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Journal of Clinical Cardiology and Cardiovascular Interventions
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Research Article

Uncontrolled diabetes mellitus; results of cytokines and endothelial function during coronary artery bypass surgery

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Received date: April 22, 2024; Accepted date: May 28, 2024; Published date: June 07, 2024

Citation: A.Tulga Ulus, Ayşegül Özgök, Sertan Özyalçın, Gül Saydam, Mevhibe Balk, et.al, (2024), Uncontrolled diabetes mellitus; results of cytokines and endothelial function during coronary artery bypass surgery, *J Clinical Cardiology and Cardiovascular Interventions*, 7(6); **DOI: 10.31579/2641-0419/374**

Abstract

Objective: Unregulated type 2 diabetes mellitus is a major risk factor for coronary artery bypass surgery [CABG]. Perioperative values of cytokines and the endothelial function of diabetic patients who have controlled and uncontrolled glucose were compared according to HbA1c levels. The parameters were analyzed and compared following the hospital admission and started to the appropriate treatment.

Methods: Forty patients undergoing CABG were included the study. Patients were divided into 3 groups according to preoperative HbA1c levels; the patients who had HbA1c level below 7 [group 2], HbA1c values in between 7-10 [group 3], above 10 [group 4] were marked as groups 1-3 and additional 10 non diabetic patients were included as the control group [group 1].

Results: The demographic data of the patients were not significantly changed among the groups except female gender. Postoperative inotropic support necessity was high especially in group 4. Preoperative endothelial dysfunction was also severely impaired in the high HbA1c groups but this difference was returned to nonsignificant level following treatment. Noninvasive endothelial function was calculated as 2.0 in control group but 0.69±0.32, 1.36±0.69, 0.99±0.15 in groups 2-4. Apelin, soluble intercellular adhesion molecule and Platelet Activating Factor levels were changed significantly among the groups [$p<0.002$].

Conclusion: We indicate that HbA1c level is an important predictor of morbidity during the CABG surgery. In our study there is a significant difference between diabetic and non-diabetic patients in terms of both endothelial function and some of the inflammatory cytokines. These parameters improved by the time and following the appropriate treatment of diabetes mellitus but effect the CABG surgery.

Keywords: diabetes mellitus; cytokines; endothelial function and coronary artery bypass surgery

Introduction

Diabetes mellitus [DM] is one of the major risk factor in coronary artery disease [CAD] and atherosclerosis is responsible for mortality and morbidity in diabetic patients. Coronary artery bypass grafting [CABG] surgery is recommended in patients with DM and multivessel CAD to improve survival free from major cardiovascular events [1-7]. DM increases the long term mortality and risk of complications after CABG surgery compared with non-diabetic patients [8]. DM is an inflammatory, proliferative and prothrombotic disease. As a result of DM, increased platelet activity and a predisposition to coagulation, adverse effects on lipid metabolism, corrupted function of polymorph nuclear leucocytes

and fibroblast proliferation, and disorders of endothelial activity may occur. There is an important correlation between blood glucose levels and the severity of disorders. HbA1c is a parameter that specifies the blood glucose regulation. Some studies presented the relationship between preoperative HbA1c levels and postoperative outcomes following CABG surgery in diabetic patients [9-11].

Endothelial dysfunction is one of the major pathologic component of CAD and DM [12-17]. Therefore, noninvasive methods have been developed to reveal endothelial dysfunction. Reactive hyperemia-peripheral arterial tonometry [RH-PAT] is a noninvasive method to assess the peripheral endothelial function [18, 19].

Patients, who had uncontrolled blood glucose levels have the highest morbidity and mortality [1]. We aimed to find out a parameter that may inform us before the surgery for the optimum timing of surgery related with the blood glucose level and diabetic severity. The purpose of this study is to determine the relationship between the level of endothelial dysfunction, inflammatory processes by measuring cytokine levels and blood glucose levels in diabetic patients who experienced CABG.

