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Impact of Glycemic Control on Myocardial Perfusion after Successful Percutaneous Coronary Intervention in Patients with Diabetes Mellitus

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Abstract : Background: Patients with diabetes mellitus have a less favorable clinical outcome at one year after successful stent placement. All adverse outcome measures such as in-stent restenosis occurred more frequently in diabetic than non-diabetic patients. Myocardial perfusion imaging is an excellent indicator for diagnosis of restenosis, estimation of disease progression, and decision of re-intervention.

Aim of the study: To evaluate the impact of glycemic control on myocardial perfusion defects after successful percutaneous coronary intervention of patients with diabetes mellitus receiving insulin versus those receivingoral hypoglycemic agents.

Methods and results: This study was conducted on 100 diabetics patients who underwentpercutaneous coronary intervention as a treatment strategy for revascularization based on positive results of myocardial perfusion imaging [MPI].Our patients were divided into two groups; Group (A): Included 50 patients who received insulin therapy , and Group (B): Included 50 patients who received oral hypoglycemic drugs and diet therapy for glycemic control. After a period of six month with glycemic control in the two groups, We noticed that tight glycemic control(HBbA1c less than 7) had been achieved by insulin group than non-insulin group. Myocardial perfusion imiging followup showed that defect size mean for the same territory after stenting in group 1 was 8.08±7.01 whereas in group 2 was 13.56 ±9.76. Difference between the two groups was statistically significant (P <0.05)which indicate that instent stenosis was higher in non isulin group.

Conclusions: Tight glycemic control by insulin after successful percutaneous coronary intervention decreased the incidence of Instent restenosis compared with less tight control with oral hypoglycemic agents.

Keywords: Acute coronary syndrome; Myocardial perfusion imaging; Diabetes mellitus; Percutaneous coronary intervention.

Introduction

Restenosis after angioplasty and stent implantation has been historically considered the most significant problem in coronary interventional treatment. Drug-eluting stents (DES)have dramatically reduced the rates of restenosis and target lesion revascularization (TLR) compared with bare-metalstents (BMS). However, a low rate of in-stent restenosis(ISR) after DES still exists, and its prevalence is not negligible because the population treated with DES is large [1]

Although the low frequency of ISR events with DES makes clinical investigation difficult, many studies have addressed the incidence, mechanism, predictors, and optimal treatment of DES restenosis. We sought to provide a concise, comprehensive overview of the pathophysiologic mechanisms, clinical presentation, morphologic patterns, and management options of ISR [2]**.**

Among AMI patients with diabetes, those with admission glucose ≥180 mg/dL had a 70% relative increase in the risk of in-hospital death compared with diabetic patients with normal admission glucose values. Similarly, [3]demonstrated a near-linear relationship between higher admission glucose levels and higher rates of left ventricular failure and cardiac death among 2127 patients with ACS[4].

Patients and Methods

A-Patient selection:-

One hundred Ischemic diabetic patients who were presented by stable angina. Their Ages ranged from 40 Years to 75 Years .they underwent PCI as a treatment strategy for revascularization based on positive results of myocardial perfusion imaging.

Our patients were divided into two groups:

- **Group (A):** Included 50 patients who received insulin therapy for glycemic control.
- **Group (B):** Included 50 patients who received oral hypoglycemic drugs and diet therapy for glycemic control

SPECT study had been performed for all patients after 6 months from the coronary intervention to compare between the site and number of perfusion defects before and after the procedure.

B-Laboratory Data:

-Plasma glucose on admission
-Random blood sugar And HBA1C at 0,2,4,6 months during follow up period
-Cholesterol, triglyceride, **LDL, HDL/chol.**

C- Exercise treadmill Tc-99 sestamibi SPECT Scintigraphy:

Each patient in this study was subjected to SPECT study twice, one of them at the begging to prove the diagnosis of IHD and to estimate the percentage of perfusion defect ,and the other one was done to compare the perfusion defects after 6month of glycemic control .

Stress and rest imaging were performed on two separate days, to avoid having residual activity from the first study contaminate the second study.

I-SPECT Analysis:

Qualitative Analysis

The myocardial segments were visually interpreted for the presence of perfusion abnormalities. The septum and anterior segments were considered to correspond to the ***left anterior descending coronary artery***, the inferior and posterior segments were considered to correspond to ***the right coronary artery***. The inferolateral and lateral segments were considered to correspond to the ***circumflex coronary artery***.

