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Estimation of the influence of hypoglycemia and body mass index on health-related quality of life, in patients with type 2 diabetes mellitus

Procena uticaja hipoglikemije i indeksa telesne mase na kvalitet života kod obolelih od šećerne bolesti tipa 2

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Abstract

Background/Aim. Recent data have shown that obese patients with type 2 diabetes mellitus (T2DM) have more commonly impaired glycemic control and complication such as neuropathy as well as a higher mortality rate than normal body weight patients with diabetes. The aim of this study was to quantify patient-reported rates of hypoglycemia, determine body mass index (BMI) and evaluate their association with health-related quality of life (HRQL) estimated by EuroQoL-EQ 5-dimensional (EQ-5D) questionnaire in individuals with T2DM after adjusting for age, duration of diabetes mellitus and presence of late diabetes complications. **Methods.** This clinical-epidemiological cross sectional study involved 269 consecutively selected adult patients of both sexes with T2DM duration longer than one year. The standardized Serbian version of the EQ-5D 3 level version – EQ-5D-3L questionnaire with a visual analogue scale-VAS (EQ-VAS), was used to assess respondents' HRQL and utility values. **Results.** The average age of participants was 65.1 ± 9.3 years; hypoglycemia was registered in 71.0%, obesity in 43.9% and chronic complications in 88.8% of the patients. Half of the patients did not reach the target value of glycated hemoglobin (HbA1c) < 7.0%. Patients that experienced episodes of hypoglycemia years compared to those with good glycemic control were significantly younger at diagnosis (54.19 *vs* 57.59 years, respectively) and less likely to be graduated at tertiary school (7.3% *vs* 35.1%, respectively). They had higher mean EQ-5D subscale score (pain/discomfort: 1.86 *vs* 1.68, respectively), lower VAS (55.99 *vs* 62.44) and EQ-5D index (0.85 *vs* 0.87, respectively). Obese patients were more likely to be female with higher systolic and diastolic pressure, triglycerides, waist circumference, subscale score (anxiety/depression 2.01 *vs* 1.80) and rates of hypoglycemia *per* year. After adjusting for confounders, the presence of hypoglycemia had 2,035 greater odds for experienced problems related to pain/discomfort. The unit increase of BMI had 1.05 greater odds for experienced problems related to mobility and anxiety/depression. Hypoglycemia was associated with significantly lower levels of the VAS score (b = -0.13). Increasing of BMI was associated with significantly lower EQ-5D index value (b = -1.78). The rates of hypoglycemia were not associated with VAS score and EQ-5D index values. **Conclusion.** Results demonstrated a significant association of hypoglycemia and obesity with impaired HRQL determined by the EQ-5D questionnaire. Lifestyle measures aimed to reduce obesity and hypoglycemia together with optimal diabetic therapy regiment can markedly improve patients' HRQL.

Key words:
diabetes mellitus, type 2; quality of life; hypoglycemia; body mass index.

Apstrakt

Uvod/Cilj. Noviji podaci sugerišu da gojazne osobe sa dijabetesom tip 2 (DMT2) češće imaju lošiju kontrolu glikemije i češće komplikacije poput neuropatije, kao i višu stopu mortaliteta u odnosu na obolele od dijabetesa sa normalnom telesnom masom. Cilj istraživanja bio je da se utvrdi učestalost hipoglikemijskih epizoda, odredi vrednost indeksa telesne mase (ITM) i proceni njihov uticaj na kvalitet života (QL) kod obolelih od DMT2 korišćenjem upitnika *EuroQoL-EQ 5-dimensional* (EQ-5D) nakon korekcije za starost, trajanje dijabetesa melitusa i prisustvo kasnih komplikacija bolesti. **Metode.** Ovom kliničko-epidemiološkom studijom preseka obuhvaćena su 269 uzastopno selektovana bolesnika oba pola, sa postavljenom dijagnozom DMT2 trajanja dužeg od jedne godine. Standardizovana verzija upitnika EQ-5D trećeg nivoa – EQ-5D-3L na srpskom jeziku i EQ vizuelna analogna skala (EQ-VAS) korišćeni su za procenu kvaliteta života u vezi sa zdravljem. **Rezultati.** Prosečna starost ispitanika iznosila je 65,1 ± 9,3 godina. Hipoglikemija je zabeležena kod 71%, gojaznost kod 43.9% i hronične komplikacije kod 88.8% isptanika. Polovina bolesnika nije dostigla ciljne vrednosti glikoziliranog hemoglobina (HbA1c) (HbA1c < 7%). Hipoglikemija je bila značajno češća kod mlađih bolesnika u trenutku postavljanja dijagnoze (54,19 *vs* 57,59) a ređa kod visokobrazovanih

