Research paper

The prevalence of hypoglycemia and its impact on the quality of life (QoL) of type 2 diabetes mellitus patients (The HYPO Study)

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ABSTRACT

OBJECTIVE: To estimate the impact of hypoglycemia on the Quality of Life (QoL) and its prevalence in patients with type 2 diabetes mellitus (T2DM) in Greece. **DESIGN:** A cross-sectional epidemiological study was conducted in 6631 patients with T2DM. QoL was assessed with the patient self-administered ADDQoL-19. Reliability analysis of patients' outcomes was performed to assess internal consistency of the ADDQoL-19. Patients were categorized according to hypoglycemia experience and diabetes control. Controlled patients were considered as having Hb1Ac <7% (53mmol/mol) and hypoglycemic episodes were defined as laboratory-confirmed clinical symptomatic events. **RESULTS:** In total, 59% of the sample had HbA1c >7% (53mmol/mol) and 20.4% of patients had a history of laboratory-confirmed hypoglycemia. The mean age was 60 years and the mean T2DM duration was 10 years. The mean QoL score was -3.09 ± 1.9 for the total sample and the mean score of non-hypoglycemic patients was -3.05 ± 2 , while the respective score of hypoglycemic patients was -3.26 ± 1.8 , ($p \leq 0.001$). Similar results were observed in the group of controlled and uncontrolled patients, who scored -2.73 ± 1.7 and -3.33 ± 1.9 , respectively ($p \leq 0.001$). Comparable results were identified in the majority of the ADDQoL-19 instrument dimensions. **CONCLUSIONS:** The QoL of T2DM patients is affected significantly by hypoglycemia and the level of disease control. In diabetes treatment, the ultimate goal should be optimal glycemic control without debilitating hypoglycemic episodes which compromise patients' QoL.

Key words: ADDQoL-19, Greece, Hypoglycemia, Quality of Life, Type 2 Diabetes

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INTRODUCTION

Type 2 diabetes mellitus is a chronic progressive disease characterized by hyperglycemia resulting from multiple abnormalities, including impaired insulin secretion, increased hepatic glucose production,

hyperglucagonemia and peripheral insulin resistance. Diabetes is a major public health concern, as it leads to serious long-term micro- and macrovascular complications that increase morbidity, mortality and healthcare costs.¹

According to the International Diabetes Federation, diabetes mellitus is becoming a globally epidemic disease with more than 366 million patients affected, while this number is expected to reach 552 million by 2030. This prediction indicates a significant increase both in the percentage of people with diabetes as well as in the prevalence of the disease.¹ In 2012, Greece was estimated as having about 638 thousand diabetic patients and a prevalence rate of 5.22%, based on the IDF atlas.¹ Higher rates were reported in an epidemiological study performed in Greece in 2002 where the estimated prevalence of T2DM was 7.6% in men and 5.9% in women.² A significant proportion of diabetic subjects (24% of men and 30% of women) were unaware of their condition, while a 10-unit increase in the diet score was associated with 21% lower odds of diabetes ($P < 0.05$).²

Hypoglycemia is a common, unpredictable and potentially dangerous side effect of diabetes therapy. The greatest clinical risk results from a lack of adequate cerebral glucose supply causing progressive cognitive impairment, confusion and finally coma.³ Hypoglycemia is also associated with lower QoL in T2DM patients. In particular, this can be seen through the events caused by this adverse reaction, the fear of this, as well as through fear of possible long-term effects.⁴ Therefore, it is evident that both diabetes and hypoglycemia negatively affect the patients' wellbeing as well as their QoL.^{4,7}