An image was considered abnormal if there was a decrease of Tc-99m sestamibi uptake in any of these segments. The presence or absence of reversibility (filling in) in any of these segments was noted as well.

Myocardial segments with diminished Tc-99m sestamibi uptake in the stress images and no evidence of filling-in (reversibility) in the rest images were considered fixed (irreversible) defects denoting on infarction and scar tissue.

Segments with partial reversibility as evidenced by incomplete filling of the initial perfusion defect were

considered partially reversible suggesting the presence of chronic total occlusion.

Segments with complete filling-in were considered completely reversible and suggested the presence of stenosis rather than total occlusion of the corresponding coronary artery.

The evaluation of the defect size pre and post revascularization was based on the defect within the territory of the target vessel.

Quantitative Analysis:

Several approaches had been devoted for the quantitative analysis. One method approached the basis of 17 segments per study [(6)]

The apical, mid, basal short axis, tomograms were divided into six segments each. Mid ventricular long axis was used to assess anteroapical and inferoapical segments. Perfusion percentage was calculated for each coronary artery (LAD, LCx, and RCA) during both stress and rest. [(8)]

SPECT study was considered positive (the patient in need for coronary revascularization) if there was reversible perfusion defects more than 5%.

D-Interventional Data:

Only patients with follow up positive MPI results were subjected to coronary angiography to asses:-

-Instant stenosis &correlation with SPECT study results.
-The occurrence of complications as coronary dissection, abrupt Closure and no reflow will be determined.

E-Statistical Analysis

Descriptive statistics are expressed as mean ± standard deviation (SD) for quantitative data or number (%) for qualitative variables. All data were tested against normality assumption.

Comparison between the mean values of different parameters in the two groups was performed using unpaired student *t* test. While comparison between pre- and post-assessment (treatment) within the same group was performed using paired student *t* test.

Comparison between categorical data was performed using Chi square test. SPSS computer program (version 20 windows) was used for data analysis. P value **< 0.05** less or equal to 0.05 was considered significant.

One-way analysis of variance (ANOVA) with repeated measure was used to compare differences among groups. Differences were considered significant if $P < 0.05$. Pair-wise comparisons using the Bonferroni procedure were administered to evaluate the differences between variables and groups.

Results

A-Demographic data:-

There were concerns regarding confounding factors affecting myocardial blood flow in both groups, such as age, gender, coexisting CAD, lipid disorders, smoking, and hypertension. In our study, we tried to adjust these confounders, to exclude any possible effect on glycemic control curve.

Inorder not to affect the follow up results as much as we can,the baseline glycemic readings espicially HbA1c were convergent with radiological data and all myopathiec patient were excluded. **Table (1a),Table (1b)**

Table (1a):Baseline characteristics across groups

Variable	Group 1=50 mean(SD)	Group 2=50 mean(SD)	p value
Age **(years)**	59.46(10.57)	59.32(10.32)	0.947
Waist **(cm)**	109.56 (16.23)	108.24(15.58)	0.679
Height **(cm)**	169.62(11.22)	169.80(10.94)	0.935
Weight **(kg)**	89.02(17.82)	88.18(17.27)	0.811
DBP **(mm.Hg)**	85.34(10.54)	86.24 (11.47)	0.684
SBP **(mm.Hg)**	136.60(15.20)	138.46 (15.36)	0.544

Table (1b):Baseline characteristics across groups

Variable		Group 1=50 N(%)	Group 2=50 N(%)	p value
Sex	Male	32 (64.0%)	27 (54.0%)	0.309
	Female	18 (36.0%)	23 (46.0%)	
Smoking	Smoker	31 (62.0%)	30 (60.0%)	0.838
	Non-Smoker	19 (38.0%)	20 (40.0%)	
Family History	Negative	17(34.0%)	22 (44.0%)	0.305
	Positive	33 (66.0%)	28 (56.0%)	

B-Laboratory Data:-

In group (1), mean baseline fasting blood sugar (FBS0) was199.70 ± 38.35 mg/dl while the mean baseline 2 hour post prandial blood sugar (PPBS0) was 248.14 ± 37.31 mg/dl, whereas the mean baseline HbA1c0 was 7.41 ± 0.726%.