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ispitanika (7,3% *vs* 35,1%). Bolesnici sa hipoglikemijom imali su veću ocenu za bol i nelagodnost (1,86 *vs* 1,68) u EQ-5D upitniku, niže vrednosti VAS skora (55,99 *vs* 62,44) i EQ-5D indeksa (0,85 *vs* 0,87) u odnosu na one sa dobrom kontrolom glikemije. Gojazni ispitanici su uglavnom bili ženskog pola, sa povišenim vrednostima sistolnog i dijastolnog pritiska, povišenim trigliceridima, obimom struka, ocenom za anksioznost i depresiju (2,01 *vs* 1,80) i većim brojem epizoda hipoglikemija na godišnjem nivou. Nakon korekcije za doprinoseće faktore, ispitanici sa hipoglikemijom imali su 2 035 puta veću šansu za teži stepen bola i nelagodnosti. Sa povećanjem ITM, šansa za probleme mobilnosti, anksioznost/depresiju povećala se 1,05 puta. Hipoglikemija je bila značajno povezana sa nižim vrednostima VAS skora (b = -0.13). Povećanje vrednosti ITM bilo je statistički značajno povezano sa nižim vrednostima EQ 5D indeksa (b = -1,78). Učestalost hipoglikemije nije bila povezana sa vrednostima VAS skorom i EQ 5D indeksa. **Zaključak.** Rezultati su pokazali značajnu povezanost hipoglikemije i gojaznosti sa smanjenim QL, procenjenim na osnovu EQ-5D upitnika. Korekcija životnih stilova usmerenih ka smanjenju gojaznosti i hipoglikemije uz optimalnu terapiju, može značajno poboljšati QL vezan za zdravlje kod bolesnika sa DMT2.

Ključne reči:
dijabetes melitus, insulin-nezavisni; kvalitet života; hipoglikemija; telesna masa, indeks.

Introduction

Diabetes mellitus is a metabolic disease with increasing incidence and prevalence in adults worldwide. The greatest increase of diabetes mellitus (DM) prevalence is registered in developing countries. The literature data showed 382 million people had diabetes mellitus worldwide in 2013 and this number will continue to increase up to 592 million by 2035 [1]. In 2013, the number of people with diabetes was estimated to be 56 million in Europe with an overall estimated prevalence of 8.5% [2].

It was estimated that there were about 600,000 patients with diabetes in Serbia (8.2% of total population) according to the Serbian registry of diabetes. There were about 15,400 newly diagnosed cases of type 2 DM (T2DM) in Serbia during 2011 [3].

The recent data from the United States and Europe have demonstrated that obese patients with T2DM have more commonly impaired glycemic control [4], and complications such as neuropathy, and have a higher mortality rate compared with normal weight individuals with diabetes [5].

Overweight and obesity, represent important risk factors for the development of T2DM. Obesity-induced insulin resistance lies in the basis of this association [6]. Since overweight and obesity are associated with metabolic disorders their presence could worsen diabetes symptoms and disease expression. Thus, reduction of body weight and obesity by lifestyle interventions (diet and increased physical activity) combined with oral antidiabetics is the first step in the therapy of DM [7]. Obesity plays an important role not only in clinical presentations and diabetes therapy choice but also had a great impact on health-related quality of life – QL (HRQL) which could be important determinator when selecting between therapies or evaluating the cost effectiveness of different diabetes treatment options [8].

Almost all diabetic patients share the same opinion that diabetes impairs their QL by making many restrictions and schedules in usual daily activities, by the development of chronic diabetic complications or by spontaneous/therapy induced hypoglycemic episodes. DMT2 decreases QL and together with obesity-associated depression could reduce patients motivation to properly control the disease.

