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Research Article

Predictive Value of Development of Macroalbuminuria for Hypoglycemia in Patients with Type 2 Diabetes Mellitus

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Abstract

Objectives: The predictive role of macroalbuminuria in the development of hypoglycemia in patients with type 2 diabetes mellitus was investigated.

Methods: Ninety-two patients diagnosed with type 2 diabetes mellitus who presented to Çukurova University Faculty of Medicine between January 2014 and January 2015 were included in the study. At the beginning of the study, the glomerular filtration rate values of 92 patients with type 2 diabetes mellitus were calculated using creatinine levels. The study was designed as a single-blind study. There were 14 patients with proteinuria at the level of macroalbuminuria (stage IV diabetic nephropathy) in the study group (group 1) and 78 patients without proteinuria at the level of macroalbuminuria (stage I–III diabetic nephropathy) in the control group (group 2). Thyroid-stimulating hormone, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, sodium, potassium, C-peptide, and HbA1c levels were measured in all patients at baseline and at 6 months. If adrenergic symptoms of hypoglycemia developed together with a capillary glucose level below 70 mg/dL, or if a measurement below 55 mg/dL was obtained regardless of the presence of hypoglycemic symptoms, the episode was recorded as a hypoglycemic event.

Results: The study was completed with 70 patients, 12 of whom were in the first group and 58 of whom were in the second (control) group. Statistical analysis was performed using SPSS version 24 after the 6-month follow-up. Twenty-six hypoglycemic attacks occurred in the macroalbuminuria group (group 1), and 37 hypoglycemic attacks occurred in the control group (group 2). The Mann–Whitney U test was applied.

Conclusion: The presence of macroalbuminuria was found to be significant for the development of hypoglycemia at the $p<0.01$ level (Sig. [2-tailed]=0).

Keywords: Hypoglycemia, proteinuria, type 2 diabetes mellitus

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Diabetes mellitus is a metabolic disorder characterized by relative or absolute insulin deficiency and/or peripheral insulin resistance and affects multiple organ systems. The World Health Organization (WHO) and the American Diabetes Association (ADA) have established diagnostic criteria for diabetes and classified its subtypes to ensure standardization.[1,2] Although several subtypes have been described, most patients with diabetes are classified as having either type 1 or type 2 diabetes mellitus. Type 1 diabetes mellitus is characterized primarily by absolute insulin deficiency, whereas the pathophysiology of type 2 diabetes mellitus (T2DM) is dominated by peripheral insu-

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lin resistance. With the rapid worldwide rise in obesity as a major public health challenge, the prevalence of diabetes has also increased steadily. According to 2021 estimates, diabetes affects approximately 530 million people globally, corresponding to a prevalence of 10.5% among individuals aged 20–79 years.[3,4] Of these patients, the overwhelming majority have T2DM.[5]

Hypoglycemia is one of the acute complications of T2DM and may be life-threatening. In particular, hypoglycemia occurring during intensive glycemic control has been shown not only to cause neuroglycopenic symptoms but also to increase cardiovascular risk.[6] In a meta-analysis of 46 studies involving patients with T2DM, the prevalence of hypoglycemia was 45%, whereas the prevalence of hypoglycemia requiring medical assistance was 6%.[7] In patients with a reduced glomerular filtration rate (GFR), oral antidiabetic agents are routinely discontinued, and insulin doses are reduced in accordance with guideline recommendations because drug elimination is impaired. However, robust evidence regarding dose reduction is lacking in patients with diabetic nephropathy who retain a preserved GFR despite established renal injury. Recent studies have shown that renal gluconeogenesis accounts for approximately 20% of total endogenous gluconeogenesis and is impaired in chronic kidney disease.[8,9] Neuropathy is another common complication of diabetes. Proposed mechanisms include activation of the polyol pathway, increased nonenzymatic glycosylation, and microvascular injury involving the vasa nervorum, leading to neuronal damage. In addition to sensory neuropathy, patients with diabetes may also develop autonomic neuropathy, which may increase the risk of hypoglycemia by reducing hypoglycemia awareness, impairing glucagon release during hypoglycemia, and delaying gastric emptying.[10,11] In the present study, we investigated whether hypoglycemia occurs more frequently in patients with established diabetic nephropathy despite a preserved GFR.

Methods

Study Design and Patient Selection

This study examined whether macroalbuminuria is a risk factor for hypoglycemia in patients with T2DM who had macroalbuminuric-range proteinuria but preserved GFR.

