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The effect of isosorbide-mononitrate on proteinuria in patients with diabetic nephropathy

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Ethics Committee Approval
The study protocol was approved by the Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee (2013-KAEK-64).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
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Abstract

Background/Aim: Diabetic nephropathy (DN) occurs in approximately 40% of patients with Type 1 and Type 2 diabetes mellitus (DM) and is one of the most common causes of end-stage renal disease (ESRD). New treatment strategies are needed to prevent DN. This study aims to investigate the effect of the use of isosorbide-mononitrate (IMN) on diabetic nephropathy.
Methods: In this study, patients with type 2 diabetes mellitus were divided into two groups, as those using and not using IMN to evaluate whether IMN reduces proteinuria. Biochemical parameters and proteinuria values were recorded and comparatively analyzed.
Results: The urea and creatinine values of patients with type 2 DM who were using IMN were significantly higher and e-GFR values were significantly lower than those of the control group (P=0.049, P=0.001, P=0.013, respectively). However, the proteinuria amounts of Type 2 DM patients using IMN (0.98 g/day [0.52-1.43]) were significantly lower than those who were not (1.61 g/day [1.02-2.69] (P=0.001)).
Conclusion: The addition of nitrate to angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) in the treatment of patients with DN may be a new alternative for reducing proteinuria.

Keywords: Diabetic nephropathy, Isosorbide-mononitrate, Proteinuria

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Introduction

Diabetes Mellitus (DM) is a metabolic disease associated with micro-and macrovascular complications. One of the most important microvascular complications is diabetic nephropathy (DN) [1]. DN is among the most common causes of end-stage renal disease (ESRD), which occurs in approximately 40% of patients with DM [2]. Accompanying diabetes proteinuria has been associated with kidney failure, cardiovascular events, and the risk of premature death, and it has been reported that these risks increase with the amount of proteinuria [3-5]. Today's proteinuria treatment strategy is based on the inhibition of the renin-angiotensin-aldosterone system (RAAS) using angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), which provide hypertension control [6, 7]. In some cases, ACEIs and ARBs fail to reduce proteinuria/albuminuria, and unfortunately, there is no other class of drugs recommended by guidelines to correct it. In this context, studies are underway to develop some new treatment agents, but most of these studies are at an early stage [8, 9]. Studies evaluating the effect of isosorbide-mononitrate (IMN) on proteinuria are quite limited. In a study in rats, IMN was used as a nitrite oxide donor in rats with exercise-induced proteinuria and a decrease in proteinuria was observed [10]. Roccatello et al. reported a decrease in proteinuria when IMN was administered to patients with Ig A nephropathy and proteinuria [11]. There is still a need for novel studies on this subject. In this study, the effect of IMN on proteinuria was investigated in patients with type 2 DM-related nephropathy.

Materials and methods

The files and records of type 2 DM patients with proteinuria despite using ACEI and/or ARB for more than 6 months who visited the nephrology outpatient clinic of Istanbul Health Sciences Kanuni Sultan Suleyman Training and Research Hospital were retrospectively analyzed and those who met the inclusion criteria were included in this study. Demographic features, drugs used, body mass indexes (BMI), some biochemical parameters (Creatinine, Urea, Na, K, Ca, P, total protein, albumin), glomerular filtration rate (e-GFR), and proteinuria values were analyzed. Creatinine clearance was calculated with the Cockcroft-Gault formula.

Ethical approval

This case-control study protocol was approved by Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee (2013-KAEK-64). The study was conducted by the principles of the Helsinki Declaration.

Study population

In the power analysis performed with the G*power 3.1 program, the effect size was 0.65 to evaluate the antiproteinuric activity of isosorbide-mononitrate (alpha error probability=0.05), and the sample size was calculated with a power of 0.80 [12].

A total of 29 patients with symptomatic ischemic heart and peripheral vascular diseases and Type 2 DM using oral IMN were included in the study. Forty-six patients with diabetic nephropathy (DN) using ACEI and/or ARB with similar demographic characteristics but who did not receive IMN treatment were included in the control group. Patients who actively used other proteinuria reducing agents such as cyclophosphamide, azathioprine, mycophenolate mofetil, prednisolone, and rituximab were not included in the study.

Statistical analysis

All statistical analyses were performed using SPSS software version 21.0 (SPSS Inc, Chicago, IL, USA). Data that did not conform to the normal distribution were shown as median (interquartile range [IQR]), while normally distributed data were given as mean±standard deviation. Mann-Whitney U test was used to compare non-normally distributed numerical data. The categorical variables in the study were compared using the chi-square or Fisher's exact tests. Values with $P<0.05$ were considered statistically significant.

Results

There were 29 patients (39%) in the IMN group and 46 patients (61%) in the control group. The female/male distribution of those in the IMN and control groups were 13(72%)/16 (28%) and 33(45%)/13(55%), respectively. The rate of females was significantly higher in the IMN group (p=0.02). Also, the mean age of patients in the IMN group (62(12) years) was significantly higher than that of the control group (55(10) years) (P=0.009). The BMIs of both groups were similar (P=0.242) (Table 1). Eighty-six percent (n=25) of the patients in the IMN group and 74% (n=34) of those in the control group were hypertensive. The smoker rates in the IMN and control groups were 35% (n=10), and 33% (n=15), respectively.