It has been shown that hypoglycemia caused by oral antidiabetic drugs or insulin treatments impaired QL (QoL) and it is associated with increased mortality in diabetics [9–11]. However, diabetes therapy is very complex and hypoglycemia represents important factor limiting therapy effectiveness and optimal glycoregulation in patients with T2DM. It is estimated that about 12–30% T2DM patients on antidiabetic therapy experienced hypoglycemia [12]. But, there is still limited data about potential effects of hypoglycemia on QL in T2DM patients in real life settings.

HRQL can be estimated by using different tools. These tools include direct valuation methods such as visual analogue scale (VAS) and time trade-off (TTO) [13], as well as indirect questionnaire-based measures such as the World Health Organization (WHO)-5 index for QL [14], the EuroQoL – EQ 5-dimensional (EQ-5D) questionnaire [13], and the Short Form Health Survey (SF 36) [15].

Determining the prevalence of hypoglycemia and measuring its impact on QLcould be of great importance because they have a significant impact on optimal diabetic treatment and prevention of diabetic late complications development [16].

The aim of this study was to provide the frequency of self-reported hypoglycemia in real life settings, to determine body mass index (BMI) and to determine the influence of hypoglycemia and obesity on HRQL and its subscale scores in EQ-5D questionnaire in patients with T2DM after adjusting for age and presence of diabetes-related late complications.

Methods

This clinical-epidemiological cross sectional study involved 269 T2DM patients, treated and examined in the Department for Diabetes, Internal Ward of the Health Center in Leskovac, Serbia. All patients were selected in a consecutive manner if they satisfied inclusion criteria. The inclusion criteria were: adult patients with T2DM older than 30 years and duration of DM longer than one year. All the participants have signed an informed consent form and anonymously filled EQ-5D and EQ-VAS questionnaires. The clinical data (presence of late diabetic complications, hypoglycemia, blood pressure and BMI) were collected by physicians from the di-

rect interview and physical examination and by checking medical documentations.

The study protocol was approved by the institutional review board and the informed consent was obtained from all patients' prior to enrolment in the study.

The standardized Serbian version of the EQ-5D 3 level version (EQ-5D-3L) questionnaire was used to determine HRQL in patients with T2DM. The five health dimensions from the EQ-5D-3L questionnaire (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) were used to determine the overall index. Each health dimension could be classified by three response levels (no, moderate, or extreme problems), which represents a matrix of 243 different health states. The patients also rated their health state using VAS (EQ-VAS) as a part of the EQ-5D-3L questionnaire. This scale had values ranging from 0-100 where 0 represented worst and 100 best health state.

Five health dimensions are converted into a weighted overall health index by applying scores from the EQ-5D preference weights derived from representative general population samples. These weights lie on a scale on which full health has a value of 1 and dead a value of 0. In this paper, we used the German TTO because this European population is similar to investigated population in Serbia [17].

According to the American Diabetes Association (ADA), we defined hypoglycemia as the presence of symptoms (hunger, shakiness, sweating, headache, dizziness, etc), and self measured blood glucose concentration ≤ 70 mg/dL (≤ 3.9 mmol/L) at the time symptoms were experienced (confirmed hypoglycemia) [18]. Unconfirmed hypoglycemia was defined as the presence of at least one symptom without a self measured blood glucose concentration ≤ 3.9 mmol/L. Patients without symptoms of hypoglycemia are marked as non hipoglycemic patients. Episodes of asymptomatic hypoglycemia (blood sugar reading of ≤ 3.9 mmol/L without symptoms) were also collected. The presence and frequency of hypoglycemia were also obtained from medical records.

The presence of DM was confirmed through anamnestic data and medical records. The patients with confirmed type 1 DM were excluded from the study. The presence of late microvascular and macrovascular diabetic complications was confirmed through medical documentation or patients' records.

The demographic data included age, sex, duration of DM, marital status (living with a partner or alone) and education (primary, secondary and tertiary school).

BMI was calculated from the most recent measurements (under one month) of weight and height and expressed as (kg/m^2). According to WHO classification, patients were divided into three BMI categories: normal (< 25 underweight and normal weight); overweight $25 \leq BMI < 30$ kg/m^2 and obese – $BMI \geq 35$ kg/m^2 [19]. These categories correspond to WHO classification and are widely employed by clinicians.