Methods

This study is a prospective randomized clinical study. The ethical committee approval was completed with the registration number 20-412. Forty-one patients who were operated for CAD in our clinic, included in this study. Patients were divided into four groups according to HbA1c levels that were obtained when they applied to the hospital first. These groups were as follows; Group 1 [10 patients] was nondiabetic patients with HbA1c<4, Group 2 [11 patients] with HbA1c 4-7, Group 3 [12 patients] with HbA1c 7-10, Group 4 [8 patients] with HbA1c ≥10. Sixty-one percent of the patients in diabetic groups [Group 2, 3, 4] had been diagnosed before the application to our hospital. The mean followed up time of diabetic patients were 5.6± 7.6 years in different endocrinology clinics. Thirteen [41%] of diabetic patients were using oral antidiabetic medication and 6 [19%] of diabetic patients were using different insulin regiments before application to our hospital. Twelve [%38] of diabetic patients were diagnosed at our hospital before CABG surgery. Male dominance is higher in some groups and insulin treatment as a part of the diabetic is higher in diabetic groups **[table 1]** but other demographic variables are statistically non-significant among the groups.

Variables	Group 1 [HbA1C<4] N=10	Group 2 [HbA1C 4-7] N=11	Group 3 [HbA1C 7-10] N=12	Group 4 [HbA1C >10] N=8	P
Male	5 [50%]	9 [81.8%]	12 [100%]	5 [62.5%]	**0.047**
Age	56.1±12.2	58.5±8.4	59.4±7.8	61.7±8	0.6
BMI	1.16±0.8	1.3±0.6	1.4±0.6	1.2±0.8	0.57
OAD		4 [36%]	6 [50%]	3 [37.5%]	0.2
Insulin			1 [8.3%]	5 [62%]	**0.001**
DM Follow-up year		4.9±5.6	9.4±8.9	9.3±9	**0.01**
Hypertension	5 [50%]	9 [81.8%]	8 [66.7%]	7 [87.5%]	0.27
Hyperlipidemia	2 [20%]	6 [54.5%]	4 [30%]	5 [62.5%]	0.21
Preoperative MI History	1 [10%]	2 [18.2%]	2 [16.6%]	4 [50%]	0.18
Preoperative Stroke History		1 [9.1%]	2 [16.6%]		0.38
Peripheral arterial disease		1 [9.1%]		2 [18.2%]	0.46
Preoperative EF [%]	57.3±5.3	57.3±6.6	56±6.1	52.5±10	0.4
Preoperative NYHA Class 1+2	8 [80%]	9 [81.8%]	10 [83.3%]	5 [62.5%]	
Preoperative NYHA Class 3	2 [20%]	2 [18.2%]	1 [8.3%]	3 [37.5%]	0.16
Preoperative medications					
Asetilsalisilic Asit	3 [30%]	7 [63.6%]	1 [8.3%]	5 [62.5%]	**0.02**
Beta Blokors	7 [70%]	8 [80%]	3 [25%]	4 [50%]	0.08
Ace Inhibitors	5 [50%]	8 [80%]	5 [41.6%]	5 [50%]	0.47

DM: Diabetes Mellitus, BMI: Body Mass Index, OAD: Oral Antidiabetics.

Table 1: Demographic variables according to the groups [p<0.05].

Patients were hospitalized minimum 2-days before the surgery in order to regulate blood glucose levels. Except metformin, the oral antidiabetic medications are continued and if the glycemic control is not effective, insulin regiment is started to regulate blood glucose levels. 200 mg/dl blood glucose level is the cutoff level to obtain permission for the operation. The blood glucose level during the operation was controlled by insulin infusion. We use the Portland Protocol peroperatively [20].

