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Корреспондент автор. *Айтпан Әсем Мұхамбетқызы, «Қазақстан-Ресей медициналық университеті» МЕББМ, магистр, Қазақстан, Алматы қ. E-mail: Asem.aitpan@bk.ru; https://orcid.org/0000-0001-7512-601X.*

Авторлардың қосқан үлесі. *Барлық авторлар тұжырымдаманы әзірлеуге, нәтижелерді орындауға, өңдеуге және мақала жазуға тең үлес қосты. Бұл материал бұрын жарияланбаған және басқа баспаларда қаралмағанын мәлімдейміз.*

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Corresponding author. *Aitpan Asem M., NEI «Kazakh-Russian Medical University», Master of Medicine, Kazakhstan, Almaty. E-mail: Asem.aitpan@bk.ru; https://orcid.org/0000-0001-7512-601X.*

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IMPACT OF ESTIMATED GLOMERULAR FILTRATION RATE ON THE 24 – MONTHS OUTCOMES AFTER DRUG-ELUTING STENTS IMPLANTATION IN PATIENTS WITH CORONARY ARTERY DISEASE AND INSULIN-TREATED DIABETES MELLITUS

***[1] Lütfi Baran, [2] Talantbek Batyraliev, [3] Mehmet Başternir, [2] Serdar Türkmen**

[1] Department of Internal Medicine, Sanko University Faculty of Medicine, Gaziantep, Turkey
[2] Department of Cardiology, Sanko University Faculty of Medicine, Gaziantep, Turkey
[3] Department of Endocrinology, Sanko University Faculty of Medicine, Gaziantep, Turkey

Summary

In patients with coronary artery disease (CAD), renal failure which can result in hemodialysis use is seen during the percutaneous coronary intervention (PCI) performed with contrast agents with iodide. This injury is more particularly in patients with diabetes with lower estimated glomerular filtration rate (eGFR) compared to the patients who have not diabetes.

Aims: The aim of this study is to investigate the alterations in the renal glomerular filtration rate after the implantation of the drug-eluting stents (DESs) in the patients with Type-2 insülin-treated diabetes mellitus (ITDM) and CAD.

Study Design: Prospective study.

Methods: In total, 463 patients with ITDM in which one or more drug-elution stents under PCI were inserted successively for last 5 years (last uptated to December 2015) were included into the study. Patients in both groups were followed with eGFR with laboratory tests and with other cardiologic parameters by the Departments of Cardiology and by the Department of Internal Medicine for 24 months with 3-month periods.

Results: The patients being included into the study were separated into two groups according to the eGFR as Group 1 including 351 patients (75,8%) with eGFR > 90 ml/min/1,73m^2 and Group 2 including 112 patients (24,2%) with eGFR between 60 and 89 ml/min/1,73m^2. Patients in both groups were followed for 24 months with 3-month periods. At the end of the study, no statistically significant change was found in both groups in eGFRs. But, a tendency to decrease in the eGFR(s) in Group 2 was found. Furthermore, when three-month eGFR measurements were compared with the first eGFR before PCI, no significant difference was found. Besides, the frequency of contrast agent-induced nephropathy (CIN) was seen more common in significant level in Group 2 when compared to Group 1 ($p<0.01$). In the 24-month cardiologic follow-up, the incidence of restenosis and revascularization, the incidence of major cardiac complications and the relative risk of death were seen more commonly significantly in Group 2 compared to Group 1 ($p<0.01$).

Conclusion: This study suggested that the reduction in the eGFR which was not statistically significant after DES but which tended to decrease in Group 2 patients could be yielded from the chronic negative effect of the diabetes mellitus (DM) on the renal functions. Furthermore, this effect has demonstrated that the risk of contrast agent-induced nephropathy after the stent application in diabetes patients with reduced eGFR led to increase in the incidence of restenosis and repeating revascularization in the twenty-four-month follow-up and that it is the determinant of the mortality risk.

Key words: *Insulin-treated diabetes mellitus, coronary artery disease, drug-eluting stent, estimated glomerular filtration* rate.

Diabetes mellitus is a chronic metabolism disease originating from the disorder in the carbohydrate, lipid and protein metabolisms due to the insufficiency of insulin production or due to the impairment of the effect of insulin and progressing with elevation in the blood sugar [1; 2]. While the diabetes prevalence of diabetes was 6,4% in adults between 20-79 years old on 2010 worldwide, it is estimated that this ratio will be 7,7% on 2030. While a 20%-increase in the number of diabetic adults between these years is estimated in developed countries, this is estimated to be 69% in the developing countries [3].

In the conducted studies, it has been observed that obesity; insufficient physical activity, smoking, and the presence of dyslipidaemia and hypertension increase the risk of ischemic heart disease with diabetes [4; 5; 6; 7]. Furthermore, epidemiologic and pathologic studies have shown that DM constitutes an independent risk factor for cardiovascular diseases [8]. On the other hand, 75% of hospitalizations and 80% of deaths are related with cardiovascular diseases in diabetic patients. DM has been detected in the 25% to 30% of the patients being hospitalized due to the heart attack, or receiving stent or bypass treatment [9].

Insulin receptors are located on the endothelium cells of both large and small vessels. It has been shown that insulin affects the secretion of endothelin-1 with endothelial growth factor and that hyperinsulinemia which is the indicator of insulin resistance is directly related with the higher coronary artery disease incidence [10]. Coronary artery disease (CAD) is more common in diabetic patients compared to non-diabetic patients and the lesion causing to vascular obstruction is thinner and longer. Furthermore, to perform the invasive therapeutic procedure to this affected vessel becomes more difficult. The probability of the re-emergence of the same stenosis after the insertion of the stent is higher in diabetic patients compared to those being non-diabetic [11]. In a study, ulcerated coronary plaque with thrombus has been found in 94% of the patients with diabetes in which unstable angina existed in the performed coronary angiography [12].

One of the important complications that increase the mortality risk in the patients with diabetes and CAD is masking of the ischemic symptoms associated with autonomous neuropathy [13]. On the other hand, beside the fact that diabetes is a very important determinant of the restenosis in the coronary interventions, it has been demonstrated that it is also the most important determinant (hazard ratio 2,4) of the mortality following the renal failure [14]. In the recent years, better results have been obtained in reducing the incidence of revascularization and the major cardiac events by defining better the mechanisms of restenosis and particularly with the widespread use of the drug-eluting stents [15]. In the studies conducted with the use of DES and with the use of stents that do not elute drug (bare- metal stent-BMS) in patients with DM and with CAD, it has been shown that DESs decrease significantly the revascularization of the target organ, stenosis and mortality compared to those that do not elute drug [16; 17; 18].