The blood pressure was measured by sphygmomanometer and the Korotkoff sound technique on the left upper arm in the sitting position after 5 min of resting [20].

The creatinine clearance was calculated by Cockcroft-Gault formula: {[(140 - age) × weight (kg) × F] / [serum creatinine (μmol/L) × 0.8136]} where F = 1 if male, and 0.85 if female, and expressed in mL/min.

Standard laboratory parameters [total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides (TG), fasting glycemia] were obtained from the medical documentation and they were accepted if not older than one month.

Statistical analyses

The data were analysed using descriptive statistical methods: frequency, percentage, mean ± standard deviation and 95% confidence interval (CI) for mean, depending on type and variable distribution.

The difference between groups of patients who experienced hypoglycemia and group without hypoglycemia was examined using χ^2 tests or Mann Whitney *U* test and *t*-tests for categorical and continuous dependent variables, respectively. Differences between patients according to BMI classification of obesity were examined using ANOVA and post-hoc test (Tukey or Dunnett's T3) depending on Levene Statistic or Kruskal–Wallis.

We used ordered logistic regressions to determine predictive importance of the BMI and hypoglycemia on EQ-5D subscale. Hierarchical multiple linear regression (Enter model) controlling for age, duration of DM and presence of diabetic late complications was applied to determine the association of the BMI and hypoglycemia on EQ-VAS score and EQ-5D index.

All analyses were conducted with SPSS version 17.0 (SPSS INC, NC) and statistical significance was set at $p < 0.05$. Where appropriate, for ordered logistic regressions beta-coefficients (b) and odds ratios (OR) were provided in the results section; for all other multivariate regressions, beta-coefficients were provided.

Results

A total of 269 diabetics aged 65.1 ± 9.3 years were analyzed. Hypoglycemia was registered in 71.0%, obesity in 43.9% and chronic complications of diabetes mellitus in 88.8% of the patients (microvascular in 85.1% and macrovascular in 46.5%) Almost half of the patients did not reach target HbA1c values under 7.0% (Table 1).

Patients experienced hypoglycemia compared to those who did not have significantly higher mean EQ-5D subscale score (pain/discomfort: 1.86 *vs* 1.68 respectively; $p < 0.01$) and significantly lower mean levels on the VAS (55.99 *vs* 62.44 respectively; $p < 0.05$) and EQ-5D index value (0.85 *vs* 0.87; $p < 0.05$) indicating poorer quality of life. Compared to those who did not report hypoglycemia, patients who did, were significantly younger at diagnosis (54.19 *vs* 57.59 respectively; $p < 0.05$) and less likely to be graduated at tertiary school (7.3% *vs* 35.1% respectively; $p = 0.01$) (Table 2).

Obese patients were more likely to be female with higher systolic and diastolic blood pressure (BP) and waist

Table 1

Demographic and clinical characteristics and complications in type 2 diabetic patients

Variable	Value
Total number of patients, n (%)	269 (100)
Males/females, n (%)	100/169 (37.2/62.8)
Age (years), $\bar{x} \pm SD$	65.1 ± 9.3
BMI (kg/m^2), $\bar{x} \pm SD$	29.7 ± 5.7
BMI WHO categories, n (%)	
normal	53 (19.7)
overweight	98 (36.4)
obese	118 (43.9)
Hypoglycemia, n (%)	191 (71.0)
Rates of hypoglycemia (event *per* patient-year)	10.8
EQ-5D index, $\bar{x} \pm SD$	0.86 ± 0.09
EQ-5D VAS, $\bar{x} \pm SD$	57.9 ± 19.3
Hypertension, n (%)	187 (69.5)
Chronic complications, n (%)	239 (88.8)
Macrovascular complications, n (%)	125 (46.5)
coronary artery disease	79 (29.4)
cerebrovascular disease	29 (10.8)
peripheral arterial disease	54 (20.1)
Microvascular complications, n (%)	229 (85.1)
retinopathy	174 (64.7)
nephropathy	37 (13.8)
polyneuropathy	200 (74.3)
Dialysis, n (%)	2 (0.8)
Renal transplantation, n (%)	0 (0.0)
Amputation, n (%)	11 (4.1)
HbA1c at target (< 7.0%), n (%)	131 (48.7)

BMI – body mass index; WHO – World Health Organization; EQ-5D – EuroQoL 5-dimensional; VAS – visual analogue scale; HbA1c – glycated hemoglobin; $\bar{x}$ – mean value; SD – standard deviation.