In group (2), mean baseline fasting blood sugar (FBS0) was 203.71 ± 18.31 mg/dl, while the mean baseline 2 hour post prandial blood sugar (PPBS0) was 257.78 ± 52.47 mg/dl whereas the mean baseline HbA1c0 was 7.48 ± 0.571%. Difference between the two groups was statistically insignificant (P > 0.05).

C-Radiological Data :-

Echocardiography study show that, in group (1) mean baseline of ejection fraction (EF) was 58.78 ± 7.7 %, while in group (2), mean baseline ejection fraction (EF) was 59.9 ± 7.63 %. Difference between the two groups was statistically insignificant (P >0.05) **Table (2).**

Table (2):Comparison of echocardiography between both groups.

Variable		Group 1=50	Group 2=50	p value
EF % mean(SD)		**58.78(7.70)**	**59.90(7.63)**	**0.467**
RWMA	No **N(%)**	7 (14.0%)	13 (26.0%)	0.134
	Yes **N(%)**	43 (86.0%)	37 (74.0%)	

Regarding comparing defect territory between both groups; in group (1) 25 patients had LAD defect territory (50%),6 patients had LCX (12%), 7 patients had OM (14%) and 12 patients had RCA defect (24%).

While in group (2) 25 patients had LAD defect territory (50%),11 patients had LCX (22%), 7 patients had OM (14%) and 7 patients had RCA defect (14%). Difference between the two groups was statistically insignificant (P > 0.05)

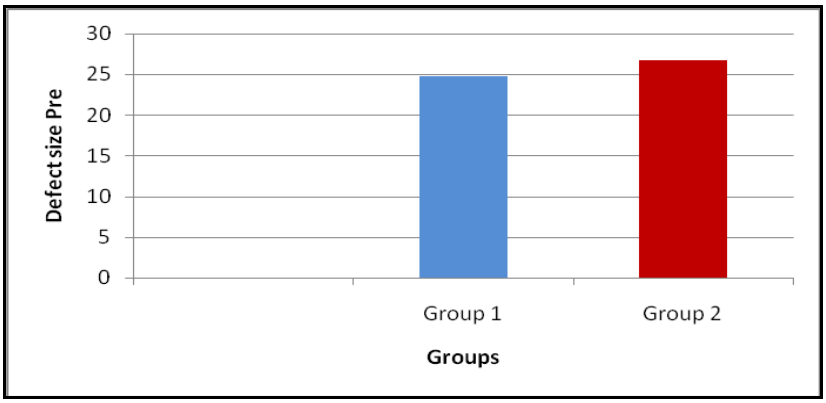

Figure (1):Mean values of defect size pre among both groups.

Baseline defect size mean in group 1 was 24.84±4.63 whereas in group 2 was 26.72 ±6.58. Difference between the two groups was statistically insignificant (P > 0.05) **Figure (1).**The patients in both group had nonstatistically significant difference regarding the perfusion defect size and site and the territory of the occluded artery was detrmined at the start**.**

Mean value of stent length per patient in group 1 was 20.20 ± 5.26 mm, while mean value of stent length per patient in group 2 was 20.24 ± 5.39 mm. Difference between the two groups was statistically insignificant (P > 0.05).

Mean value of stent diameter per patient in group1 was 3.24 ± 0.32 mm, while mean value of stent diameter per patient in group 2 was 3.22 ± 0.32 mm. Difference between the two groups was statistically insignificant (P > 0.05).

Follow up after 6 months

a- LaboratoriesFollow up: (PPBS2,4,6, FBS2,4,6, HBAIC3,6)

Patients were followed up at 2, 4 and 6 months for PPBS, FBS and HbA1c.

Two months post treatment; In group (1), mean baseline fasting blood sugar (FBS0) was 199.70 ± 38.35 mg/dl while the mean baseline 2 hour post prandial blood sugar (PPBS0) was 248.14 ± 37.31 mg/dl, whereas the mean baseline HbA1c0 was 7.41 ± 0.726 mg/dl. In group (2), mean baseline fasting blood sugar (FBS0) was 203.71 ± 18.31 mg/dl, while the mean baseline 2 hour post prandial blood sugar (PPBS0) was257.78 ± 52.47 mg/dl whereas the mean baseline HbA1c0 was 7.48 ± 0.571 mg/dl. Difference between the two groups was statistically insignificant (P > 0.05) (Table3).