Patients older than 65 years were excluded, as were those with baseline serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels >35 IU/mL, uncontrolled hypertension, chronic inflammatory disease, chronic liver disease, chronic heart failure, rheumatic disease, inflammatory bowel disease, chronic infection, adrenal insufficiency, or risk factors for pituitary insufficiency. Risk factors for pituitary insufficiency included radiotherapy, cranial surgery, a relevant family history, and compatible biochemical findings. Patients with thyroid-stimulating hormone (TSH) levels outside the normal range were also excluded.

At baseline, patients with 24-hour urinary albumin excretion >300 mg/day were assigned to group 1 (macroalbuminuria; study group), whereas those with microalbuminuria or normoalbuminuria were assigned to group 2 (control group). Patients were followed according to the nutritional recommendations of the 2013 guideline of the Turkish Society of Endocrinology and Metabolism, together with self-monitoring of blood glucose tailored to the treatment regimen, ranging from three measurements per week to six measurements per day, depending on therapy.[12]

Capillary glucose values <70 mg/dL accompanied by adrenergic symptoms and values <55 mg/dL, irrespective of symptoms, were recorded as hypoglycemic events. Device standardization was performed monthly, telephone follow-up was conducted every 2 months, and in-person visits were scheduled at months 3 and 6. During clinic visits, HbA1c, blood urea nitrogen (BUN), creatinine, AST, ALT, sodium, and potassium levels were remeasured. In patients with dyslipidemia at baseline, lipid profiles were reassessed at month 6. Four patients whose medical treatment was changed because of adverse drug effects and two patients who underwent angiography followed by coronary intensive care monitoring because of coronary artery disease were excluded during follow-up. In addition, seven patients with elevated AST, ALT, or creatinine levels and nine patients who did not maintain regular follow-up were excluded. The final analysis included 12 patients in the macroalbuminuria group and 58 in the control group.

Collection of Blood and Urine Samples and Measurement Methods

Patients presented to the clinic after completing a 24-hour urine collection. Urinary albumin levels were measured using the Jaffe method and classified according to the Mogensen classification (Table 1).

Plasma glucose was measured in venous blood obtained after 12 hours of fasting using the glucose oxidase method. Follow-up HbA1c levels were measured by high-performance liquid chromatography, and the treatment target was an HbA1c level below 7%. The reference range for C-peptide was 1.1–3 ng/mL. The normal range for ALT and AST was 0–35 IU. Total cholesterol was measured using the Lieberman–Burchard method.

Table 1. Stages of diabetic nephropathy

Diabetic nephropathy	Characteristic	GFR	Albuminuria	Blood pressure	Time since diagnosis
Stage 1	Glomerular hyperfiltration	Increased	Absent	Normal-Increased	At diagnosis
Stage 2	Thickened basement membrane (silent stage)	Normal	Normal or <30 mg/day	Normal-Increased	5 years
Stage 3	Microalbuminuria	Normal	30-300 mg/day	Normal-Increased	5-15 years
Stage 4	Macroalbuminuria	Normal-Decreased	>300 mg/day	Hypertension	15-25 years
Stage 5	Uremia	Progressive decrease	Variable	Hypertension	25-30 years

GFR: Glomerular filtration rate.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA).[13] Regression analysis and the Mann–Whitney U test were used for statistical evaluation.

Written informed consent was obtained from all participants. Patients were enrolled in a blinded manner. Ethical approval was granted by Çukurova University on December 2, 2016 (meeting no. 59).

Results

Demographic Characteristics, Biochemical Parameters, and Complications of the Study Population

Patients were divided into two groups: a control group (microalbuminuria–normoalbuminuria) and a macroalbuminuria group. Table 2 summarizes the demographic characteristics, biochemical parameters, and complications of the study population. The cohort comprised 43 women and 27 men, including 12 patients in the study group and 58 in the control group. The mean age of all participants was 54.7±7.7 years. The mean HbA1c and C-peptide levels were 7.4±1.6% and 2.5±1.1, respectively. The mean duration of diabetes was 8.8±6.8 years. A significant between-group difference was observed in diabetes duration (MVU=182.5, p=0.010), whereas no statistically significant difference was found in HbA1c or C-peptide levels (MVU=28.1, p=0.3).

We also evaluated neuropathy as an important clinical variable. Patients with electrophysiologically confirmed peripheral neuropathy accompanied by autonomic symptoms were considered positive. As expected, body mass index analysis showed that most patients were in the overweight or obese categories (Fig. 1). Ten patients had a normal body mass index, eight of whom had a first-degree family history of T2DM. Of the 28 patients classified as obese (BMI≥30), 20 were receiving insulin therapy.