Table 2

Characteristics of patients experiencing hypoglycemia and those without hypoglycemia

Variable	Hypoglycemia symptoms (low blood sugar), n = 191	No hypoglycemia symptoms (no low blood sugar), n = 78	*p* – value
Males, n (%)	73 (38.2)	27 (35.1)	NS
Rural, n (%)	101 (52.9)	42 (53.8)	NS
Education			
no education, n (%)	54 (28.3)	23 (29.5)	NS
primary, n (%)	44 (23.0)	15 (19.5)	NS
secondary, n (%)	66 (34.6)	26 (33.8)	NS
tertiary, n (%)	14 (7.3)	27 (35.1)	< 0.01
Married/living with partner, n (%)	139 (72.8)	60 (76.9)	NS
Age (years), $\bar{x} \pm SD$	65.62 ± 8.99	64.06 ± 10.15	NS
Age at diagnosis (years), ($\bar{x} \pm SD$)	54.19 ± 10.39	57.59 ± 10.07	< 0.05
Quality of life, (95% CI)			
mobility	1.63 (1.55–1.71)	1.57 (1.44–1.71)	NS
self care	1.35 (1.27–1.44)	1.31 (1.18–1.45)	NS
usual activities	1.78 (1.68–1.88)	1.77 (1.59–1.94)	NS
pain/discomfort	1.86 (1.79–1.93)	1.68 (1.56–1.79)	< 0.01
anxiety/depression	1.93 (1.83–2.03)	1.84 (1.70–1.99)	NS
EQ-5D index value, $\bar{x}$ (95% CI)	0.85 (0.84–0.86)	0.87 (0.85–0.89)	< 0.01
Visual analogue scale, $\bar{x} \pm SD$	55.99 ± 18.75	62.44 ± 20.23	< 0.01
Laboratory			
creatinine (μmol/L), $\bar{x} \pm SD$	91.71 ± 68.55	91.99 ± 49.49	NS
creatinine clearance (mL/min), $\bar{x} \pm SD$	86.05 ± 36.33	89.91 ± 45.97	NS
waist circumference (cm), $\bar{x} \pm SD$	104.04 ± 14.51	101.83 ± 14.02	NS
body mass index (kg/m^2), $\bar{x} \pm SD$	29.65 ± 5.27	30.22 ± 6.70	NS

CI – confidence interval; $\bar{x}$ – mean value; SD – standard deviation; NS – no significant; EQ-5D – EuroQoL 5-dimensional.

circumference. The obese patients compared to those with normal BMI had significantly higher mean EQ-5D subscale score (anxiety/depression: 2.01 *vs* 1.82 and 1.80 respectively, $p < 0.05$) while there was no significant difference in VAS and EQ-5D index value. The proportion of patients who experienced hypoglycemic episodes was similar between BMI groups, but the rates of hypoglycemia *per* year were significantly higher in obese patients (Table 3).

In multivariate models, adjusting for confounders, patients who experienced hypoglycemic events had a 0.71 increase in the log odds of being in a higher level of pain/discomfort EQ-5D subscale. The one unit increase in BMI was accompanied with 0.05 increases in the log odds being in a higher level of mobility and anxiety/depression EQ-5D subscale; all of the other variables in the model were held constant. In presence of hypoglycemia there were 2.035 greater odds for experienced extreme problems *vs* no or moderate problems as well as experienced extreme and moderate problems *vs* no problems related to pain/discomfort ($p < 0.05$). Also, the unit increase of BMI had 1.05 greater odds for experienced extreme problems *vs* no or moderate problems as well as experienced extreme and moderate problems *vs* no problems related to mobility and anxiety/depression ($p < 0.05$) (Table 4).