In patients with CAD, renal failure which can result in hemodialysis use is seen during the PCI performed with contrast agents with iodide [19; 20; 21]. This injury is more particularly in patients with diabetes with lower eGFR compared to the patients who have not diabetes [22; 23]. Therefore, even though there is evidence about that treatments such as N-Acetyl-cysteine, phenoldopa, statins, simultaneous hemofiltration are tried with success [24; 25; 26; 27]. It is suggested in other studies that the guidelines for preventing excessive contrast agent are not required, and that only prophylactic hydration treatment is sufficient [28; 29].

Materials and methods. In total, 463 patients receiving previously insulin treatment by establishing Type-2 diabetes mellitus in which one or more DES under PCI were inserted successively for last 5 years were included into this study. Only patients with acute coronary syndrome (ACS) having laboratory tests concerning myocardium injury with negative unstable angina with the patients experiencing chest pain increasing with which are 2 to 4 according to the Canadian Cardiovascular Society Angina (CCSA) classification were included into the project [35].

According to the K/DOQI criteria [36] the patients who have chronic renal failure grading as 3-4-5 or having eGFR < 60 ml/min/1,73m^2 were excluded from the study. Estimated GFR was computed by using CKD-EPI formula [36; 37; 53].

Criteria used for percutaneous coronary intervention were based on the absence of definite contraindication belonging to the stent implantation for affected vessel segments. Patients having any revascularization history were not included into the study. Furthermore, patients having lesion in the left main coronary artery in which ST elevation related with the myocardial infarction (MI) was seen in the first 7 days in addition to the patients in which no ST elevation was seen but having positive laboratory tests such as Troponin were excluded from the study. On the other hand, those having allergy to contrast agents and those having intolerance to Aspirin or Clopidogrel were excluded from the study. As angiographic criterion, the patients in whom the diameter of the obstructed vessel is less than 2,5 millimeters or greater than 4,5 millimeters and those having curvature more than 60° in the stenosis location were not included into the study.

Coronary angiography and percutaneous coronary intervention were approved by the Clinical Ethical Committee and the patients were signed informed consent form. Before PCI, sufficient hydration which was not less than 100 cc was applied to all patients for the prophylaxis of the CIN. Furthermore, nephrotoxic medications were restricted. In addition, 600-milligram-per-day N-Acetylcysteine infusion

was administrated for 48 hours. Low-osmolar non-ionic contrast agents were administrated to all patients in fashion that it would not exceed 600 milliliters per day during coronary angiography and stent insertion process. 25%-increase from the initial value of the serum creatinin within the 48-72 hours following the administration of the contrast agent or an absolute increase more than 0,5 milligrams per deciliters were accepted as criterion [36].

The patients being included into the study were separated into two groups according to the GFR as Group 1 including 351 patients (75,8%) with eGFR > 90 ml/min/1,73m^2 and Group 2 including 112 patients (24,2%) with eGFR between 60 ml/min/1,73m^2 and 89 ml/min/1,73m^2.

In all patients, only contrast agent iodixanol was used. Following the percutanous coronary intervention, patients in both groups were followed with eGFR with laboratory tests and with other cardiologic parameters by the Departments of Cardiology and by the Department of Internal Medicine for 24 months with 3-month periods. In case of repeating angina or in case of other complications, the patients were investigated by hospitalizing the patients.

Statistical methods. All data were analyzed by means of Statistical Package for Social Sciences for Windows, version 22.0 (SPSS Inc. Chicago, IL, US). One-way ANOVA test was used in the comparison of different groups having normal distribution. In repeating measurement values Repeated-Measures ANOVA test was done. In the comparison of the groups which did not have normal distribution Student's paired t-test, Mann-Whitney-U or Kruskal-Wallis tests were used. $\chi 2$ or Fisher's exact test were used in the results indicating qualitative character. Some data were compared with Yates-corrected z – test.

Correlation analyses were done for significant relative risk computation with 95%-confidence interval in the relationship between indicators. Significance value was accepted as $p<0.05$ in all analysis tests.

Results. Clinical and angiographic characteristics of patients. The demographic and the clinical parameters of the patients which were separated as Group 1 including 351 patients (75,8%) with eGFR > 90 ml / min/1,73m^2 and Group 2 including 112 patients (24,2%) with eGFR between 60-89 ml/min/1,73m^2 were summarized in Table 1. The ages of the patients belonging to both group were ranging between 38 years old and 75 years old and most of them were male (62,6%). All of the patients were Type-2 DM patients and they were receiving subcutaneous insulin treatment. The level of the glycosylated hemoglobin (HbA1c) was significantly higher in Group 2 compared to Group 1 ($p<0.01$).

Arterial hypertension was diagnosed in 59,8% of the patients. 19% of the patients in which, stent was inserted experienced previously MI. Patients with ACS who were

Table 1. *Baseline demographics and clinical parameters of patients before PCI.*

Parameter	Group 1 (n = 351)	Group 2 (n = 112)	p value
Characteristics	eGFR > 90	eGFR 60-89	-
of renal function (ml/min/1,73m^2) (ml/min/1,73m^2)		-	-
Age (years)	54 + 10,4	57 + 9,36	NS
Male sex	227 (64,6%)	75 (67%)	NS
Blood urea nitrogen 21 + 4,8		23 + 6,1	NS
(mg/dl) Creatinine (mg/d	0,93 ± 0,14	1,18 ± 0,34	NS
Estimated GFR	100,14 + 12,3	82,25 +	<0,01
(ml/min/1,73m^2) Microalbuminuri (mg/g)	40 ± 6,7	78 ± 10,7	<0,01
HbA1c (%)	7,4 ± 0,93	8,9 ± 1,1	<0.01
Duration of diabetes 9 ± 7,21 (years)		13 ± 9,7	<0,01
Current smoking	125 (35,6%)	36 (32,1%)	NS
Obesity*	77 (22%)	39 (34,8%)	<0,007
Congestif Heart Failure†	7 (2%)	2 (1,8%)	NS
Hypertension	203 (57,8%)	74 (66%)	0,03
Dyslipidemia	200 (57%)	71 (63%)	NS
Prior MI	56 (15,9%)	31 (27,6%)	<0,001
LV EF	51% (44-70%)	52% (41-	NS
median (range)	-	-	-

Data are shown as percentage and mean + standart deviation NS = non-significant

* Body mass index >30 kg/m^2

† Framingham criteria

stabilized by hospitalizing before coronary angiography constituted 12% of the total number of patients. Blood-urea nitrogen (BUN) and creatinine tests of both groups were within the normal limits. But the level of 24-hour microalbuminuria was significantly higher in Group 2 when compared with Group 1 (p<0.01).