Evaluation of Hypoglycemia and Related Conditions in the Study Groups

At least one hypoglycemic episode occurred in 10 of 12 patients in the macroalbuminuria group (Fig. 2), compared with 12 of 58 patients in the microalbuminuria–normoalbuminuria control group. Patients in the macroalbuminuria group experienced 26 hypoglycemic episodes, whereas 37 episodes occurred in the control group. Two episodes led to hospital presentation with neuroglycopenic symptoms, whereas all other episodes resolved after oral carbohydrate intake. No glucagon injection was

Table 2. Demographic characteristics, biochemical parameters, and complications of the study population (mean±SD)

	Group 1 (Macroalbuminuria)	Group 2 (microalbuminuria-normoalbuminuria)
Age (years)	56.1±6.0	54.4±8.1
Sex (F/M) (%)	7/5 (%58)	36/22 (%62)
BMI	3/12 (%25)	25/58 (%43.1)
Duration of diabetes (years)	13.8±7.8	7.7±6.1
Glucose (mg/dL)	146±11.5	135±8.4
HbA1c (%)	7.5±1.1	7.4±1.7
C-peptide	2.0±0.8	2.6±1.2
Diabetic neuropathy n (%)	6 (%50)	15 (%25.8)
Oral antidiabetic therapy		
Pioglitazone	2/12 (%16.6)	8/58 (%13.7)
Metformin	11/12 (%91.6)	56/58 (%96.5)
Secretagogue	2/12 (%16.6)	28/58 (%48.2)
Insulin therapy		
Intensive	2/12 (%16.6)	4/58 (%6.8)
Basal	1/12 (%8.3)	10/58 (%17.2)
Mixed	3/12 (%25)	2/58 (%3.4)

SD: Standard deviation.

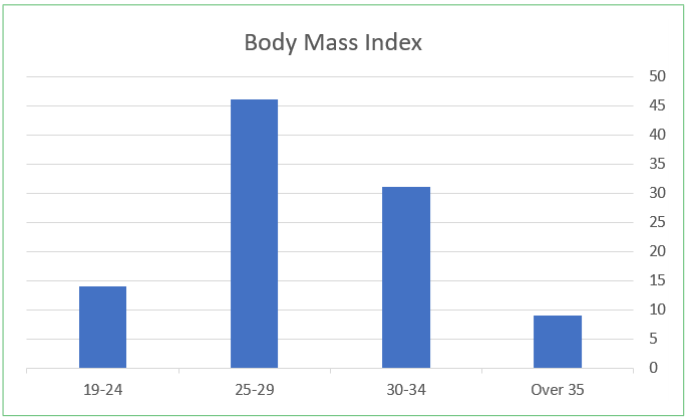

Figure 1. Distribution of body mass index among participants.

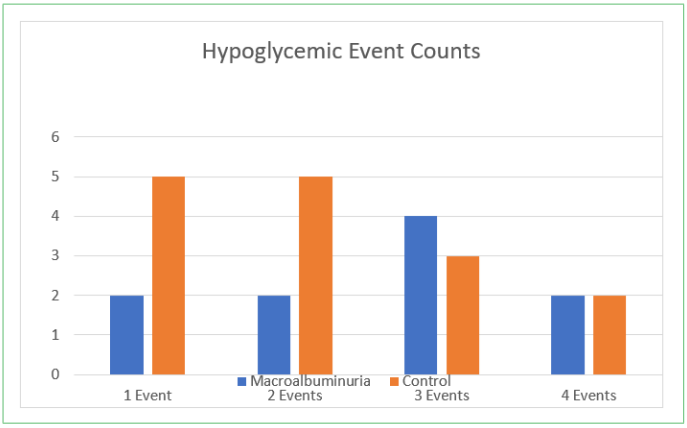

Figure 2. Frequency of hypoglycemia in the case and control groups.

administered during any episode, and only one of the 70 patients carried glucagon. No hospitalization occurred because of hypoglycemia. None of the episodes was associated with alcohol use. According to patient histories, all events were related to dietary nonadherence or exercise. Because of the limited sample size and nonhomogeneous distribution, parametric tests were not applied; instead, the Mann–Whitney U test was used. The presence of macroalbuminuria was significantly associated with the development of hypoglycemia at the $p<0.01$ level (Sig. [2-tailed]=0). Overall, hypoglycemic episodes occurred significantly more frequently in the macroalbuminuria group than in the control group.

Correlation analysis was performed to examine the relationship between hypoglycemic episodes and HbA1c levels. A strong positive association was observed ($r=0.482$, $p<0.001$), indicating that hypoglycemic episodes occurred more frequently in patients with higher HbA1c levels.

In logistic regression analysis, bolus insulin use was associated with hypoglycemia (OR, 3.7; $R^2=0.54$; $p<0.01$), and basal insulin use was likewise associated with hypoglycemia (OR, 2.9; $R^2=0.40$; $p<0.01$).