Hypoglycemia was associated with significantly lower levels on the VAS score (b = -0.13, $p < 0.05$). The increase of BMI was associated with significantly lower EQ-5D index value (b = -1.78, $p < 0.05$). The rates of hypoglycemia *per* year were not significantly associated with EQ-5D VAS and EQ-5D index scores (Table 5).

Discussion

In this cross-sectional observational study, we measured HRQL using the EQ-5D, questionary which is widely used in Europe and Asian T2DM patients [21]. We used VAS scale direct methods to capture values that patients assign to their own health state [22]. We analyzed demographic characteris-

Table 3

Characteristics of patients according to body mass index (BMI) classification of obesity

Variables	Normal (BMI 20–24.9 kg/m^2) n = 53	Overweight (BMI 25–29.9 kg/m^2) n = 98	Obese (BMI > 30 kg/m^2) n = 118	
Males, n (%)	28 (52.8)	38 (38.8)	34 (28.8)[b]	< 0.01
Rural, n (%)	30 (56.6)	48 (49.0)	65 (55.1)	NS
Education, n (%)				
no education	14 (26.4)	29 (29.6)	34 (28.8)	NS
primary	10 (18.9)	23 (23.5)	26 (22.0)	NS
secondary	18 (34.0)	29 (29.3)	45 (38.1)	NS
tertiary	11 (20.8)	17 (17.3)	13 (11.0)	NS
Married/living with partner, n (%)	35 (66.0)	75 (76.5)	89 (75.4)	NS
Age (years), $\bar{x} \pm SD$	66.91 ± 11.54	65.63 ± 8.73	64.06 ± 8.63	NS
Age at diagnosis (years), $\bar{x} \pm SD$	56.30 ± 13.14	55.39 ± 9.75	54.60 ± 9.61	NS
Quality of life, mean (95% CI)				
mobility	1.55 (1.37–1.73)	1.60 (1.48–1.72)	1.65 (1.56–1.74)	NS
self care	1.43 (1.23–1.63)	1.34 (1.21–1.47)	1.30 (1.21–1.39)	NS
usual activities	1.75 (1.52–1.97)	1.76 (1.61–1.92)	1.79 (1.68–1.91)	NS
pain/discomfort	1.88 (1.73–2.04)	1.76 (1.65–1.87)	1.79 (1.72–1.87)	NS
anxiety/depression	1.80 (1.61–2.00)	1.82 (1.70–1.95)	2.01 (1.88–2.14)[a]	< 0.05
EQ-5D index value, mean (95% CI)	0.86 (0.83–0.88)	0.86 (0.85–0.88)	0.85 (0.84–0.87)	NS
Visual analogue scale, $\bar{x} \pm SD$	54.63 ± 22.19	60.35 ± 18.40	57.39 ± 18.75	NS
Waist circumference (cm), $\bar{x} \pm SD$	87.32 ± 8.56	100.09 ± 10.47[a]	113.28 ± 11.28[a]	< 0.01
sBP (mmHg), $\bar{x} \pm SD$	133.30 ± 16.11	138.37 ± 13.99	141.95 ± 16.33[b]	< 0.01
dBP (mmHg), $\bar{x} \pm SD$	82.08 ± 9.16	84.29 ± 8.21	85.51 ± 9.85[b]	< 0.01
Hypoglycemia, n (%)	34 (64.1)	75 (76.5)	82 (69.4)	NS
Rates of hypoglycemia *per* year, mean (95% CI)	17.23 (11.3–23.5)	17.1 (13.1–21.1)	31.7 (21.6–41.8)[a]	< 0.05
Late diabetes complication, n (%)	45 (84.9)	89 (90.8)	105 (88.9)	NS

[a]$p < 0.05$ or 0.01 *vs* other groups, [b]$p < 0.01$ *vs* group with normal BMI; NS – no significant; CI – confidence interval; sBP – systolic blood pressure; dBP – diastolic blood pressure. For other abbreviations see under previous tables.