The distribution of vascular disease after angiography belonging to the patients is shown in Table 2. The disease of single vessel was more common in Group 1, when compared to Group 2 (p<0.001). The disease of two vessels was more common in Group 2, when compared to Group 1 (p<0.001). No significant difference could be found between groups in the disease of three vessels.

The immediate results of the study. Direct results belonging to revascularization are listed in Table 3. Stents coated with drugs such as sirolimus and paclitaxel were implanted into the patents without encountering any dissection, occlusion or no-reflow phenomenon. The success rate was 99,5% in Group 1 and 97,7% in Group 2 respectively. During the percutaneous intervention, totally 554 drug-coated stents were inserted to Group 1 and totally 180 drug-coated stents were inserted to Group 2. For the stent dilatation, 15- to 20- atmosphere pressure was applied having mean value of 15 ± 2,5 atmospheres. For the optimal implantation of each stent, 2 to 4 dilatation procedures which the mean value is 3.1 ± 0.72 were done.

Table 2. *Baseline angiographic parameters.*

Parameter	Group 1 (n = 351)	Group 2 (n = 112)	p value
One vessel disease	158 (45%)	49 (33%)	<0,001
Two vessel disease	112 (32%)	52 (46%)	<0,001
Triple vessel disease	74 (21%)	31 (28%)	NS
Total stricken vessel	604	246	-

Complete revascularization index of both groups was slightly higher, but this was not statistically significant. The amount of the administrated contrast agent was significantly greater in Group 1 compared to Group 2 (p<0.01). There was no difference between the stenosis radius gains of both groups.

Table 3. *The immediate results of revascularization.*

Parameter	Group 1 (n = 351)	Group 2 (n = 112)	p value
Revascularizated stenosis	535	163	-
Completeness of revascularization index	0,91	0,87	NS
Number of implanted stents per patient	1,58	1,61	NS
Amount of the entered contrast (ml)	538 + 66	326 + 47	<0,01
Gain of diameter of stenosis (mm)	2,10 + 0,51	2,16 + 0,48	NS
Percentage of stenosis (%)	6,1 + 3,8	7,3 + 4,1	NS

Data are shown as percentage and mean + standart deviation
NS = non-significant

Hospital findings. Although preventive precautions were taken previously, CIN was developed in 5 patients (1,4%) in Group 1 and in 6 patients (5,3%) in Group 2, 2 to 4 days following the PCI (Table 4). The occurrence of CIN was significantly higher in Group 2 compared to Group 1 (p<0.001). Mannitol infusion or furocemide with low-dose dopamine treatments were administrated to the patients in which CIN was seen.

Subacute thrombosis was observed in 1 patient (0,3%) in Group 1 and in one patient (0,9%) in Group 2 within 3 days following the percutaneous coronary intervention (PCI). Acute coronary syndrome which was seen either as myocardial infarction with ST elevation or as non-ST elevation myocardial infarction/unstable angina was observed in one patient (0.3%) in Group 1 and in 2 patients (1.8%) in Group 2. In these cases, tirofiban infusions were done as treatment. Furthermore, since hemorrhages were seen in one case (0,3%) in Group 1 and in 1 case (0,9%) in Group2, blood transfusion was done. During the hospitalization, the incidence of non- fatal complications seen in 12 (10,7%) in Group 2 was significantly higher than that of non-fatal complications seen in 4 patients in Group1 (1,1%) (p < 0.001). Besides, while no mortality was seen in Group 1, it was seen in one case (0,9%) in Group 2.

Remote results of the study. While CIN was developed in 1 patient (20%) in Group1, CIN was developed in 2 patients (33,3%) in Group 2. Mortality analyses with CIN and without CIN until 24 months were summarized in Table 5. While there was no significant relative mortality risk in Group 1, a statistically significant relative mortality risk as 5,8 was found in Group 2 (95% of CI: 1.49- 23.23, p<0.001).

The follow-up results of the patients until 24 months are indicated in Table 6. BUN and creatinine tests of both groups were found within the normal limits. The levels of the HbA1c were higher in Group 2 compared to Group 1 (p<0.04). Furthermore, 24-hour microalbuminuria levels were found significantly higher in Group 2 compared to Group1 (p<0.01). Restenosis is higher in Group 2 (29 patients, 13,1%) when compared to Group 1 (15 patients, 8,2%) (p < 0.001). In cases

Table 4. *Hospital results of PCI.*

Parameter	Group 1 (n = 351)	Group 2 (n = 112)	p value
Discharged patient	351	111	-
Hospital ACS (MI/NA)	1 (0,3%)	2 (1,8%)	NS
CIN	5 (1,4%)	6 (5,3%)	<0,001
Large hemorrhage	1 (0,3%)	1 (0,9%)	NS
Transfusion	1 (0,3%)	1 (0,9%)	NS
Subacute thrombosis	1 (0,3%)	1 (0,9%)	NS
Repeated revascularizations	1 (0,3%)	2 (1,8%)	NS
Hospital mortality	0	1 (0,9%)	NS
Non-fatal complications	4 (1,1%)	12 (10,7%)	<0,001

NS = non-significant.

Table 5. *The relative risk of death up to 24 months in view of CIN after PCI.*

Group	with CIN	without CIN	Relative risk (95% CI)	p value
1	1 (20%)	13 (3,7%)	5,3 (0,85 - 33,26)	NS
2	2 (33,3%)	6 (5,5%)	5,8 (1,49 - 23,23)	<0,001

CI = confidence interval; NS = non-significant.