At 4 months post treatment; In group (1), mean baseline fasting blood sugar (FBS0) was 199.70 ± 38.35 mg/dl while the mean baseline 2 hour post prandial blood sugar (PPBS0) was 248.14 ± 37.31 mg/dl, whereas the mean baseline HbA1c0 was 7.41 ± 0.726 mg/dl. In group (2), mean baseline fasting blood sugar (FBS0) was 203.71 ± 18.31 mg/dl, while the mean baseline 2 hour post prandial blood sugar (PPBS0) was257.78 ± 52.47 mg/dl whereas the mean baseline HbA1c0 was 7.48 ± 0.571 mg/dl. Difference between the two groups was statistically insignificant (P > 0.05) (Table 3).

Final follow Two months post treatment; In group (1), mean baseline fasting blood sugar (FBS0) was 199.70 ± 38.35 mg/dl while the mean baseline 2 hour post prandial blood sugar (PPBS0) was 248.14 ± 37.31 mg/dl, whereas the mean baseline HbA1c0 was 7.41 ± 0.726 mg/dl. In group (2), mean baseline fasting blood sugar (FBS0) was 203.71 ± 18.31 mg/dl, while the mean baseline 2 hour post prandial blood sugar (PPBS0) was257.78 ± 52.47 mg/dl whereas the mean baseline HbA1c0 was 7.48 ± 0.571 mg/dl. Difference between the two groups was statistically insignificant (P > 0.05).

Table (1):Comparison of glycemic control between both groups

Variable		Group 1=50 Mean(SD)	Group 2=50 Mean(SD)	p value
PPBS (units)	**2**	199.02**(**31.27**)**	290.02**(**40.92)	**0.001**
	4	189.34**(**29.17**)**	288.60**(**47.10**)**	**0.001**
	6	195.30**(**28.76**)**	288.12**(**42.17**)**	**0.001**
FBS (units)	**2**	178.74**(**23.83**)**	203.32**(**18.34**)**	**0.001**
	4	177.82**(**22.42**)**	203.98**(**18.64**)**	**0.001**
	6	176.48**(**22.69)	200.48**(**15.49**)**	**0.001**
HbA1C %	**3**	7.09**(**0.79**)**	8.65**(**1.01**)**	**0.001**
	6	6.94**(**0.75**)**	8.58**(**1.05)	**0.001**

We noticed that tight glycemic control had been achieved by insulin group than non insulin group.

b-SPECT follow up:-

Myocardial perfusion imiging followup showed that defect size mean in group 1 was 8.08±7.01 whereas in group 2 was 13.56 ±9.76. Difference between the two groups was statistically significant (P <0.05).

Table (4):Comparison of defect size between both groups after 6 month

Variable	Group 1=50	Group 2=50	p value
Defect size post (mm) Mean(SD)	8.08(7.01)	13.56(9.76)	0.002

In group1, five patients were supjected to coronay intervension, one patient (20%) had diffuse lesion while four patients (80%) had focal lesion, PTCA for three of them was done and stenting for the other two paients had done.

In group2, nine patients were supjected to coronay intervension, five patients (55.6%) had diffuse lesion while four patients (44.4%) had focal lesion, PTCA for three of them was done and stenting for another three patients & the last three patients were referd to CABG.**Table (5).**

Table (5):Results of coronary intervension between both groups

Variable		Group 1=50 N(%)	Group 2=50 N(%)	p value
ISR	Diffuse	1(20%)	5(55.6)	
	Focal	4(80%)	4(44.4%)	0.301
Treatment	CABG	0(0%)	3(33.3%)	
	PTCA	3(60%)	3(33.3)	
	STENTING	2(40%)	3(33.3)	0.326

4-Discussion

Aiming to clear answer to the question about the best way of glycemic control strategy for diabetic patients, we performed this study on 100 patients. All our patients were diabetics who underwent PCI as treatment strategy for revascularization based on positive results of myocardial perfusion imaging.