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. T2DM can be objectively measured through clinical assessment of patients' health status, but also by taking into account the patients' subjective

views on various dimensions which affect their QoL. Specifically designed questionnaires are used for the measurement of subjective evaluation of health.⁸ It is worth mentioning that the impact assessment of T2DM on QoL and well-being of patients has been the subject of research in both clinical and health economic research. Furthermore, patients with diabetes have impaired physical and mental well-being, while they also feel emotional distress and helplessness.⁹⁻¹³ It is noteworthy that patients with diabetes have lower levels of QoL than their healthy peers,¹⁴⁻¹⁶ while the progress of disease and its complications negatively affect the improvement of QoL.^{17,18} For assessment of health status, the above items are added to demographic characteristics, obesity, hypertension and any pre-existing heart problems.¹⁹ The relation between T2DM and socioeconomic status and its impact on the lower income classes has been recently investigated by clinicians and health economists.^{20,21} Cost effectiveness analysis has been used to evaluate the impact on an individual's budget and the expenses involved for the improvement of QoL.²²

The objective of this study was to estimate the prevalence of hypoglycemia in type 2 diabetic patients and its impact on their quality of life.

MATERIALS AND METHOD

The present study was a cross-sectional epidemiological research conducted in 6631 Greek patients with T2DM within a 6-month time period. The study population was selected by a random sampling in accordance with geographical distribution around Greece.

The ADDQoL-19 QoL instrument was self-administered and completed by each patient. Patient demographic data, medical history, number of hypoglycemic episodes and historical measurements of Hb1Ac were analyzed by internists and endocrinologists specialized in diabetes. Patients' categorization was based on the following parameters: experience of hypoglycemia or not and controlled or uncontrolled. Controlled patients were considered as having Hb1Ac $< 7\%$ (53mmol/mol). Hypoglycemic episodes were defined as laboratory-confirmed clinical symptomatic events.

Each patient completed one questionnaire concerning his/her QoL [Greek edition of the Audit

of Diabetes Dependent QoL Questionnaire (ADDQoL-19)]. Additionally, each physician filled in the patients' clinical characteristics and glycated hemoglobin (HbA1c) as well as providing a questionnaire related to hypoglycemia symptoms, severity and frequency during the previous year.

The ADDQoL-19 instrument was designed and developed by Bradley et al., 1999, in order to measure the individual's perception of HRQL when suffering from diabetes. The questionnaire assesses 19 domains: leisure activities, working life, travel, holiday, physical activities, family life, social life, personal life, sex life, physical appearance, self-confidence, motivation, reaction from others, feelings about the future, financial situation, living conditions, reliance on others, freedom to eat and freedom to drink. The score of each item ranged from -9 to 3 with a lower score indicating a worse health state. Finally, the questionnaire includes two overview items which report the general QoL.²³

In addition, the data were analyzed using the statistical program SPSS 17.00. The demographic characteristics (gender, age, duration of disease, Body Mass Index, HbA1c) of the sample were presented as frequencies and rates. The mean value and standard deviation were used for the quality-of-life parameters.

The assessment of the psychometric properties of the HRQL instrument, and in particular reliability, was performed using Cronbach's coefficient $\alpha_{Cronbach}$.

Cronbach's α has been proven to underestimate the true reliability and is therefore a conservative measurement. Thus, the 0.7 alpha coefficient is considered as a cut-off value, above which the HRQL questionnaire is considered reliable.²⁴

The statistical significance of the results was investigated using the chi-square (χ^2) test (for percentages) and the mean values were compared using the Student's t-test when the variables followed the normal distribution, and the Mann-Whitney U-test when the variables were not normally distributed.

Finally, the correlation analysis was conducted using the *Pearson R* coefficient for normally distributed variables, and the *Spearman* coefficient for non-normally distributed variables. The instructions of Cohen were used for the interpretation of these coefficients. Specifically, it was assumed that a coef-

ficient of 0.10 indicates low correlation, a coefficient of 0.30 indicates moderate correlation and a coefficient of 0.50 reveals a high correlation.²⁵

RESULTS

In total, 6631 patients with T2DM were enrolled in the study. The age groups ranged from 19 to more than 90 years old. 35.1% of the patients were 61-70 and 30% were in the age group of 51-60. In total, 2979 patients (45%) were female, while 3642 patients (55%) were male. As far as Body Mass Index is concerned, 59% (3890) of the patients were overweight, followed by 22.5% (1481) who were characterized as obese class I (BMI 30-35). 44.4% of patients had suffered from the disease from 0 to 5 years and 27.8% 6 to 10 years. According to the last HbA1c test results, 41% of patients were controlled, while 59% were uncontrolled. Specifically, 2957 (44.7%) patients were moderately uncontrolled (7-7.99%/53-64 mmol/mol) and the remaining 943 (14.3%) were severely uncontrolled (>8%/64 mmol/mol) (Table 1).