We studied RH- PAT system two times on all patients before the surgery as baseline and 7 day following the CABG surgery to evaluate the endothelial dysfunction and effects on DM and CABG surgery. The RH-PAT system is a rapid and noninvasive technique that is used to assess endothelial vasodilator function, duplex ultrasonography is the most common technique to assess flow-mediated vasodilation, but this technique is operator dependent and takes time. The equipment for Rh-

PAT system is cheaper than duplex ultrasonography. This device [Endopat 2000, Itamar Medical Ltd., Caesarea, Israel] consists of two probes which are mounted to fingers. These probes includes inflatable latex air-cushions within a rigid external case. Endothelium-mediated changes in the digital pulse waveforms are recorded by PAT [peripheral Arterial Tone] device. The changes in the PAT signal are elicited by creating a downstream hyperemic response. Hyperemia is induced by occluding blood flow through the brachial artery for 5 minutes using an inflatable cuff on one hand. Reactive hyperemia automatically calculated by the system. By calculation of pre and post occlusion n values, a PAT ratio is created. These values are normalized to measurements from the contra-lateral arm. This arm serves as control for non-endothelial systemic effects. The RH-PAT studies were performed in the supine position and both hands on the same level of the patient. One of the upper arms is chosen for placing for blood pressure cuff [study arm], while the contralateral arm served as a control [control arm]. Finger I of each hands are used to place RH-PAT probes. Pulsatile blood volume responses from both hands were recorded continuously. After 5 minutes of first recording period, the blood pressure cuff on the study arm was inflated to 60 mm Hg above systolic pressure for 5 min. The cuff was then deflated to induce RH, whereas PAT recording was continued for five minutes. The response to reactive hyperemia is calculated automatically by the system. Pat ratio is below 1.5 is severe endothelial dysfunction, 1.5 – 2.1 is moderate endothelial dysfunction and 2.1 and above is normal endothelial functions is determined by the manufacturer. EndoPat results are shown in **table 2.**

Variables	Group 1 [HbA1C<4] N=10	Group 2 [HbA1C 4-7] N=11	Group 3 [HbA1C 7-10] N=12	Group 4 [HbA1C >10] N=8	P
Preoperative endothelial function	2.00±0.42	0.69±0.32	1.36±0.69	0.99±0.15	0.01
Postoperative endothelial function	1.56±0.25	1.86±0.37	1.54±0.44	1.22±0.32	0.15

Table 2: Preoperative and postoperative endothelial function [Endopat] measurements [p<0.05].

Surgical Intervention

All patients have multivessel coronary artery disease including proximal left anterior descending artery [LAD] or left main coronary artery (LMCA). Left internal thoracic artery [LITA] is used for LAD in all patients. Other coronary arteries are bypassed by using saphenous vein grafts. We have used mean 2.9 ± 0.8 grafts / patient in this study.

The CABG was performed with standard cardiopulmonary bypass technique and using cross-clamp. Myocardial protection was established by hypothermia (28-30 °C), topical cooling and initial cold crystalloid cardioplegia followed by blood cardioplegia solution [Plegisol-ABBOT©] were applied in 20-minute intervals. The last dose of cardioplegia was given as warm blood cardioplegia. A moderate degree of hypothermia and hemodilution was used. Operative and postoperative data are given in table 3.

Inflammatory Cytokines

We studied cytokine levels at four time points to evaluate inflammatory processes and its' effects in diabetic patients. We collected blood samples during and after CABG surgery as; before the induction of anesthesia, when the cardiopulmonary bypass was started, when the cardiopulmonary bypass was ended and at first postoperative day. Soluble vascular adhesion molecule-1 [**sVCAM-1**], soluble intercellular adhesion molecule-1 [**sICAM-1**], soluble E-selectin [**sE-selectin**] and soluble P-selectin [**sP-selectin**] were measured in duplicate using commercially available enzyme-linked immunosorbent assay [ELISA] kits. [RayBiotech®, Georgia,USA]. **IL-6**, **IL-1β** and **TNF**α were measured in duplicate using commercially available enzyme amplified sensitivity immunoassay kits [Diasource®, Nivelles, Belgium]. Also **Endotelin -1**, Nitric Oxide [**NO**], Myeloperoxidase [**MPO**], Homocysteine, Asymmetric dimethyl-L-arginin [**ADMA**], Von Wilebrand Factor [**VWF**], Platelet Activating Factor [**PAF**] and **Apelin** were measured in duplicate using comerciallay avaiable ELİSA kits. [Biomedica®, Wien, Austria], [Enzolifesiences®, New York, USA], [eBioscience®, Vienna, Austria], [Axis-Shield Diagnostics®, Dundee, UK], Immundiagnostik®, Bensheim, Germany], [Assaypro®, Missouri, USA], [Life Science Inc.®, Wuhan,China], [Phoneix Pharmaceuticals Inc®., California, USA] were analyzed with immunoassay kits respectively. The cytokine levels are given in **Table 4.**

Statistical Analysis

One way ANOVA test was used for statistical comparison of continuous variables between the groups. Chi-square test was used for comparison of categorical variables between the groups. Paired t-test was also used to determine the differences in the same group during the different measurement intervals. All values were reported as mean±SD. A p-value <0.05 was considered statistically significant.