Our patients were divided into two groups:

- **Group (A):** Included 50 patients who received insulin therapy for glycemic control.
- **Group (B):** Included 50 patients who received oral hypoglycemic drugs and diet therapy for glycemic control

Myocardial perfusion imiging followup showed that defect size mean in group 1 was 8.08±7.01 whereas in group 2 was 13.56 ±9.76. Difference between the two groups was statistically significant (P <0.05)

In group1, five patients were supjected to coronay intervension, one patient (20%) had diffuse lesion while four patients (80%) had focal lesion, PTCA for three of them was done and stenting for the other two paients had done.

In group2, nine patients were supjected to coronay intervension, five patients (55.6%) had diffuse lesion while four patients (44.4%) had focal lesion, PTCA for three of them was done and stenting for another three patients & the last three patients were referd to CABG.

This is explained by hyperglycemia which directly causes endothelial dysfunction by decreasing the production of endothelium-derived relaxing factor, increasing oxidative stress by vascular protein glycation and free radical formation, and decreasing prostacyclin production. Also, lipoprotein abnormalities may impair endothelium-dependent relaxation. All these mechanisms may also lead to a pronounced intimal hyperplasia, the main mechanism of restenosis in diabetic patients.

Hong JA, et al [5] followed 152 coronary stent diabetic patients. Single-photon emission computed tomography (SPECT) performed five months after stenting showed reversible perfusion defects in 47 patients; 70% of diabetic patients were on hypoglycemic drugs with diet only. Adverse events (MI or death) occurred in 28% of patients, including death in 15% ,compared to 13% of adverse events in insulin group (MI or death).(5)

Albrecht T et al [7] who discussed the association of glycemic control with mortality in patients with diabetes mellitus undergoing percutaneous coronary intervention where 3008 patients with diabetes mellitus undergoing percutaneous coronary intervention between 1998 and 2006 were identified from their institutional database. (7)

Characteristics and outcomes of patients were compared based on HbA1c categories (≤7%, 7.1%-8.0%, 8.1%-9.0%, 9.1%-10.0%, and >10.0%).Among 3008 patients, 1321 had HbA1c ≤7%, 782 with HbA1c 7.1% to 8.0%, 401 with HbA1c 8.1% to 9.0%, 229 with HbA1c 9.1% to 10.0%, and 275 with HbA1c >10%. On multivariable Cox proportional hazards modeling, survival analysis demonstrated a trend toward higher mortality with higher HbA1c, which was primarily seen among non insulin users.

Conversely, the **Stella et al** [10] suggested that intensive diabetic control was disadvantageous in patients with long-standing diabetes and established CAD. They observed that HgbA1c level had less apparent effect on the coronay circulation suggesting that when the microcirculation has been irreversibly affected by chronic glycemic elevations, there may be no benefit to achievement of tighter glycemic control.

The findings of our study regarding insulin therapy and ISR were disagreed with **McCallister BD** [11] who found insulin requiring diabetics relative to non-insulin requiring diabetics to have high rates of restenosis as 28% versus 17.6% and lower cardiac event free survival as 60% versus 70% poststenting.

Staehr P, et al [14] showed higher mortality in insulin requiring diabetics than non insulin requiring diabetics as 9.3% versus 2.4%, after 13 months follow up post PCI , also found higher mortality post PCI in insulin requiring diabetics than non insulin requiring diabetics as 3.05% versus 1.75%. **Staehr P, et al** [14] explained the role of insulin in the pathogenesis of ISR as: Stimulation of smooth muscle cell migration and proliferation. Insulin stimulates extracellular matrix formation. Introduction of coronary spasm. Insulin decrease fibrinolysis by producing more PAI-1 which enhances thrombosis at stent struts.(14)

5-Conclusions

- Tight glycemic control by insulin after successful percutaneous coronary intervention decreased the incidence of Instant restenosis compared with less tight control with oral hypoglycemic agents**.**
- Percentage of perfusion defects were highly significant predictors of ISR in diabetic patients.

6-Recommendation

For diabetic patients who were recently subjected to PCI it is recommended to use insulin therapy instead of oral hypoglycemic drugs for glycemic control in the first six month after coronary intervention.

7-Study Limitations

- The small number of the study is a limiting factor to consolidate our findings and to validate the relationship equation derived from its results.
- Short duration for follow up. As longer duration for follow up would have been a plus to make the results more conclusive. Lack of measure of fasting serum insulin for detection of hyperinsulnimia.

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