Table 6. *Remote results of PCI up to 24 months.*

Parameter	Group 1 (n = 351)	Group 2 (n = 112)	p value
Blood urea mitogen (mg/dl)	22 + 6,12	23 + 8,20	NS
Creatinine (mg/dl)	1,1 + 1,10	1,2 + 1,35	NS
HbA1c (%)	6,8 + 0,82	7,5 + 0,92	<0,04
Microalbuminuria (mg/g)	55 + 6,7	97 + 10,7	<0,01
Restenosis	29 (8,2%)	15 (13,1%)	<0,001
Repeated PCI	25 (7,1%)	13 (11,6%)	<0,001
Survived patients	337 (96%)	104 (92,8%)	NS
Rethrombosis of index	8 (2,2%)	5 (4,1%)	NS
Mortality	14 (3,9%)	8 (7,1%)	<0,04
Non-fatal complications	51 (14,5%)	27 (24,1%)	<0,001

Data are shown as percentage and mean + standart deviation.
NS = non-significant.

of restenosis or new stenosis, PCI was applied again to 13 patients (11,6%) in Group 1 and 15 patients (7,1%) in Group1 again where this was greater in Group 2 compared to Group 1 ($p < 0.001$). Furthermore, there was no difference between groups in terms of rethrombosis index. While mortality was seen in 14 patients (3,9%) in Group 1 due to either cardiac or non-cardiac causes, mortality was seen significantly more in 8 patients (7,1%) in Group 2 compared to Group 1 ($p<0.04$). Likewise, while non-fatal complications were seen in 51 patients (14,5%), these complications were seen significantly more in 27 patients (24,1%) in Group 2 compared to Group 1 ($p<0.04$).

Table 7. *Results of e-GFR parameters up to 24 months after PCI.*

3-month periods	Group 1-eGFR (n = 351)	Group 1-eGFR (n = 112)
3	97,72+11,40	83,78+12,36
6	98,30+13,25	85,23+14,77
9	104,65+14,40	84,35+17,22
12	103,82+11,35	78,75+14,40
15	100,35+10,72	80,42+15,73
18	99,53+13,80	79,80+10,23
21	98,14+12,46	78,40+13,66
24	102,27+13,28	76,35+15,82
p value	NS	NS

Data are shown as mean + standart deviation; NS = non-significant.

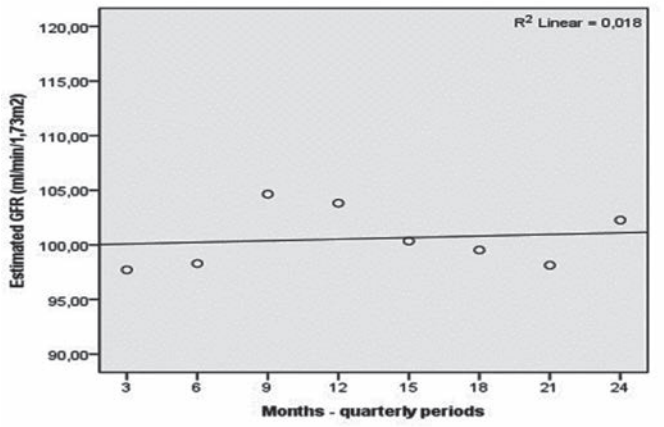

Figure 1. *eGFR parameters up to 24 months in view of Group 1 after PCI.*

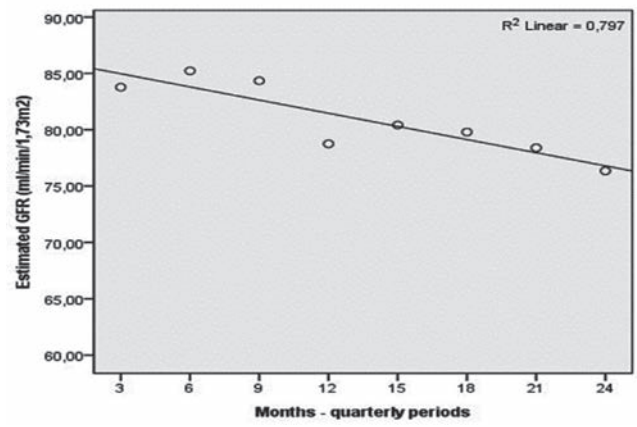

Figure 2. *eGFR parameters up to 24 months in view of Group 2 after PCI.*

Estimated GFR results of both groups until the 24 months being measured in each 3 months following PCI are listed in Table 7. No statistically significant change was found in eGFR in both groups. But a tendency was seen in the values of eGFR) in the followed months (Figure 2). No tendency was seen in the values of the eGFR of Group 1 (Figure 1). Furthermore, no significant difference was found between them when 3-month eGFR measurements in both groups following the PCI with first eGFR (s) before PCI.

Discussion. It has been shown in many studies that successful results have been obtained with percutaneous ballon angioplasty and then, increasing stent application to the CAD [38; 39]. The BMSs which have been used first in PCI are being replaced by the applications of DES [40].

The clinical situations of BMS and DES in patients with diabetes and those without diabetes have been continuing to be debated about some of the most important problems of the PCIs such as stent thrombosis, target lesion revascularization, target vessel revascularization and major adverse cardiac event. Even though some studies [15; 16; 18; 41] about that DES applications in patients with DM had demonstrated better clinical results in long- term compared to BMS have been reported, studies showing that there is no significant difference between BMS and DES during the follow-up time in terms of complications have been also published [42; 43].

On the other hand, one of the earlier complications that can be seen after PCI performed to those with CAD is CIN (19,21). Risk for CIN after inserting stent is seen higher particularly in patients with DM who have lower eGFR [44; 45]. Advanced glycation end-products (AGE) being occurred as a result of the sugar levels that progress in higher level have been reported to play role in the development of microvascular and macrovascular complications as the common cause of the nephropathy in patients with DM [46; 47]. Accordingly, the monitoring of the measurements of the AGE and that of the measurements of the AGE receptors are suggested as the prognostic biomarkers in patients with CAD and DM in which stent was inserted [48]. On the other hand, it has been demonstrated that increase in vascular endothelial growth factor as potent mitogen as a result of the long-term persistence of the AGE accelerates to progress to renal failure [49].