41.9% of patients (n=2779) stated that they had experienced the symptoms of hypoglycemia during the last three months, whereas only 20.4% (n=1.354) had laboratory-confirmed hypoglycemia. The disposition of 41.9% is analyzed as follows: 25.5% with only one hypoglycemic event, 11.1% with two, while lower percentages were observed in patients with more than three events during the last three months. Finally, 11.6% (767) of patients had experienced severe hypoglycaemia and were transferred to hospital (Table 2).

The disposition of hypoglycemic events among the controlled and uncontrolled patients is presented in Table 3. Between the hypoglycemic and the non-hypoglycemic population there was a statistical significant difference ($p=0.001$) in HbA1c levels. The group of uncontrolled patients had 1.419-fold increased risk of having hypoglycemic events, in comparison to the controlled patients (CI: 1.610-1.971).

The impact of diabetes on QoL of the patients of the whole study sample, i.e. the hypoglycemic and non-hypoglycemic groups as well as the controlled and uncontrolled groups, is presented in figure 1. Lower QoL scoring was observed in hypoglycemic and uncontrolled patients. A statistically significant difference was found between hypoglycemic and non-hypoglycemic patients, as well as between the

Table 1. Demographic and disease characteristics

		Number	Percentage
Age group (years)	19-30	18	0.3
	31-40	154	2.3
	41-50	844	12.7
	51-60	1984	30.0
	61-70	2326	35.1
	71-80	1130	17.1
	81-90	157	2.4
	90+	8	0.1
Gender	Male	3642	55
	Female	2979	45
Body Mass Index* (Kg/m ²)	Underweight (<19)	24	0.4
	Normal (20-25)	898	13.6
	Overweight (26-29)	3890	59.0
	Obese Class I (30-35)	1481	22.5
	Obese Class II-III (>36)	299	4.5
Duration of T2DM (years)**	0-5	2939	44.4
	6-10	1844	27.8
	11-15	651	9.8
	16-20	267	4
	21-25	94	1.4
	25-30	41	0.6
	31-35	12	0.2
	35-40	6	0.1
	41+	4	0.1
HbA1c	Controlled (<7%-53mmol/mol)	2714	41
	Moderately Uncontrolled ($\geq 7 - 7.99\%$ -53-64 mmol/mol)	2957	44.7
	Uncontrolled ($\geq 8\%$ -64 mmol/mol)	943	14.3

*According to NICE Guideline 43 2006 **The remaining 11.6% is of unknown disease duration.

Table 2. Hypoglycemia incidence

		Frequency	Percentage
Hypoglycemia	Hypoglycemia	2,779	41.9
	Laboratory-confirmed Hypoglycemia	1,354	20.4
	Severe Hypoglycemia	767	11.6

controlled and uncontrolled. More specifically, the mean QoL score of the total sample was -3.1 ± 1.9 , the mean score of non-hypoglycemic patients was -3.05 ± 2 and the scoring of the hypoglycemic group was -3.26 ± 1.8 , ($p \leq 0.001$). This signifies that type 2

Table 3. Confirmed hypoglycemic events in controlled & uncontrolled patients

HbA1c	Hypoglycemia			
	NO		YES	
	%	N	%	N
Controlled	82.8%	2237	17.2%	466
Uncontrolled	77.2%	3000	22.8%	887

diabetes has a greater impact on QoL when coexisting with hypoglycemia. In addition, non-hypoglycemic patients stated that their QoL would be a little better if they did not have diabetes (-1.58 ± 0.85), in contrast

Figure 1. Average weighted QoL impact score of the study sample and subgroups.

to the hypoglycemic patients who stated that it would be much better (-1.89 ± 0.76). Similar results are presented for the group of controlled patients, who scored -2.73 ± 1.7 and -3.33 ± 1.9 for uncontrolled, with statistical significant difference ($p \leq 0.001$).