Results

There was no difference in between the groups in terms of age. Mean age of all patients was 58.8±9.1 [38 to 78]. Male gender is more dominant in all groups. The use of insulin and diabetic patient follow up time are increased relative to level of HbA1c [p=0.001, p=0.01 respectively] [Table 1]. In terms of concomitant diseases, preoperative medications, preoperative MI and stroke history were similar in all groups.

Endothelial dysfunction was measured by using the Rh-Pat system moderate to severe levels. The mean Pat ratio measured 2.00±0.42 in control group [group 1] but 0.69±0.32, 1.36±0.69, 0.99±0.15 in groups 2, 3 and 4 preoperatively [p<0.01, figure 1, table 2]. The mean Pat ratios are statistically not different among the groups and get increased in groups 2, 3 and 4 [p>0.05] postoperatively. The positive inotropic support ratio is higher in diabetic groups but group 4 has the highest ratio with 50% [p<0.03, **table 3].**

Variables	Group 1 [HbA1C<4] N=10	Group 2 [HbA1C 4-7] N=11	Group 3 [HbA1C 7-10] N=12	Group 4 [HbA1C >10] N=8	P
Cross clamp Time [min]	49±20	62±24	58±10	69±20	0.2
CPB Time [min]	81±35	103±19	96±21	113±25	0.07
Number of CABG grafts	2.6±1.0	3.1±0.6	3±0.6	2.8±1.2	0.53
Postop bleeding [ml]	738±448	520±220	662±518	668±315	0.65
Extubation time [Hour]	11±5.2	7.3±2.8	9.8±3.7	11.3±4.1	0.1
ICU Stay [days]	1.3±0.9	1±0.3	1±0.3	1.25±0.7	0.5
Postoperative inotropic support	0.0 %	18.2 %	8.3 %	50.0 %	**0.03**
Hospital Stay [days]	5.9±1.6	5.3±0.8	6.3±4.5	6.25±1.4	0.8

CPB: Cardio Pulmonary Bypass, ICU: Intensive Care Unit

Table 3: Operative and postoperative measurements [p<0.05].

We studied cytokine levels at four different time points as baseline [preoperatively] and postoperatively [when the cardiopulmonary bypass was started, when the cardiopulmonary bypass was ended and at first postoperative day]. The cytokine levels according to the diabetic severity presented many important results. Nitric oxide levels did not differ among the groups but it decreased significantly in group 1, control group. It slightly but nonsignificantly increased in group 3 and 4 that could be explained by the result of insulin treatment. Soluble vascular adhesion molecule levels did not differ among the groups but significantly increased in all groups during the follow up. Soluble intercellular adhesion molecule levels reached a significant level at the 4th measurement point [at first postoperative day], with the lowest value at group 4 [p<0.04]. The measured levels increased gradually in all groups during time. E-selectin, P-selectin, interleukin-6, endothelin, interleukin 1β, TNFα, myeloperoxidase, Von Willebrand factor, homocysteine and ADMA levels did not differ among the groups but changed significantly during the follow up. Platelet activating factor level was significantly low in group 3 at the last measurement [p<0.03]. Apelin level was lowest in group 4 in all measurements and it was significant at first and third measurements [p<0.002] **[Table 4].**