In our study, although the amount of the contrast agent was lower compared to Group 1 in patients in which DES was inserted after PCI, CIN complication was seen more in Group 2 compared to Group 1 ($p<0.001$). Furthermore, in the follow-up of the patients up to 24 months, while no significant mortality relative risk was found in Group 1, mortality relative risk was found significantly higher in Group 2 (RR 5,8, $p<0,001$). Besides, DM is in conjunction with increased atherothrombotic risk [50]. This situation is developing with diverse underlying mechanisms associated with hyperglycemia in conjunction with insulin resistance [10] and it increases the risk for stent thrombosis and target lesion revascularization by altering coagulation and platelet functions in time [51]. Furthermore, repeating revascularization following PCI and the mortality rate show an increase with the progression of DM. It has been shown that recurrent stenosis being developed after the stent insertion is in conjunction with insulin resistance and hyperglycemia in these patients [52].

We encountered similar results in the presented study. We found higher restenosis, repeated PCI, non-fatal complications ($p<0.001$) and mortality incidence ($p<0.04$) compared to Group 1 (Table 6). On the other hand, there was no statistically significant change in the eGFR of both groups which had been measured for 24 months with 3-month periods. But there was a declining tendency in the values of the eGFR in Group 2 in the following months (Figure 2). There was no tendency in Group1 (Figure 1). Moreover, there was no significant difference in both groups between 3-month eGFR the after PCI and eGFR before PCI.

The observation of the declining tendency in the eGFR in Group 2 may be related with two factors. First, Group 2 has higher body mass index, time for DM and HbA1c levels compared to Group1 ($p<0.01$) and, the second is that although no change has been observed in both groups in long-term BUN and creatinine levels, microalbuminuria is higher in Group2 ($p<0.01$). All of these indicate that DM can increase either the progression of the renal injury or the complication risk in the follow-up after PCI in the patient with an accompanying ischemic heart disease by increasing the negative chronic effect of DM on renal functions.

In conclusion, this study revealed no statistically significant change in the eGFR in the 24-month follow-up between the patients included into Group 1 and those included into Group 2 after DES insertion. But, the reduction of the eGFR which

demonstrated a declining tendency in Group 2 suggested that it can be yielded from negative chronic effect of the DM as an independent determinant on the renal functions. Moreover, this effect showed that it led increase in the risk of CIN, restenosis, repeated PIC and non-fatal complications in the diabetic patients with decreased eGFR after the insertion of the stent and that it was the determinant of the mortality risk. The monitoring of the eGFR after the PCI can be beneficial to determine the patients who have chronic renal disease. In addition, randomized-controlled studies are required for determining the changes in the renal systems after the insertion of DES in the diabetic patients that use insulin.

References:

1. International Diabetes Federation. Sixth edition, Diabetes Atlas. IDF Publ., Brussels, 2013.

2. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1: Diagnosis and classification of diabetes mellitus. Geneva: World Health Organization, 1999.

3. Shaw J.E., Sicree R.A., Zimmet P.Z. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010; 87:4-14.

4. Grundy S.M., Benjamin I.J., Burke G.L., Chait A., Eckel R.H., Howard B.V., Mitch W., Smith S.C. Jr., Sowers J.R. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation. 1999 Sep 7; 100 (10): 1134-46.

5. Smith Sidney C. Multiple Risk Factors for Cardiovascular Disease and Diabetes Mellitus. American Journal of Medicine, Mar 2007; Supplement 1, Vol. 120, pS3-S11.

6. Chiha M., Njeim M., Chedrawy E.G. Diabetes and coronary heart disease: a risk factor for the global epidemic. Int J Hypertens. 2012; 2012: 697240.

7. Chillarón J.J., Roux J.A., Benaiges D., Pedro-Botet J. Subclinical cardiovascular disease in type 2 diabetes mellitus: To screen or not to screen. World J Clin Cases. 2014 Sep 16;2(9):415-21.

8. Wilson P.W., D'Agostino R.B., Levy D., Belanger A.M., Silbershatz H., Kannel W.B. Prediction of coronary heart disease using risk factor categories. Circulation. 1998; 97:1837–1847.

9. Luscher T.F., Creager M.A., Beckman J.A., Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: Part II. Circulation.2003;108:1655-61.

10. Melidonis A., Dimopoulos V., Lempidakis E., Hatzissavas J., Kouvaras G., Stefanidis A., et al. Angiographic study of coronary artery disease in diabetic patients in comparison with nondiabetic patients. Angiology 1999; 50: 997-1006.

11. Aronson D., Bloomgarden Z., Rayfield E.J. Potential mechanisms promoting restenosis in diabetic patients. J Am Coll Cardiol 1996; 27: 528 – 535.

12. Silva J.A., Escobar A., Collins T.J., Ramee S.R., White C.J. Unstable angina. A comparison of angioscopic findings between diabetic and nondiabetic patients. Circulation. 1995 Oct 1; 92 (7): 1731 - 6.

13. Vinik A.I., Erbas T., Casellini C.M. Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease, J. Diabetes Investig. 2013 Jan;4 (1): 4-18. Epub 2013 Jan 29.

14. Stone G.W., Mehran R., Dangas G., Lansky A.J., Kornowski R., Leon M.B. Differential impact on survival of electrocardiographic Q-wave versus enzymatic myocardial infarction after percutaneous intervention: a device-specific analysis of 7147 patients. Circulation 2001; 104:642-7.

15. Scheen A.J., Warzee F., Legrand V.M. Drug-eluting stents: metaanalysis in diabetic patients. Eur Heart J. 2004; 25: 2167 - 8.

16. Bangalore S., Kumar S., Fusaro M., Amoroso N., Kirtane A.J., Byrne R.A., Williams D.O., Slater J., Cutlip D.E., Feit F. Outcomes with various drug eluting or bare metal stents in patients with diabetes mellitus: mixed treatment comparison analysis of 22,844 patient years of follow-up from randomised trials. BMJ. 2012 Aug 10; 345: e5170.

17. Kumbhani D.J., Bavry A.A., Kamdar A.R., Helton T.J., Bhatt D.L. The effect of drug-eluting stents on intermediate angiographic and clinical outcomes in diabetic patients: insights from randomized clinical trials. Am Heart J. 2008 Apr;155 (4): 640-7.

18. Mulukutla S.R., Vlachos H.A., Marroquin O.C., Selzer F., Holper E.M., Abbott J. D., Laskey W.K., Williams D.O., Smith C., Anderson W.D., Lee J.S., Srinivas V., Kelsey S.F., Kip K.E. Impact of drug-eluting stents among insulin-treated diabetic patients: a report from the National Heart, Lung and Blood Institute Dynamic Registry. JACC Cardiovasc Interv. 2008 Apr;1 (2): 139-47.