Taking into consideration the dimensions leisure activities, working life, travel, holiday and physical activities of the ADDQoL-19, it was reflected that hypoglycemia significantly affects them. Specifically, the most influenced dimension was the “holiday”. However, hypoglycemic and uncontrolled individuals’ QoL were more affected compared to the non-hypoglycemic and controlled.

Regarding the dimensions family life, social life, personal life and sex life, hypoglycemia patients confronted more difficulties than non-hypoglycemia with the lowest score being noted in the dimension of sex life. Similar results were found in the second group.

Hypoglycemic patients seemed to have been more negatively influenced than the non-hypoglycemic group in the dimensions of self-confidence, motivation and feelings about the future, though not in those of physical appearance and reaction from others. The same evidence was provided among the uncontrolled individuals with the exception of motivation.

The last five dimensions of the ADDQoL questionnaire (financial situation, living conditions, reliance on others, freedom to eat, freedom to drink) showed a negative effect on patients’ quality of life. Hypoglycemic patients had difficulties in living conditions, freedom to eat and, especially, in reliance on others. Moreover, the dimension with the lowest mean value in both hypoglycemic and uncontrolled samples was the freedom to eat parameter, which is related to the individuals’ perception about their eating ability.

Statistically significant differences were found in 10 out of the 19 ADDQoL dimensions regarding both groups ($p \leq 0.05$) and specifically in: a) leisure activities, b) working life, c) travel, d) holiday, e) physical activities, f) family life, g) social life, h) physical appearance, i) living conditions and j) reliance on others.

Logistic regression was performed between hypoglycemic and non-hypoglycemic patients and the ADDQoL-19 dimensions. The dependent variable was set in the existence of hypoglycemia or not (hypoglycemia = 1, non-hypoglycemia = 0), while the 19 dimensions of the instrument were used as independent variables. The factor of multiple determination was $R^2 = 11.1\%$. The observed values agreed in 83.7% of the total observations. Table 4 presents the regression model with the odds ratios for all quality of life parameters

of the study sample for both hypoglycemia and control levels. More specifically, if diabetic patients scored 1 unit less in working life, then the relative probability of the occurrence of hypoglycemia will decrease by 0.0111, for physical activities by 0.0136, reliance on others by 0.0122 and 'if I didn't have diabetes my quality of life would be better' by 0.0222. In the event that diabetic patients scored 1 unit extra, then the relative probability of the occurrence of hypoglycemia in diabetic patients will increase in the parameters of personal life by 0.0116, reaction from others 0.0124, financial situation 0.0110, freedom to drink 0.0057 and, in general, quality of life by 0.0536. A similar logistic regression model was also carried out for controlled and uncontrolled patients. Specifically, the coefficient determination was $R^2 = 0.0109$. If diabetic patients answered 1 unit less in the quality of life questionnaire, then the relative probability of being controlled will decrease in all dimensions, apart

from holiday, and in general 'my present quality of life is...', which have a positive association.

DISCUSSION

Hypoglycemia is an important element affecting the QoL of T2DM patients. Based on the results of the present analysis, it is observed that hypoglycemic events and severe hypoglycemic events are higher than those presented in the international literature.^{26,27} During the first decade of the UK Prospective Diabetes Study (UKPDS), mean proportion of patients with any hypoglycemic episode ranged from 1.2% with diet alone to 11-17%, with a sulphonylurea reaching 36.5% with insulin. During the same period, major hypoglycemic episodes ranged between 0.4%-0.6% for sulphonylureas and were 2.3% for insulin.²⁶ Similarly, a population-based study of health services published in 2003 reported that 7.3% of patients with T2DM

