

## Correlation between Angiographic in-Stent Restenosis and Post-procedural Glycosylated Hemoglobin Level in Diabetic Patients underwent Percutaneous Coronary Intervention with Drug eluting Stent

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### الخلاصة:

#### خلفية الموضوع:

مرض السكري، شائع، معقد، وهو اضطراب أيضي مزمن ويعتبر كعامل خطورة مهم لأمراض القلب والأوعية الدموية، يمكن تعديله ويعتبر عامل تخميني مستقل لتكرار تضيق الشبكة بعد إجراء عملية التداخل التاجي عن طريق الجلد.

#### الأهداف:

تحديد تأثير مستوى (HbA<sub>1c</sub>) على نسبة تردد تضيق الشبكة الدوائية لدى مرضى السكري الذين أجريت لهم عملية التداخل التاجي الاختياري عن طريق الجلد .

#### المرضى والطرق:

تم تقييم 89 مريض كان قد اجري لهم عملية التداخل التاجيالاختياري عن طريق الجلد وتم وضع شبكة دوائية لهم، ادخلوا إلى المركز العراقي لأمراض القلب لغرض إجراء قسطرة الشرايين التاجية الاختيارية مع او بدون تداخل قسطاري للفترة بين نيسان 2013- مايس 2014 وتم تقييم حالتهم جيدا. تم استثناء 26 مريض من الدراسة لأسباب متعددة . تم تقييم حالة 63 مريض لمعرفة انفتاح الشبكة خلال عملية إجراء القسطرة. 29 مريض كانت الشبكة لديهم غير متضيقة. 34 مريض كان لديهم تضيق في الشبكة وتم إجراء تحليل HbA<sub>1c</sub> لهم. يعرف مرض السكري عندما يكون تركيز السكر بالدم في حالة الصوم  $\leq 126$  dl/mg، نسبة السكر العشوائي  $\leq 200$  dl/mg مع أعراض إحصائية أو وجود تاريخ مرضي موجب لمرض السكري مع حمية غذائية أو في حالة استعمال الأدوية المخفضة للسكر عن طريق الفم أو زرق الأنسولين أثناء فترة الرقود في المستشفى. تم تصنيف مرضى السكري إلى مجموعتين طبقا إلى معدل مستوى HbA<sub>1c</sub>، مستوى سيطرة سكري جيد ( $\geq 7$  %HbA<sub>1c</sub>) ومستوى سيطرة سكري ضعيف ( $< 7$  %HbA<sub>1c</sub>).

#### النتائج:

تضيق الشبكة موجود عند 19 (55.9%) ذكور و15 (44.1%) اناث. في الجدول رقم 2 وجد ذو قيمة بأن 27 (79.45%) من المرضى المصابين بالسكري ولديهم مستوى سيطرة ضعيف هم أكثر أصابة بتضيق الشبكة الدوائية (P.value <0.005). الجدول رقم 4، تضيق الشبكة أكثر حدوثا في الشريان الأمامي النازل (الجزء الوسط والبعيد) بعد إجراء عملية التداخل التاجي الاختياري في 20 مريض من اصل 27 في حالة وجود مستوى سيطرة ضعيف على السكري (P.value <0.005).

#### الاستنتاجات:

تشير هذه الدراسة الى وجود ارتباط وثيق بين مستوى سيطرة ضعيف على السكري وبين زيادة تضيق الشبكة الدوائية عند المصابين بمرض السكري . ان مستوى السيطرة الضعيف على السكري يساعد على تضيق الشبكة الدوائية عند إجراء التداخل القسطاري في الشريان التاجي الأمامي النازل (الجزء الوسط والبعيد) لدى المصابين بمرض السكري.

#### Abstract:

**Background:** Diabetes mellitus is a common, complex, and chronic metabolic disorder act as an important modifiable risk factor for cardiovascular disease and has been shown to be an independent predictor for in-stent restenosis after percutaneous coronary intervention.

**Objectives:** To determine the influence of HbA<sub>1c</sub> level on the frequency of in-stent restenosis in diabetic patients after elective percutaneous coronary intervention.