19. Katsiki N., Athyros V.G., Karagiannis A., Mikhailidis D.P., Contrast-Induced Nephropathy: An "All or None" Phenomenon. Angiology. 2014 Sep 14.

20. Weisbord S., Palevsky P. Radiocontrast-induced acute renal failure. J Intensive Care Med. 2005; 20: 63-75.

21. Mehran R., Nikolsky E. Contrast-induced nephropathy: Definition, epidemiology, and patients at risk. Kidney Int Suppl. 2006: S11-S15.

22. Manske C., Sprafka J., Strony J., et al. Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. Am J. Med 1990; 89: 615-20.

23. Tajiri K., Maruyama H., Sato A., Shimojo N., Saito T., Endo M., Aihara H., Kawano S., Watanabe S., Sakai S., Aonuma K. Prediction of chronic renal insufficiency after coronary angiography by an early increase in oxidative stress and decrease in glomerular filtration rate. Circ J. 2011;75(2): 437-42. Epub 2010 Nov 16.

24. Marenzi G., Assanelli E., Marana I., et al. N-acetyl-cysteine and contrast-induced nephropathy in primary angioplasty. N Engl J. Med 2006; 354:2773-82.

25. Stone G., McCullough P., Tumlin J., et al. Fenoldopam mesylate for the prevention of contrast-induced nephropathy: A randomized controlled trial. JAMA 2003; 290:2284-91.

26. Liu Y.H., Liu Y., Duan C.Y., Tan N., Chen J.Y., Zhou Y.L., Li L.W., He P.C. Statins for the Prevention of Contrast-Induced Nephropathy After Coronary Angiography/ Percutaneous Interventions: A Meta-analysis of Randomized Controlled Trials. J Cardiovasc Pharmacol Ther. 2014; Sep 5.

27. Rey J.R., Iglesias D., López De Sá E, Armada E., Moreno R., Salvador O., Monedero Mdel C., Blas S.G., Iniesta A.M., López- Sendon J.L. Prevention of contrast-induced nephropathy with haemofiltration in high-risk patients after

percutaneous coronary intervention. Acute Card Care. 2011 Sep; 13 (3):164-9.

28. Au T.H., Bruckner A., Mohiuddin S.M., Hilleman D.E. The Prevention of Contrast-Induced Nephropathy. Ann Pharmacother. 2014 Oct; 48 (10):1332-1342.

29. Moos S.I., Nagan G., de Weijert R.S., van Vemde D.N., Stoker J., Bipat S. Patients at risk for contrast-induced nephropathy and mid-term effects after contrast administration: a prospective cohort study. Neth J. Med. 2014 Sep; 72 (7):363-71.

30. Roumie C.L., Hung A.M., Greevy R.A., Grijalva C.G., Liu X., Murff H.J., Elasy T.A., Griffin M.R. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. Ann Intern Med. 2012 Nov 6;157(9):601-10.

31. Forst T., Hanefeld M., Jacob S., Moeser G., Schwenk G., Pfützner A., Haupt A. Association of sulphonylurea treatment with all-cause and cardiovascular mortality: a systematic review and meta-analysis of observational studies. Diab Vasc Dis Res. 2013 Jul;10 (4):302-14.

32. Monami M., Genovese S., Mannucci E. Cardio-vascular safety of sulfonylureas: a meta-analysis of randomized clinical trials. Diabetes Obes Metab. 2013 Oct;15(10):938-53.

33. Phung O.J., Schwartzman E., Allen R.W., Engel S.S., Rajpathak S.N. Sulphonylureas and risk of cardiovascular disease: systematic review and meta-analysis. Diabet Med. 2013 Oct; 30(10): 1160 - 71.

34. Rensing K.L., Reuwer A.Q., Arsenault B.J., von der Thüsen J.H., Hoekstra J.B., Kastelein J.J., Twickler T.B. Reducing cardiovascular disease risk in patients with type 2 diabetes and concomitant macrovascular disease: can insulin be too much of a good thing? Diabetes Obes Metab. 2011 Dec; 13(12): 1073-87.

35. Smith E.R. The angina grading system of the Canadian Cardiovascular Society. Can J Cardiol. 2002 Apr;18 (4):439, 442.

36. National Kidney Foundation. K/DOQI Clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39 (Suppl 1): Sl-266.

37. Cockcroft D.W., Gault MH. Prediction of creatinine clearance from serum creatinine.Nephron. 1976; 16 (1): 31-41.

38. Van Belle E., Bauters C., Hubert E., Bodart J.C., Abolmaali K., Meurice T., et al. Restenosis rates in diabetic patients: a comparison of coronary stenting and balloon angioplasty in native coronary vessels. Circulation 1997; 96: 1454-60.

39. Savage M.P., Fischman D.L., Rake R., Leon M.B., Schatz R.A., Penn I., et al. Efficacy of coronary stenting versus balloon angioplasty in small coronary arteries. Stent Restenosis Study (STRESS) Investigators. J. Am Coll Cardiol 1998; 31:307-11.

40. Geng D.F., Meng Z., Yan H.Y., Nie R.Q., Deng J., Wang J.F. Bare- metal stent versus drug-eluting stent in large coronary arteries: meta-analysis of randomized controlled trials. Catheter Cardiovasc Interv. 2013 Jun 1; 81 (7):1087-94.

41. Iijima R., Byrne R.A., Dibra A., Ndrepepa G., Spaulding C., Laarman G.J., Menichelli M., Valgimigli M., Di Lorenzo E., Kaiser C., Tierala I., Mehilli J., Suttorp M.J., Violini R., Schömig A., Kastrati A. Drug-eluting stents versus bare-metal stents in diabetic patients with ST-segment elevation acute myocardial infarction: a pooled analysis of individual patient data from seven randomized trials. Rev Esp Cardiol. 2009 Apr; 62(4):354- 64.

42. Qin S.Y., Zhou Y., Jiang H.X., et al. The association of diabetes mellitus with clinical outcomes after coronary stenting: a meta-analysis. PLoS One. 2013 Sep 16; 8(9): e72710.

43. Vogt A., Schoelmerich A., Pollner F., et al. Comparison of outcome in 1809 patients treated with drug- eluting stents or bare-metal stents in a real-world setting. Vasc Health Risk Manag. 2011;7: 693-9.