Table 4. Logistic regression analysis for hypoglycemia and control levels

Subscale ADDQOL-19 Hypoglycemia	B	ODDS RATIO	95% Confidence Interval		P value
			Lower	Upper	
Working Life	-0.117	0.889	0.835	0.947	0.001
Physical Activities	-0.082	0.922	0.864	0.983	0.012
Personal Life	0.110	1.116	1.047	1.190	0.001
Reaction from Others	0.117	1.124	1.053	1.200	0.001
Financial Situation	0.105	1.110	1.045	1.180	0.001
Reliance on Others	-0.130	0.878	0.831	0.928	0.001
Freedom to Drink	0.056	1.057	1.001	1.117	0.045
In general, my present quality of life is...	0.429	1.536	1.369	1.723	0.001
if I did not have diabetes, my quality of life would be...	-0.251	0.778	0.660	0.918	0.003
Constant	-2.299	0.100	0.895	1.017	0.001
Subscale ADDQOL-19 Control Levels	B	ODDS RATIO	95% Confidence Interval		P value
			Lower	Upper	
Leisure Activities	-0.580	0.942	0.896	0.989	0.017
Holiday	0.052	1.054	1.007	1.103	0.025
Family Life	-0.050	0.951	0.907	0.998	0.040
Sex Life	-0.042	0.959	0.920	0.999	0.046
Reaction from Others	-0.052	0.949	0.904	0.996	0.034
Reliance on Others	-0.069	0.933	0.894	0.975	0.002
Freedom to Drink	-0.066	0.937	0.899	0.976	0.002
In general, my present quality of life is...	0.324	1.382	1.260	1.516	0.001
Constant	-1.492	0.225	0.896	0.989	0.001

treated with insulin and 0.8% of patients treated via oral hypoglycemic therapy suffered at least one severe hypoglycemic event.²⁷ On the other hand, in the UK Hypoglycemia Group Study, 7% of severe hypoglycemic events have been reported in the population, which is much higher than previous reported studies.³ In the current study, the percentages of laboratory-confirmed hypoglycemia was 20.4%, which is quite similar to those of the UKPDS study. However, in the case of severe hypoglycemia, a great difference is recorded, with 11.6% having experienced at least one severe event, which is similar to insulin-treated patients. The high number of hypoglycemic events might be attributed to the relatively higher percentage of controlled and moderately uncontrolled patients, leading to higher frequency of hypoglycemic events. Alternatively, the difference might be due to the under-reporting of severe hypoglycemic events in previous studies. In the current study, the number of controlled patients was 41%, which is in accordance with the control levels reported in the international literature (35-59%).²⁸⁻³⁰ Furthermore, the hypoglycemia in patients with T2DM is clinically assessed on the basis of administered treatment profiles.³⁰⁻³³

The findings concerning patients' QoL of the current study have both similarities and differences from the international literature. The major comparable result of the current study and the international literature reveals that hypoglycemic and uncontrolled patients have lower QoL than their controlled counterparts and patients without hypoglycemia.^{4,7,32-37} However, lack of consistency is noticed in the international literature in terms of hypoglycemic event classification and QoL questionnaires used in order to capture the different utility levels.^{4,9,10,12,14} The questionnaire used to capture QoL in the current study was the ADDQOL-19 and only Costa FA et al³⁸ have used this hypoglycemia-specific QoL questionnaire. In most of the international literature the generic instrument EQ-5D was used.^{4,10,17,30,31,39-40} Additionally, certain methodological differences may be observed between the current study and the international literature. In the current study, mainly patients with T2DM on oral antidiabetic drugs (OADs) were recruited, which might be considered as a limitation of the study. The only studies reporting QoL data from OADs were

those of Marrett et al and Solli et al.^{4,17} Nevertheless, it is not clear whether hypoglycemia events emerging from OADs or insulin are of the same severity and what their impact is on patient's quality of life.

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 holidays, sex life, self-confidence, travel, motivation, feelings about the future, living conditions, freedom to eat and reliance on others.^{11,35} 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.

CONCLUSION

The current results highlight the fact that patients experiencing hypoglycemia and uncontrolled patients confront significant restrictions in many dimensions of their living conditions. In addition, the existence of hypoglycemia and high levels of HbA1c has a negative impact on important aspects of QoL and well-being of patients. Effective health policy interventions need to focus on specific treatments and strategies aiming at improving the overall well-being of diabetic patients. In diabetes treatment, the ultimate goal should be good glycemic control without debilitating hypoglycemic episodes which compromise patients' QoL.

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