glucose. Wändell[27] in his study found that poor glycemic control (HbA1c>7%) was only associated with impaired cognitive function but not the other components of quality of life in the elderly diabetic patients compared to the patients with good control (HbA1c<7%). Abolfotouh *et al.*[28] found no significant association between glycemic control and QoL scores. Moreover, as QoL is a subjective measure, and indeed Choi *et al.*[29] found that in diabetic patient's subjective factors such as depressive symptom and psychological stress affected HRQoL, but objective factors related to diabetic status did not appear to affect HRQoL. In particular, HbA1c, an indicator of glycemic control, was not associated with impaired HRQoL. As diabetic patients with good glycemic status follow many restrictions in food intake and lifestyle, there may be a subjective feeling of impaired quality of life.[30-32] However, lack of consistency is noticed in the international literature in terms of hypoglycemic event classification and QoL questionnaires used to capture the different utility levels.[18,33,34] The questionnaire used to capture QoL in the current study was the ADDQOL-19. Costa *et al.*[35] have used this hypoglycemia-specific QoL questionnaire. In most of the international literature, the generic instrument EQ-5D was used[18,33,36,37] certain methodological differences may be observed between the current study and the international literature. Future analyses are needed to identify management strategies and treatment factors that may mitigate hypoglycemia risk.

As far as the instrument's dimensions are concerned, both hypoglycemia and high level of HbA1c negatively affect the self-perceived QoL and more specifically, the dimensions of freedom to eat, physical health, reliance on others, financial situation, self-confidence, sex life, and journey. Based on the current study, hypoglycemia, as well as high levels of HbA1c, were negatively correlated with the dimensions of the ADDQoL-19 instrument. There is a paucity of studies in the literature on the measurement of the QoL of diabetic patients with the ADDQoL-19 instrument. The results of the present study are likely to contribute to filling this gap in our knowledge about health-related QoL measurement for diabetic patients and the need for effective health strategies and social policies in the field of diabetic treatment.

Conclusions

Hypoglycemia is often reported as a "safety" issue, but a wider research focus, including measurement of the impact of hypoglycemia on quality of life as a co-primary endpoint alongside glycemic control, is required to acknowledge and quantify the detrimental personal, social and economic impact of hypoglycemia on people with diabetes. The present study shows hypoglycemia was negatively correlated with the dimensions of the ADDQoL-19 instrument. This type of study is now essential in determining the value of treatment in QoL evaluations and implies that there is much scope for improvement in health status from hypoglycemia. Our findings suggest a heavy humanistic and financial impact of increasing severity and frequency of hypoglycemia. Finally, the findings reinforce the need to ensure that people with diabetes are fully informed about hypoglycemia and that efforts are made to reduce the incidence of hypoglycemia and thus lower the burden of quality of life while striving to achieve good control.

Conflicts of interest

There are no conflicts of interest.

References

1. Holt RI, Cockram C, Flyvbjerg A, Goldstein BJ, editors. Textbook of Diabetes. 4th ed. West Sussex: Blackwell Publishing Ltd.; 2010.
2. Jayawardena R, Ranasinghe P, Galappatthy P, Malkanthi R, Constantine G, Katulanda P, *et al.* Effects of zinc supplementation on

diabetes mellitus: A systematic review and meta-analysis. Diabetol Metab Syndr 2012;4:13.

3. International Diabetes Federation. IDF Diabetes Atlas. 6th ed. IDF. Brussels: International Diabetes Fderation; 2013. Available from: at: https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/19-atlas-6th-edition.html.

4. Hsu PF, Sung SH, Cheng HM, Yeh JS, Liu WL, Chan WL, *et al.* Association of clinical symptomatic hypoglycemia with cardiovascular events and total mortality in type 2 diabetes: A nationwide population-based study. Diabetes Care 2013;36:894-900.

5. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA, *et al.* Increased mortality of patients with diabetes reporting severe hypoglycemia. Diabetes Care 2012;35:1897-901.

6. Ha WC, Oh SJ, Kim JH, Lee JM, Chang SA, Sohn TS, *et al.* Severe hypoglycemia is a serious complication and becoming an economic burden in diabetes. Diabetes Metab J 2012;36:280-4.

7. Cryer PE. Hypoglycaemia: The limiting factor in the glycaemic management of type I and type II diabetes. Diabetologia 2002;45:937-48.

8. McCrimmon RJ, Frier BM. Hypoglycaemia, the most feared complication of insulin therapy. Diabete Metab 1994;20:503-12.

9. Bradley C. FIT: A paradigm shift that recognizes the importance of dietary freedom and QoL in diabetes management. Health Psychol 2001;10:74-5.

10. Botija Yague MP, Lizan Tudela L, Gosalbes Soler V, Bonet Pla A, Fornos Garrigós A. How does intensive therapy of cardiovascular risk factors affect health-related quality of life in diabetic patients?. Atencion primaria / Sociedad Española de Medicina de Familia y Comunitaria 2007;39:227-34.

11. Tabaei BP, Shill-Novak J, Brandle M, Burke R, Kaplan RM, Herman WH, *et al.* Glycemia and the quality of well-being in patients with diabetes. Qual Life Res 2004;13:1153-61.