44. Heyman S.N., Rosenberger C., Rosen S., Khamaisi M. Why is diabetes mellitus a risk factor for contrast-induced nephropathy? Biomed Res Int. 2013; 2013: 123589.

45. Shul'zhenko L.V., Pershukov I.V., Batyraliev T.A., Fettser D.V., Sidorenko B.A. The role of reduction of glomerular filtration rate in outcomes of drug-eluting stents implantation in patients with ischemic heart disease and chronic kidney disease. Kardiologiia.2010; 50 (4): 4-11.

46. Friedman EA. Advanced glycation end-products in diabetic nephropathy. Nephrol Dial Transplant. 1999;14 Suppl 3:1-9.

47. Eui-Young Choi, Hyuck Moon Kwon, Chul-Woo Ahn, et al. Serum levels of advanced glycation end products are associated with in-stent restenosis in diabetic patients. Yonsei Med J. 2005 Feb 28;46 (1): 78-85. doi: 10.3349/ymj.2005.46.1.78. PMID: 15744809 PMCID: PMC2823061 glycation end products are associated with in-stent restenosis in diabetic patients. Yonsei Med J. 2005 Feb 28; 46 (1):78-85.

48. Shen Y., Pu L.J., Lu L., Zhang Q., Zhang R.Y., Shen W.F. Serum advanced glycation end-products and receptors as prognostic biomarkers in diabetics undergoing coronary artery stent implantation. Can J. Cardiol. 2012 Nov-Dec; 28(6):737-43.

49. Schrijvers B.F., Flyvbjerg A., De Vriese A.S. The role of vascular endothelial growth factor (VEGF) in renal pathophysiology. Kidney Int. 2004 Jun;65 (6):2003-17.

50. Stratmann B., Tschoepe D. Atherogenesis and atherothrombosis-focus on diabetes mellitus. Best Pract Res Clin Endocrinol Metab. 2009 Jun; 23 (3): 291-303.

51. Nishio K., Fukui T., Tsunoda F., Kawamura K., Itoh S., Konno N., Ozawa K., Katagiri T. Insulin resistance as a predictor for restenosis after coronary stenting. Int J Cardiol. 2005 Aug 18; 103 (2): 128-34.

52. Dahm J.B. Feldrappe A. Hummel A. Moex B. Staudt A. Voelzke H. Vogelgesang D. Insulin resistance and hyperglycaemia are associated with recurrent stenosis in diabetic patients after percutaneous coronary intervention. Journal of Clinical and Basic Cardiology 2002; 5 (3), 241-246.

53. Zhang Z., Zhu M., Wang Z., Zhang H. Associations between different eGFR estimating equations and mortality for CVD patients: A retrospective cohort study based on the NHANES database. Medicine (Baltimore). 2022 Sep 23; 101 (38): e30726. doi: 10.1097/MD.0000000000030726. PMID: 36197188.

ИНСУЛИНМЕН ЕМДЕЛГЕН ЖҮРЕКТІҢ ИШЕМИЯЛЫҚ АУРУЫ ЖӘНЕ ҚАНТ ДИАБЕТІ БАР ЕМДЕЛУШІЛЕРДЕ ДӘРІЛІК СТЕНТТЕРДІ ИМПЛАНТАЦИЯЛАҒАННАН КЕЙІН 24 АЙДАН КЕЙІНГІ ГЛОМЕРУЛЯРЛЫҚ ФИЛЬТРАЦИЯНЫҢ БОЛЖАМДЫ ЖЫЛДАМДЫҒЫНЫҢ НӘТИЖЕЛЕРІНЕ ӘСЕРІ

[*1] Lütfi Baran, [2] Т. Батыралиев, [3] Mehmet Baştemir, [2] Serdar Türkmen
[1] Санко Университеті, Медициналық факультетінің, Ішкі аурулар бөлімшесі, Газиантеп, Түркия
[2] Санко Университеті, Медициналық факультетінің, Кардиология бөлімшесі, Газиантеп, Түркия
[3] Санко Университеті, Медициналық факультетінің, Эндокринология бөлімшесі, Газиантеп, Түркия

Түйінді

Жүректің ишемиялық ауруы (ЖИА) бар емделушілерде гемодиализді қолдануға әкелуі мүмкін бүйрек жеткіліксіздігі йодидпен контрастты заттарды қолдану арқылы орындалатын тері астындағы коронарлық араласу кезінде байқалады. Бұл зақым қант диабеті жоқ пациенттермен салыстырғанда гломерулярлық фильтрацияның болжамды жылдамдығы төмен қант диабетімен ауыратын науқастарға тән.

Мақсаттары: бұл зерттеудің мақсаты инсулинмен емделген 2-ші типті қант диабеті және ЖИА бар емделушілерде дәрілік стенттерді имплантациялаудан кейінгі бүйректің шумақтық сүзілу жылдамдығының өзгеруін зерттеу болып табылады.

Зерттеу дизайны: перспективалық зерттеу.

Әдістері: зерттеуге соңғы 5 жыл ішінде (соңғы 2015 жылдың желтоқсанына дейін) PCI-де дәрі-дәрмектерді жою үшін бір немесе бірнеше стент орнатылған ITDM бар барлығы 463 пациент енгізілді. Екі топтағы пациенттер рскф-ны зертханалық зерттеулермен және Кардиология және ішкі аурулар бөлімшелерінде басқа кардиологиялық параметрлермен 24 ай бойы 3 айлық кезеңмен бақылады.

Нәтижелер: зерттеуге енгізілген пациенттер гФБЖ сәйкес екі топқа бөлінді: гФБЖ> 90 мл/мин/1,73 м^2 бар 351 пациентті (75,8%) қамтитын 1 топ және рскф 60-тан 89 мл/мин/1,73-ке дейінгі 112 пациентті (24,2%) қамтитын 2 топ м^2. Екі топтағы пациенттер 3 айлық кезеңмен 24 ай бойы бақылауда болды. Зерттеудің соңында екі топта да egfrs-те статистикалық маңызды өзгерістер табылған жоқ. Бірақ 2-ші топта гФБЖ(лар) төмендеу тенденциясы анықталды. Сонымен қатар, гФБЖ-ның үш айлық өлшеулері бірінші РСКФ-мен PCI-ге дейін салыстырылған кезде айтарлықтай айырмашылық табылған жоқ. Сонымен қатар, контрастты заттан туындаған нефропатия жиілігі 1-ші топпен салыстырғанда 2-ші топта айтарлықтай деңгейде жиі болды (p<0,01). 24 айлық кардиологиялық бақылау кезінде рестеноз және реваскуляризация жиілігі, жүректің ауыр асқыну жиілігі және өлімнің салыстырмалы қаупі 2-ші топта 1-ші топпен салыстырғанда жиі және сенімді түрде байқалды (p<0,01).