Discussion

Previous studies have partly clarified the etiology and pathophysiological mechanisms of hypoglycemia in patients with T2DM. Vigorous exercise, escalation of antidiabetic therapy, inadequate food intake, progressive decline in GFR, and delayed renal insulin clearance have all been identified as common causes.[14] Hypoglycemia is associated with both adrenergic and neuroglycopenic manifestations. Adrenergic symptoms include tremor, cold sweating, palpitations, hunger, and paresthesia, whereas neuroglycopenic symptoms include headache, dizziness, speech difficulty, weakness, and confusion. Our study was based on the hypothesis that the progression of diabetic nephropathy may impair renal gluconeogenesis and reduce the availability of substrates for both hepatic and renal gluconeogenesis during the proteinuric stage.

Our findings indicate that macroalbuminuria is associated with a higher frequency of hypoglycemia. No significant association was observed between hypoglycemia and neuropathy or the use of secretagogue agents. Only a limited number of studies have evaluated the relationship between macroalbuminuria and hypoglycemia. This paucity may reflect the multifactorial nature of hypoglycemia in diabetes, substantial interindividual variability in response to insulin secretagogues, frequent polypharmacy due to comorbid conditions, and marked variation in treatment adherence. In addition, adherence to medical nutrition therapy and exercise is inherently difficult to monitor, which complicates the design and conduct of such studies. Furthermore, the number of patients with preserved GFR despite macroalbuminuria is relatively small. The most comparable study is the 2013 prospective study by Yun et al.[15], which evaluated the relationship between macroalbuminuria and hypoglycemia. In that study, the mean follow-up duration was 10.2 years, and severe hypoglycemia developed in 111 of 878 patients. Severe hypoglycemia was defined as an event requiring glucose administration by another person or hospital presentation. By contrast, because our study had a shorter follow-up period, we used closer glucose monitoring and a more sensitive definition of hypoglycemia, recording glucose values <55 mg/dL and values <70 mg/dL when accompanied by adrenergic or neuroglycopenic symptoms. Unlike Yun et al.[15], we limited the upper age to 65 years because of concerns regarding creatinine-based GFR estimation in older adults. We also excluded patients using mixed insulin and analyzed basal and bolus insulin as separate variables. In our clinic, hypoglycemia is particu-

larly common among patients receiving mixed insulin, and many such episodes are related to dietary nonadherence in individuals using two or three daily doses. In the study by Yun et al.[15], diabetic neuropathy was not considered, and insulin therapy was assessed as a single variable without distinction by duration of action. However, lipid profiles and fasting C-peptide levels were monitored more regularly in that study at 3- to 6-month intervals. Cox proportional hazards regression analysis identified advanced age ($p<0.001$), insulin use ($p<0.001$), macroalbuminuria ($p<0.001$), and sulfonylurea use ($p<0.003$) as significant predictors.

The frequency of hypoglycemia increased with increasing HbA1c levels. Adherence to exercise recommendations appeared partial, whereas adherence to medical nutrition therapy appeared poorer. It is therefore plausible that both hypoglycemic episodes and elevated HbA1c levels arose from the same underlying factor, namely dietary nonadherence. Patient reports supported this interpretation, as many described clinical histories linking hypoglycemia to failure to follow dietary recommendations. Similarly, in an observational study of T2DM, Zhao et al. reported an increase in hypoglycemia-related hospitalizations with higher HbA1c levels.[16]

In the systematic review by Pratiwi et al.[17], autonomic neuropathy was identified as an important risk factor for hypoglycemia. In our study, however, no significant relationship was found between neuropathy and hypoglycemia. This discrepancy may be attributable to the limited sample size and short follow-up duration.

The main limitations of this study include the small sample size, the inability to fully meet guideline-recommended standards for blood glucose monitoring, only partial adherence to diet and exercise recommendations, and reliance on patient self-reports for the accuracy of these data.

Conclusion

In conclusion, in patients with type 2 diabetes mellitus, the presence of macroalbuminuria was associated with a higher frequency of hypoglycemic episodes. By contrast, no increased risk of hypoglycemia was observed in association with diabetic neuropathy, pioglitazone use, or secretagogue use (glinides and sulfonylureas). Insulin use was significantly associated with hypoglycemic episodes, and all recorded events were linked to dietary nonadherence.

Taken together with current molecular evidence, our findings suggest that patients who develop macroalbuminuria may remain at increased risk of hypoglycemia even when GFR is preserved.

Disclosures

Ethics Committee Approval: Ethics committee approval was obtained from Çukurova University Faculty of Medicine Ethics Committee on December 2, 2016, with meeting number 59.

Informed Consent: Informed consent forms were obtained from all patients participating in the study.

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