Variables	Group 1 [HbA1C<4]	Group 2 [HbA1C 4-7]	Group 3 [HbA1C 7-10]	Group 4 [HbA1C >10]	P
	Nitricoxide [24-54 µmol/L]				
NO 1	68.1±35.9	53.9±29.4	57.1±38.2	61.9±36.4	0.5
NO 2	38.3±17.2*	51.5±24.7	55±37.7	71.2±29.5	0.3
NO 3	59.3±28.8*	51±21.1	42.6±29.3	76.8±28	0.1
NO 4	55.0±11.9	51.3±29.6	81.5.±48.4	51.1±35.7	0.88
P [in group]	*	-	-	-	-
SVCAM1 [134-550 ng/ml] **[soluble vascular adhesion molecule]**					
SVCAM 1	488.4±87.8*	469.3±83.3*	488.5±73.5*	489.8±61.2*	0.32
SVCAM 2	568.4±72.9*	533.5±54.1*	550.7±46.5*	546.4±82.8*	0.41
SVCAM 3	585.2±68.3*	557.7±55.2	550.7±46.5	589.9±44.2	0.41
SVCAM 4	525.9±46.7	518.2±88.8	540.3±41.6	575.2±37.7	0.19
P [in group]	*	*	*	*	-
SICAM [152-362 ng/ml] **[soluble intercellular adhesion molecule]**					
SICAM 1	135±32.4*	142.4±26.4*	146.6±27.2*	131.6±31*	0.62
SICAM 2	157±34.8*	157.4±25.6*	177.3±25.6*	154.1±24.6*	0.39
SICAM 3	170.5±41.9*	165.8±33.5*	184.7±23.3*	180.6±43.2*	0.45
SICAM 4	152.2±19.2	157.4±35.7	181.2±26.8	135.2±25.4*	**0.04**
P [in group]	*	*	*	*	-
E-SELECTIN [20.3-105.5 mg/L]					
ESELECTIN 1	31.8±12.9*	30.9±7.6*	32.1±14.5*	22.7±9.3*	0.47

ESELECTIN 2	21.7±6.5*	22.2±5.8*	25.1±12.9*	19.2±8.1*	0.8
ESELECTIN 3	30.3±13.2	29.5±9.3	28.2±11.6	21.7±9.9	0.76
ESELECTIN 4	25.3±9.9*	28.2±6.9	23.8±9.7	21.7±9.9	0.76
P [in group]	*	*	*	*	-
P-SELECTIN [84-213 mg/L]					
P-SELECTIN 1	237.8±110.4	174.4±49.0	169.4±62.9	195.5±91.7	0.21
P-SELECTIN 2	160.3±48.0	191.8±86.3	171.4±71.7	188.0±124.1	0.76
P-SELECTIN 3	186.3±55.4	205.6±116.8	198.7±111.7	168.0±73.8	0.93
P-SELECTIN 4	152.7±73.1	159.5±44.7	164.6±116.4	162.5±92.7	0.98
P [in group]	-	-	-	-	-
Interleukin 6 [0-50 pg/ml]					
IL6 1	29.2±19.5*	21.4±4.3*	30.4±24.2*	39.6±33.2*	0.41
IL6 2	254±219.8*	328±180.1*	400.0±157.3*	401.4±206.7*	0.3
IL6 3	128.1±103.3*	157.2±120.9*	199.4±120.9*	229.9±145.1*	0.28
IL6 4	53.4±18.3*	46.9±13.1*	49±13.1*	77±43.7*	0.07
P [in group]	*	*	*	*	-
ENDOTHELIN [0.36-1.14 pg/ml]					
ENDOTELIN 1	0.69±0.43*	0.50±0.16*	0.52±0.29*	0.47±0.28*	0.38
ENDOTELIN 2	0.37±0.23*	0.21±0.09*	0.26±0.14*	0.21±0.12*	0.12
ENDOTELIN 3	0.49±0.26	0.36±0.29	0.43±0.22	0.56±0.32	0.29
ENDOTELIN 4	0.63±0.29	0.44±0.32	0.56±0.25	0.60±0.36	0.65
P [in group]	*	*	*	*	-
Interleukin 1β [0-17 pg/ml]					
IL1β 1	62.3±41.5	50.8±31.0	30.8±12.3	43.7±22.6	0.17
IL1β 2	34.1±15.4	60.1±30.3	36.2±18.5	46.2±19.7	0.06
IL1β 3	38±11.2	37.1±18.4	28.4±11.5	34.9±26.8	0.4
IL1β 4	42.5±16.2	33.4±15.9	28.1±16.5	25.1±16.9	0.12
P [in group]	-	-	-	-	-
	TNFα [4.6-12.4 pg/ml]				
TNF 1	8.2±6.2*	5.5±2.1*	6.7±3.6*	9.6±7.1	0.37
TNF 2	13.3±8.0*	14.8±11.0*	13.7±7.9*	21.9±12.7	0.25
TNF 3	9.7±5.4	8.8±6.3	11.1±10.8	15.7±12.7	0.33
TNF 4	9.3±3.6	11.4±4.2*	9.4±2.7*	9.7±3.5	0.61
P [in group]	*	*	*	-	-
	Platelet Activating Factor [72-160 pg/mol]				
PAF 1	184.4±116.8*	200.6±43.6*	119.5±64.6*	192.8±81.0*	0.17
PAF 2	89.1±62.7*	77.5±44.5*	60.9±25.4*	98.5±50.7*	0.49
PAF 3	140.5±91.5*	108.7±39.7*	83.4±24.3*	108.5±52.9*	0.15
PAF 4	188.6±102.4	141.6±47.1*	80.0±32.2	187.5±90.4	**0.03**
P [in group]	*	*	*	*	-
Myeloperoxidase [1.45-72.67 ng/ml]					
MPO 1	21.8±15.9*	18.5±13.6*	11.5±6.0*	17.8±7.8*	0.22
MPO 2	39±29.1*	34.2±30.5*	47.3±30.9*	31.1±11.6*	0.54
MPO 3	38.9±25.6*	36.6±26.9	32.5±23.7*	46.1±33.4	0.66
MPO 4	27.9±17.7	36.8±20.6	24.7±15.6*	37.9±55.2	0.7
P [in group]	*	*	*	*	-
APELIN [1.01-2.38 ng/ml]					