Table 1: Demographic data of the cases

Parameters		Control group	IMN group	*P*-value
Gender	Female (n)	33	13	0.020
	Male (n)	13	16	
Age (years)		55 (10)	62 (12)	0.009
Height (cm)		162 (1.58-1.65)	168 (1.61-1.72)	0.131
Weight (kg)		74 (68-83)	78 (75-83)	0.040
BMI (kg/m^2)		27.48 (26.50-28.41)	28.58 (26.37-30.80)	0.242
Creatinine (mg/dL)		0.85 (0.70-1.38)	1.20 (1.08-1.50)	0.001
Urea (mg/dL)		41 (29-60)	52 (41-65)	0.049
Na (mmol/L)		141 (139-142)	140 (139-142)	0.974
K (mmol/L)		4.9 (0.5)	4.8 (0.5)	0.216
Ca (mg/dL)		9.5 (9.1-9.8)	9.5(8.9-10.0)	0.870
P (mg/dL)		3.8 (0.4)	3.5 (0.7)	0.039
Protein (g/dL)		7.30 (6.80-7.50)	7.10 (6.80-7.50)	0.506
Albumin (g/dL)		4.1 (3.9-4.4)	4.3 (3.6-4.4)	0.948
e-GFR (mL/min/1.73m^2)		73 (46-96)	50 (41-72)	0.013
Proteinuria (g/day)		1.61 (1.02-2.69)	0.98 (0.52-1.43)	0.001

BMI: Body mass index, Na: Sodium, K: Potassium, Ca: Calcium, P: Phosphorus, GFR: glomerular filtration rate

The number of patients using ACEIs, ARBs and combined ACEI/ARBs in the IMN and control groups were 11, 16, 1 and 22, 22, and 2, respectively. The creatinine and urea values of patients with Type 2 DM using IMN in our study were significantly higher compared to the control group (P=0.001, P=0.049, respectively).

The Na, K, and Ca values were similar between the groups ($P>0.05$), while mean the serum phosphorus level of patients in the IMN group was significantly lower compared to the control group (P=0.039).

In terms of total protein and albumin values, there was no significant difference between Type 2 DM patients using and not using IMN ($P>0.05$).

The e-GFR values of the patients in the IMN group were significantly lower than those of patients in the control group (P=0.013). Despite this, proteinuria amounts of Type 2

DM patients using IMN were significantly lower compared to non-users (*P*=0.001) (Table 2).

Table 2: Comparison of biochemical data of patients in IMN and control group

	IMN group (n=29)	Control group (n=46)	*P*-value
Proteinuria (g/day)	0.98 (0.48-1.46)	1.61 (1.02-2.69)	0.001
e-GFR (mL/min/1.73 m^2)	50 (41-72)	73 (46-96)	0.013
Albumin (g/dL)	4.05 (0.61)	4.09 (0.48)	0.745
Total protein (g/dL)	7.03 (0.75)	7.09 (0.66)	0.721
Calcium (mg/dL)	9.4 (0.65)	9.3 (0.80)	0.591
Sodium (mmol/L)	140 (3.1)	140 (2.2)	0.103
Potassium (mmol/L)	4.75 (0.46)	4.89 (0.47)	0.216
Phosphorus (mg/dL)	3.48 (0.67)	3.75 (0.44)	0.039

Discussion

In this study, the proteinuria amounts of type 2 DM patients with DN who did and did not use IMN were compared. There are a limited number of studies on the effect of IMN in reducing proteinuria in DN. However, some studies evaluated the effect of IMN on proteinuria in various diseases. In a study conducted by Gündüz et al. [10], rats with exercise-induced proteinuria used IMN as a nitrite oxide donor and had decreased proteinuria.

In another study, when patients with IgA nephropathy and proteinuria were given IMN, a decrease in proteinuria was reported [11]. In our study, creatinine clearance was calculated with the Cockcroft-Gault formula [13]. The creatinine and urea values were higher and e-GFR was lower among IMN users compared to non-users. Despite this, patients in the IMN group had significantly lower proteinuria values, which shows that IMN use may have a proteinuria-reducing effect among DN patients.

Approximately 40% of diabetic patients have diabetic nephropathy. The treatment aims to prevent the progression of micro and macroalbuminuria, protect kidney function in patients with macroalbuminuria, and prevent cardiovascular events [14]. Besides, changes in serum glucose levels, especially hypoglycemia, in diabetic patients cause endothelial dysfunction by affecting cardiac functions [15]. DN is an independent risk factor for cardiovascular disease and one of the leading causes of end-stage renal failure (ESRD) worldwide [16].

Limitations

There are some limitations to the study. First, this study is a retrospective, single-center study with small sample size. Second, when comparing DN patients who did and did not use IMN, linear regression analysis, in which many factors such as hypertension, smoking, gender, age, and duration of diabetes disease were evaluated together, could not be performed due to the limited data.

Conclusion

The addition of IMN therapy to ACEI or ARB may be a novel alternative in the treatment of proteinuria in DN patients. It would be beneficial to conduct prospective, randomized, controlled, and multicenter studies to examine the effect of IMN treatment on proteinuria in patients with DN.

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