Table 4

Adjusted effects of hypoglycemia, rates of hypoglycemia and body mass index (BMI) on health outcomes

Quality of life: ordered logit	b	95% CI (lower–upper)	OR	X^2	*p**
Presence of hypoglycemia					
EQ-5D: mobility	0.08	-0.50–0.66	1.084	0.07	NS
EQ-5D: self-care	0.04	-0.61–0.70	1.048	0.01	NS
EQ-5D: usual activities	0.07	-0.47–0.62	1.075	0.06	NS
EQ-5D: pain/discomfort	0.71	0.08–1.34	2.035	4.89	0.026
EQ-5D: anxiety/depression	0.187	-0.365–0.740	1.206	0.44	NS
Rates of hypoglycemia					
EQ-5D: mobility	0.003	-0.005–0.01	1.004	0.58	NS
EQ-5D: self-care	0.004	-0.003–0.01	1.004	1.17	NS
EQ-5D: usual activities	-0.003	-0.012–0.004	0.991	0.75	NS
EQ-5D: pain/discomfort	0.002	-0.008–0.012	1.002	0.16	NS
EQ-5D: anxiety/depression	0.018	-0.008–0.08	1.001	0.017	NS
BMI					
EQ-5D: mobility	0.05	0.006–0.09	1.054	5.04	0.024
EQ-5D: self-care	0.003	-0.04–0.05	1.003	0.01	NS
EQ-5D: usual activities	0.028	-0.01–0.07	1.028	1.71	NS
EQ-5D: pain/discomfort	0.017	-0.030–0.065	1.017	0.530	NS
EQ-5D: anxiety/depression	0.05	0.015–0.100	1.059	7.17	0.007

***p* adjusted for age, duration of diabetes mellitus and presence of diabetic late complications; OR – odds ratio. For other abbreviations see under previous tables.**

Table 5

Adjusted effects of hypoglycemia, rates of hypoglycemia and body mass index (BMI) on health outcomes

Quality of life: multiple regression	b	95% CI (lower-upper)	t	*p**
Presence of hypoglycemia				
EQ-5D: VAS	-0.13	-10.975 / -0.246	2.05	0.040
EQ-5D: index value	-0.993	-0.037 / 0.012	-0.99	NS
Rates of hypoglycemia				
EQ-5D: VAS	-0.005	-0.08 / 0.08	-0.085	NS
EQ-5D: index value	-1.572	-1.76 / 0.901	-1.57	NS
BMI				
EQ-5D: VAS	-0.042	-0.549 / 0.265	-0.68	NS
EQ-5D: index value	-1.787	-0.04 / -0.01	-1.98	0.045

***p* adjusted for age, duration of diabetes mellitus and presence of diabetic late complications. For other abbreviations see under previous tables.**

tics, duration of DM, the presence of late diabetes complication, obesity and hypoglycemic episodes and investigated their impact on HRQL.

A total of 269 diabetics aged 65.1 ± 9.3 years were analyzed. Hypoglycemia was registered in 71.0%, obesity in 43.9% and chronic complications of DM in 88.8% of the patients (microvascular in 85.1% and macrovascular in 46.5%). The gender distribution and age of examined patients reported in large SHIELD study [23] are similar to those reported in our study. The values of EQ-5D index 0.77 were lower while VAS score of 66.8 was larger in SHIELD study compared to our cohort of patients with T2DM. Almost half of the patients did not reach target HbA1c under 7.0%.

This study shows that QoL measured by ED-5D index and VAS scale was lower among T2DM that had experienced hypoglycemia. Significantly more patients among those reporting hypoglycemia indicated problems in the EQ-5D dimensions ‘‘pain/discomfort’’ which is in line with results observed by other authors. The Exhype study [24] also found problems in the EQ-5D dimension ‘‘anxiety/depression’’ which is not registered in our cohort of patients.

A significant proportion of diabetics experience hypoglycemic episodes regardless of HbA1c value and reaching HbA1c less then 7.0%. It must be mentioned that almost half of the examined diabetics did not reach target HbA1c under 7.0% which indicates poor management of

diabetics at the primary and secondary level of health care. The proportion of the patients in this study who reported hypoglycemia was somewhat larger than in other studies that examined diabetics on different types of hypoglycemic therapy. The prevalence of all hypoglycemia (mild and severe) in the group with insulin-treated type 2 diabetes was 45%[25] and 31% in patients treated with glibenclamide in UK prospective study of therapies for maturity onset diabetes (UKPDS)[26]. Patients who experienced hypoglycemia were significantly younger at diagnosis, and less likely to be with higher education which is often seen result in other similar studies[24, 27]. This is not in concordance with usual belief that low blood sugar was more prevalent among older diabetics and patients with long duration of DM, though older patients are generally considered to be at greater risk for hypoglycemia[28]. This could be explained in part that the older patients often may not recognize these symptoms or may attribute them to other chronic conditions. Duration of diabetes is proved as an important factor for hypoglycemia occurrence in this paper and previous studies. Having in mind these results, the prepared regression analysis was adjusted for age, duration of diabetes and presence of comorbidities.