APELIN 1	1.1±0.47*	1±0.42*	1.6±0.47*	0.7±0.14*	**0.002**
APELIN 2	0.6±0.20*	0.50±0.18*	0.65±0.18*	0.46±0.12*	0.16
APELIN 3	0.93±0.82	0.70±0.20	1.0±0.38*	0.62±0.22*	**0.02**
APELIN 4	1.0±0.77	0.79±0.46	1.4±0.95	1.0±0.70	0.21
P [in group]	*	*	*	*	-
Von Wilebrand Factor [0.3-1.57] IU/ml					
VWF 1	1.53±0.37*	2.18±1.77*	1.81±0.64*	1.92±0.52*	0.57
VWF 2	3.0±2.3	3.0±2.0	3.4±2.1*	2.1±0.60	0.45
VWF 3	3.5±1.6*	3.3±1.6	3.4±1.4*	2.8±0.65*	0.77
VWF 4	3.7±1.9*	3.4±0.83*	3.7±1.0*	3.1±0.45*	0.87
P [in group]	*	*	*	*	-
HOMOCYSTEINE [0-11.4µmol/L]					
HOMOCYSTEINE 1	10±5.0	11.1±7.3	10.1±4.5	11.2±7.0	0.95
HOMOCYSTEINE 2	10.6±7.7	10.1±5.3	11.7±5.9	12.0±7.4	0.97
HOMOCYSTEINE 3	9.1±8.8	7.8±5.1	8.5±5.2	4.0±2.1	0.49
HOMOCYSTEINE 4	18.5±18.0	19.8±14.9	13.1±3.8	10.2±5.3	0.58
P [in group]	-	-	-	-	-
ADMA [0.22-0.69 µmol/L] **[Asymmetric dimethyl-L-arginin]**					
ADMA 1	0.64±0.15	0.58±0.9*	0.59±0.17	0.68±0.14*	0.67
ADMA 2	0.63±0.13	0.63±0.11	0.57±0.12	0.63±0.13	0.58
ADMA 3	0.53±0.19	0.44±0.16*	0.49±0.16	0.45±0.15*	0.66
ADMA 4	0.73±0.12	0.64±0.27	0.56±0.11	0.64±0.10	0.35
P [in group]	-	*	-	*	-

Inflammatory cytokine levels according to groups [p<0.05], below each row [*<0.05] in group differences according to the baseline measurement.