Қорытынды: бұл зерттеу США-дан кейін статистикалық маңызды емес, бірақ 2-ші топтағы пациенттерде төмендеу үрдісі бар rscf төмендеуі қант диабетінің бүйрек функциясына созылмалы теріс әсерінің нәтижесі болуы мүмкін екенін көрсетті. Сонымен қатар, бұл әсер қант диабетімен ауыратын науқастарда стент қойылғаннан кейін контрастты заттан туындаған нефропатия қаупі рестеноз жиілігінің жоғарылауына және жиырма төрт айлық бақылауда реваскуляризацияға әкелетінін және бұл өлім қаупінің анықтаушы факторы екенін көрсетті.

Кілт сөздер: *инсулинмен емделген қант диабеті, жүректің ишемиялық ауруы, дәрі-дәрмекпен қапталған стент, гломерулярлық фильтрацияның болжамды жылдамдығы.*

ВЛИЯНИЕ РАСЧЕТНОЙ СКОРОСТИ КЛУБОЧКОВОЙ ФИЛЬТРАЦИИ НА РЕЗУЛЬТАТЫ ЧЕРЕЗ 24 МЕСЯЦА ПОСЛЕ ИМПЛАНТАЦИИ СТЕНТОВ С ЛЕКАРСТВЕННЫМ ПОКРЫТИЕМ У ПАЦИЕНТОВ С ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА И САХАРНЫМ ДИАБЕТОМ, ПОЛУЧАВШИХ ИНСУЛИН

[*1] Lütfi Baran, [2] Т. Батыралиев, [3] Mehmet Baştemir, [2] Serdar Türkmen
[1] Отделение внутренних болезней медицинского факультета Университета Санко, Газиантеп, Турция
[2] Отделение кардиологии, медицинский факультет Университета Санко, Газиантеп, Турция
[3] Отделение эндокринологии, медицинский факультет Университета Санко, Газиантеп, Турция

Аннотация

У пациентов с ишемической болезнью сердца (ИБС) почечная недостаточность, которая может привести к использованию гемодиализа, наблюдается во время чрескожного коронарного вмешательства (ЧКВ), выполняемого с использованием контрастных веществ с йодидом. Это повреждение более характерно для пациентов с диабетом с более низкой расчетной скоростью клубочковой фильтрации (рСКФ) по сравнению с пациентами, у которых диабета нет.

Цели: Целью данного исследования является изучение изменений скорости клубочковой фильтрации почек после имплантации стентов с лекарственным покрытием (САШы) у пациентов с сахарным диабетом 2 типа, получавших инсулин и ИБС.

Дизайн исследования: Проспективное исследование.

Методы: В общей сложности в исследование были включены 463 пациента с ИТДМ, которым последовательно в течение последних 5 лет (последний раз до декабря 2015 года) были установлены один или несколько стентов для

удаления лекарств при ЧКВ. Пациенты в обеих группах наблюдались за рСКФ с лабораторными тестами и другими кардиологическими параметрами в отделениях кардиологии и внутренних болезней в течение 24 месяцев с 3-месячными периодами.

Результаты: Пациенты, включенные в исследование, были разделены на две группы в соответствии с рСКФ: группа 1, включающая 351 пациента (75,8%) с рСКФ > 90 мл/мин/1,73 м^2 и группа 2, включающая 112 пациентов (24,2%) с рСКФ от 60 до 89 мл/мин/1,73 м^2. Пациенты в обеих группах находились под наблюдением в течение 24 месяцев с 3-месячными периодами. В конце исследования в обеих группах не было обнаружено статистически значимых изменений в рСКФ(ов). Но была обнаружена тенденция к снижению рСКФ(ов) во 2-й группе. Более того, когда трехмесячные измерения рСКФ сравнивались с первой рСКФ до ЧКВ, существенной разницы обнаружено не было. Кроме того, частота нефропатии, вызванной контрастным веществом, была более распространена на значительном уровне во 2-й группе по сравнению с 1-й группой ($p<0,01$). В течение 24-месячного кардиологического наблюдения частота рестеноза и реваскуляризации, частота серьезных сердечных осложнений и относительный риск смерти наблюдались чаще и достоверно во 2-й группе по сравнению с 1-й группой ($p<0,01$).

Заключение: Это исследование показало, что снижение рСКФ, которое не было статистически значимым после САШ, но имело тенденцию к снижению у пациентов 2-й группы, может быть результатом хронического негативного влияния сахарного диабета (СД) на функции почек. Кроме того, этот эффект продемонстрировал, что риск нефропатии, вызванной контрастным веществом, после установки стента у пациентов с сахарным диабетом со сниженной рСКФ привел к увеличению частоты рестеноза и повторной реваскуляризации в течение двадцати четырех месяцев наблюдения и что это является определяющим фактором риска смертности.

Ключевые слова: *сахарный диабет, лечимый инсулином, ишемическая болезнь сердца, стент с лекарственным покрытием, расчетная скорость клубочковой фильтрации.*

Конфликт интересов. *Все авторы заявляют об отсутствии потенциального конфликта интересов, требующего раскрытия в данной статье.*

Корреспондирующий автор. *Dr. Lütfi Baran, Кафедра внутренних болезней медицинского факультета Университета Санко, Газиантеп, Турция. E-mail: lutfibaran@hotmail.com; https://orcid.org/0000-0001-8615-5908.*

Вклад авторов. *Все авторы внесли равноценный вклад в разработку концепции, выполнение, обработку результатов и написание статьи. Заявляем, что данный материал ранее не публиковался и не находится на рассмотрении в других издательствах.*

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Corresponding author. *Dr. Lütfi Baran, Department of Internal Medicine, Sanko University Faculty of Medicine, Gaziantep, Turkey. E-mail: lutfibaran@hotmail.com; https://orcid.org/0000-0001-8615-5908.*

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