The current study compared outcomes between BMI subgroups (normal, overweight and obese). Obesity was registered in 43.9% of the patients and obese patients were more likely to be female with a higher systolic and diastolic BP, a higher level of triglycerides and waist circumference. Similar data were published by other authors who analyzed obese patients with T2DM. Compared with the normal and overweight group, patients in the obese group were younger and significantly more were female. They were more often presented with dyslipidemia, hypertension, or both conditions compared to patients with normal BMI range[29]. The prevalence of micro and macrovascular complications was similar between BMI categories and no significant differences were noted for these conditions.

Patients in the obese group reported worse EQ-5D subscale score "anxiety/depression" compared with patients in the normal and overweight BMI groups. There was no significant difference in VAS score and EQ-5D index. The study by Ji et al.[29] showed obese patients significantly more reported having difficulty with mobility, difficulty completing usual activities, experienced moderate or extreme pain/discomfort or experienced moderate or extreme anxiety or depression. Obese patients with T2DM had a significantly greater disability and worse HRQL compared with non-obese patients with T2DM. Similarly, results from the Study to Help Improve Early Evaluation and Management of Risk Factors Leading to Diabetes, showed that patients with comorbid T2DM, obesity, and hypertension had a lower quality of physical and mental health, as well as moderate-to-severe depression compared to patients with diabetes only[30].

The proportion of patients' experienced hypoglycemic episodes was similar between BMI groups, but the rates of hypoglycemia *per* year were significantly higher in obese patients.

The prevalence of macrovascular and microvascular complications was very high with no significant differences between BMI categories which are results also observed by other authors[29]. The overall proportion of late diabetes complications in multinational A1chieve study[31] was 26%, but it was much higher in Russia (72.4%), which is similar to data obtained in our cohort of patients. This indicates great comorbidity load of examined patients with a high rate of hypoglycemia and prevalence of obesity which had a huge impact on HRQL.

In multivariate regression, the hypoglycemia and increased BMI, but not rates of hypoglycemia, have a significant association with HRQL, even after adjusting for age, duration of DM and presence of late diabetic complications. Those who experienced hypoglycemia were about 2.03 times more likely to experience extreme or moderate problems related to pain and discomfort compared with those who do not experience hypoglycemia. Hypoglycemia was associated with significantly lower levels of the VAS score. Similarly, those with a unit increase of BMI were 1.05 times more likely to experience extreme and moderate problems related to mobility and anxiety or depression. Also, increasing of BMI was associated with the significantly lower EQ-5D index value.

The similar study evaluating relationship between BMI and HRQL suggests that the functional relationship between BMI and utilities was nonlinear, with optimal health near 26 kg/m^2 and significantly decreasing health utilities with increasing levels of overweight and obesity[32] which could be explanation for lacking relationship between EQ-5D utilities – VAS scale with BMI in our study.

Estimation of the association between BMI and hypoglycemia with health utilities is important in economic evaluations of diabetes treatment options and obesity prevention programmes. BMI and hypoglycemia were significantly associated with EQ-5D health utilities even after adjustment for macro- and microvascular complications, duration of diabetes and age. This suggests that increased BMI and hypoglycemia symptoms in patients with T2DM are predictors of impaired health-related QL *per se*, and not only through its association with higher rates of comorbidities.

Conclusion

The results demonstrated a significant relationship between hypoglycemia and obesity with impaired HRQL determined by the EQ-5D utilities (subscale, index and VAS score), even after adjusting for an age, duration of diabetes and diabetic late complications. This indicates that lifestyle measures to reduce obesity and hypoglycemia together with optimal diabetic therapy regimen can markedly improve patients' health-related quality of life.

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