Discussion

There is an anxiety related with quickly growing diabetes epidemic which is a significant health problem. It was calculated as 16.5 % [6.5 million adults] in TURDEP II population based survey as a prevalence which was including 26,499 adults in Turkey. The increment rate was 90 % when compared with the TURDEP I study during the last 12 years [21]. Approximately, 30-40 % of patients undergoing coronary artery bypass surgery [CABG] have diabetes mellitus with many have undiagnosed diabetes or impaired glucose tolerance [22, 23]. Furthermore, diabetic coronary artery bypass patients are more probable to have a repeat revascularization procedure. They have a 24% increased risk of secondary procedure for cardiac-related issues, and a 44% higher risk for rehospitalization [24, 25]. Diabetic patients have more diffuse coronary artery disease, impaired fibrinolytic and platelet function and abnormal endothelial function. All these decrease the graft patency's and eventually increase the perioperative mortality [26, 27]. Although these outcomes were thought to be irreversible, it was shown that by achieving glycemic control in patients with diabetes mellitus undergoing CABG surgery, perioperative morbidity and mortality can be reduced, long-term survival improved, and the incidence of recurrent ischemic events decreased [25-27].

Diabetes is a marker for high-risk mortality-morbidity effect and expensive health care after CABG [1]. It is obvious that the increasing proportion of patients needing CABG who have diabetes, are a growing challenge. The oscillations in levels of glycemic control have continued for a research subject in the heterogeneous ICU population. Therefore, regarding the risks and benefits of tight glycemic homeostasis in this specific patient group, it is important to schedule the operating time following the glycemic control. It is so necessary to understand the pathology that exists in this diabetic patient population. Uncontrolled glucose levels particularly in patients who will experience CABG surgery and extracorporeal circulation has more dramatic consequences than any other operative scenario. The response to cardiac surgery and cardiopulmonary bypass with release of cytokines is significant. All of these factors play an important role in glucose metabolism and consequences. Hyperglycemia has numerous deleterious effects as, decreased vasodilation through impaired endothelial nitric oxide generation, increased expression of endothelial adhesion molecules and increased cytokine levels. These changes may reach undesirable response that causes to increased inflammation and organ dysfunction [1-5, 28-32].

Vascular endothelium is not a barrier, it is an organ that plays a main role in vasoregulation, platelet aggregation, leukocyte adhesion, vessel growth and fibrinolysis [27-28]. Endothelium regulates the blood flow according to myocardial need by releasing both vasodilator [NO, prostacyclin] and vasoconstrictive [Endothelin – 1, thromboxane] molecules. Endothelium also protects the internal vascular surface from cellular adhesion. Endothelium derived NO and prostacyclin inhibits platelet aggregation. Endothelial cells are non- adhesive to circulating leucocytes in normal conditions. Endothelium also regulates leukocyte differentiation and smooth muscle differentiation [31]. NO and TGFβ1 inhibits the cell growth while, PAF and Endothelin-1 promotes the cell growth.

Rh-Pat system shows endothelial dysfunction in all patients in diabetic groups [groups 2-4] who underwent coronary bypass surgery. The scores get increased following the surgery and the difference was lost. This could

be the result of the aggressive insulin and antidiabetic treatment used preoperatively. Although we recognized the positive response of endothelial function for the high glucose treatment, it is difficult to realize the duration of the treatment to reach normal endothelial function. The positive inotropic support ratio is higher in diabetic groups, especially it was reached the highest ratio with 50% in group 4. This is another index of detrimental effect of diabetic injury for the coronary artery disease.

Atherosclerosis is the first step of the endothelial dysfunction. Low density lipoproteins and incorporated immune complexes are probably the main cause of endothelial dysfunction. When these molecules are oxidized on the endothelium, it cannot degrade and express surface bound molecules and release cytokines. These molecules cause migration of inflammatory cells to subendothelial space. Endothelial dysfunction occurs by two different mechanisms. First one is the acute mechanism, endothelial cells retracts, Wiedel Palade body's expose P-Selectin and releases Von Willebrand Factor. Second mechanism is characterized by de novo protein synthesis and gene expression of E-selectin, IL8 and ICAM-1 [30-32].