12. Petterson T, Lee P, Hollis S, Young B, Newton P, Dornan T, *et al.* Well-being and treatment satisfaction in older people with diabetes. Diabetes Care 1998;21:930-5.

13. Hill-Briggs F, Gary TL, Hill MN, Bone LR, Brancati FL. Health-related quality of life in urban African Americans with type 2 Diabetes. J Gen Intern Med 2002;17:412-9.

14. Chung JO, Cho DH, Chung DJ, Chung MY. An assessment of the impact of type 2 diabetes on the quality of life based on age at diabetes diagnosis. Acta Diabetol 2014;51:1065-72.

15. Speight J, Sinclair AJ, Browne JL, Woodcock A, Bradley C. Assessing the impact of diabetes on the quality of life of older adults living in a care home: Validation of the ADDQoL Senior. Diabet Med 2013;30:74-80.

16. Chung JO, Cho DH, Chung DJ, Chung MY. Assessment of factors associated with the quality of life in Korean type 2 diabetic patients. Intern Med 2013;52:179-85.

17. Kuznetsov L, Griffin SJ, Davies MJ, Lauritzen T, Khunti K, Rutten GE, *et al.* Diabetes-specific quality of life but not health status is independently associated with glycaemic control among patients with type 2 diabetes: A cross-sectional analysis of the Addition-Europe trial cohort. Diabetes Res ClinPract 2014;104:281-7.

18. 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.

19. Bradley C, Speight J. Patient perceptions of diabetes and diabetes therapy: Assessing quality of life. Diabetes Metab Res Rev 2002;18 Suppl 3:64-9.

20. Demirci H, Cinar Y, Bayram N, Bilgel N. Quality of life in type II diabetic patients in primary health care. Dan Med J 2012;59:A4468.

21. Wang HF, Yeh MC. The quality of life of adults with type 2 diabetes in a hospital care clinic in Taiwan. Qual Life Res 2013;22:577-84.

22. Rombopoulos G, Hatzikou M, Latsou D, Yfantopoulos J. The prevalence of hypoglycemia and its impact on the quality of life (QoL) of type 2 diabetes mellitus patients (The HYPO study). Hormones (Athens) 2013;12:550-8.

23. Papazafiropoulou AK, Bakomitrou F, Trikallinou A, Ganotopoulou A, Verras C, Christofilidis G, *et al.* Diabetes-dependent quality of life (ADDQOL) and affecting factors in patients with diabetes mellitus type 2 in Greece. BMC Res Notes 2015;8:786.

24. Rubin RR, Peyrot M. Quality of life and diabetes. Diabetes Metab Res Rev 1999;15:205-18.

25. Leese GP, Wang J, Broomhall J, Kelly P, Marsden A, Morrison W, *et al.* Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: A population-based study of health service resource use. Diabetes Care 2003;26:1176-80.

26. Heller SR. Minimizing hypoglycemia while maintaining glycemic control in diabetes. Diabetes 2008;57:3177-83.

27. Wändell PE. Quality of life of patients with diabetes mellitus. An overview of research in primary health care in the Nordic countries. Scand J Prim Health Care 2005;23:68-74.

28. Abolfotouh M, Salam M, Al-Turaif D, Suliman W, Al-Issa H, Alrowaily M. Predictors of Quality of Life and Glycemic Control Among Saudi Adults with Diabetes. Int J Med Sci 2013; 46: 1360-1370.

29. Choi YJ, Lee MS, An SY, Kim TH, Han SJ, Kim HJ, *et al.* The relationship between diabetes mellitus and health-related quality of life in Korean adults: The Fourth Korea National Health and Nutrition Examination Survey (2007-2009). Diabetes Metab J 2011;35:587-94.

30. Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes 2008;57:3169-76.

31. Alvarez-Guisasola F, Yin DD, Nocea G, Qiu Y, Mavros P. Association of hypoglycemic symptoms with patients' rating of their health-related quality of life state: A cross sectional study. Health Qual Life Outcomes 2010;8:86.

32. Lundkvist J, Berne C, Bolinder B, Jönsson L. The economic and quality of life impact of hypoglycemia. Eur J Health Econ 2005;6:197-202.

33. Currie CJ, Morgan CL, Poole CD, Sharplin P, Lammert M, McEwan P, *et al.* Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. Curr Med Res Opin 2006;22:1523-34.

34. Grandy S, Fox KM. EQ-5D visual analog scale and utility index values in individuals with diabetes and at risk for diabetes: Findings from the study to help improve early evaluation and management of risk factors leading to diabetes (SHIELD). Health Qual Life Outcomes 2008;6:18.

35. Costa FA, Guerreiro JP, Duggan C. An audit of diabetes dependent quality of life (ADDQoL) for Portugal: Exploring validity and reliability. Pharm Pract (Granada) 2006;4:123-8.

36. Marrett E, Stargardt T, Mavros P, Alexander CM. Patient-reported outcomes in a survey of patients treated with oral antihyperglycaemic medications: Associations with hypoglycaemia and weight gain. Diabetes Obes Metab 2009;11:1138-44.

37. Levy AR, Christensen TL, Johnson JA. Utility values for symptomatic non-severe hypoglycaemia elicited from persons with and without diabetes in Canada and the United Kingdom. Health Qual Life Outcomes 2008;6:73.