The endothelial function is affected in different therapeutically approaches. Enhanced deposition of VWF, the overexpression of NO synthase and endotelin-1 is demonstrated in animal models after coronary balloon dilatation [32]. In coronary bypass surgery, arterial grafts has better long term results because these conduits has better endothelial layers. They adapts to blood flow changes and preserves antithrombotic states better than venous conduits. Arterial grafts maintains NO and prostacyclin mechanisms [33-34]. In presence of atherosclerosis, platelets express more selectins [P- Selectin], integrins [VCAM] even the endothelium is intact but dysfunctional. The activated platelets releases IL-1 and ICAM-1 to secrete monocyte chemotactic protein-1 [MCAM-1] [35]. In response to inflammatory mediators [IL-1, TNF-α, MCAM-1] that are released from activated monocytes, smooth muscle cells secrete growth factors that enhance atherogenesis. TNF- alpha is early response cytokines mainly produced by activated macrophages [monocytes]. It induces the production of several other inflammatory mediators such as IL-1, IL-6, and colony stimulating factors, prostaglandins, platelet-activating factor [PAF].

Nitric oxide levels did not show any difference among the groups but it decreased significantly in group 1, control group with time. It slightly but none significantly increased in group 3 and 4 that could be explained by the result of insulin treatment. The diabetic groups especially 3 and 4 needed to have important insulin infusions to reach the treatment targets of Portland protocol. İnsulin amount is positively correlated with the levels of apelin and so with the nitric oxide. Apelin also increased especially in group 4 with time. Although it has the lowest value among the groups, it reached a normal level with treatment. Apelin is a member of the adipokine family. It has effects on blood pressure via activation of the endothelial nitric oxide synthase and controlled by insulin resistance, obesity and hyperinsulinemia. In an observational study, serum apelin and vaspin levels were found significantly higher in patients with metabolic syndrome and coronary artery atherosclerosis. It could be used as a specific marker for insulin resistance [25].

Soluble vascular adhesion molecule levels did not differ among the groups but significantly increased in all groups during the follow up. Soluble intercellular adhesion molecule levels reached a significant level at the 4th measurement point [at first postoperative day], with the lowest value at group 4. The measured levels increased gradually in all groups during time. E-selectin, P-selectin, interleukin-6, endothelin, interleukin 1β, TNFα, myeloperoxidase, Von Willebrand factor, homocysteine and ADMA levels did not differ among the groups but changed significantly during the follow up.

Asymmetric dimethyl arginine [ADMA] is an endogenous inhibitor of nitric oxide [NO] synthases. ADMA causes endothelial dysfunction, vasoconstriction, elevation of blood pressure, and aggravation of atherosclerosis. Several studies in humans have revealed that ADMA plasma concentration is elevated in vascular diseases and increases the cardiovascular risk. Homocysteine is another marker of risk of cardiovascular disease. Studies found that for every 5-μmol/L increase in serum homocysteine concentration, the risk of ischemic heart disease increased 20% to 30%. The levels of ADMA decreased first and increased again during the measurement time points but there is not any significant difference in between the groups could be recognized.

In our study there is a significant difference between diabetic and non-diabetic patients in terms of both endothelial function and some of the inflammatory cytokines. The limitation of our study is the small number of patients in groups. It is not quite possible to find a patient with uncontrolled blood glucose level. Majority of the patients had diagnosed diabetic before the surgery and treated. Another limitation was insulin level and insulin resistance of the patients. It could be more valuable to match the results according to insulin resistance and c-peptide level. The glycemic control and insulin treatment may normalized the both endothelial function and homeostasis of mediators.

Many studies demonstrated an association between perioperative hyperglycemia and morbidity in the cardiac surgery patients. The timing of the surgery and the diabetic control are extremely important to reduce the morbidity so, the endothelial function and cytokine levels are important.

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DOI:10.31579/2641-0419/374