**Patients and Methods:** 89 diabetic patients with recurrent ischemia had history of previous percutaneous coronary intervention and stented coronary arteries with drug eluting stent were admitted to the Iraqi Center for Heart Diseases for elective coronary catheterization with or without percutaneous coronary intervention in period between April 2013 and March 2014. All patients were evaluated thoroughly. 26 patients were excluded for different reasons. 63 patients were assessing for stent patency during catheterization. 29 patients with patent stents. 34 patients with in-stent restenosis were investigated with HbA<sub>1c</sub> level. Diabetes mellitus was defined as fasting blood sugar concentration  $\geq 126$  mg/dl, random blood sugar  $\geq 200$  mg/dl with suggestive symptoms or positive history of diabetes mellitus with diet control or use an oral hypoglycemic agent(s) or insulin at the time of admission. Patients with in-stent restenosis were categorized into two groups based on their HbA<sub>1c</sub> level, good glycemic control (HbA<sub>1c</sub>  $\leq 7\%$ ) and poor glycemic control (HbA<sub>1c</sub>  $> 7\%$ ).

**Results:** Males represent 19 (55.9%) and females represent 15 (44.1%) of diabetic patients with in-stent restenosis. In table 2, 27 (79.45%) diabetic patients with poor glycemic control more likely to have in-stent restenosis than 7 (20.6%) patients with good glycemic control, P.value  $< 0.005$ . In table 4 in-stent restenosis more likely to occur in non-proximal left anterior descending artery after elective PCI in 20 out of 27 patients with poor glycemic control, P.value  $< 0.005$ .

**Conclusions:** Our study reveals that there is a correlation between poor glycemic control and increased frequency of in-stent restenosis of drug eluting stents in diabetic patients. Poor glycemic controlled diabetic patients are more liable for in-stent restenosis of drug eluting stents after intervention in non-proximal left anterior descending artery.

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### Introduction:

Atherosclerosis defined as chronic inflammatory disease caused by sustained injury to the vascular wall often initiate in childhood, usually manifested in middle or old age and remains the major cause of death and premature disability in developed societies<sup>(1)</sup>.

Arterial stenosis due to atherosclerosis tends to occur focally, typically in certain predisposed regions, often form at branching points of arteries, regions of disturbed blood flow<sup>(2)</sup>. Atherosclerotic cardiovascular diseases (CVD) refers to the diffuse condition of

atherothrombosis, involving coronary arteries, carotid, vertebral, cerebral arteries, aorta, and peripheral arteries<sup>(3)</sup>. The clinical expressions of atherosclerosis may be chronic, as in the development of stable, effort-induced angina pectoris and reproducible intermittent claudication. Alternatively, a dramatic acute clinical event, such as myocardial infarction, stroke, or sudden cardiac death, may first herald the presence of atherosclerosis<sup>(4)</sup>.

Major non modifiable risk factors of atherosclerosis including male gender, age (male  $\geq 45$  years, female  $\geq 55$  years) and positive family history of premature

coronary heart diseases (CHD) (male first-degree relative < 55 years, female first-degree relative < 65 years)<sup>(5)</sup>.

The modifiable conventional risk factors including:

1. Smoking: ischemic heart disease causes 35% to 40% of all smoking-related deaths. Smoking affects atherothrombosis through several other mechanisms<sup>(6)</sup>.

2. Hypertension: blood pressure  $\geq 140/90$  mmHg or patient on antihypertensive medication<sup>(8)</sup>.

3. Dyslipidemia with elevated low density lipoprotein (LDL), reduced high density lipoprotein (HDL) [ $< 1.0$  mmol/L ( $< 40$  mg/dL)], and impairment of apolipoprotein levels: cross-sectional population studies have consistently revealed a relationship between serum cholesterol levels and CHD death<sup>(10)</sup>.

4. Metabolic syndrome, insulin resistance, and diabetes mellitus (DM): metabolic syndrome is a complex factor that arises from insulin resistance accompanies abnormal adipose deposition and function. It is a risk factor for CHD as well as for DM and fatty liver<sup>(12)</sup>.

5. Mental stress, depression, and cardiovascular risk: both depression and mental stress predispose to increased vascular risk. The adrenergic stimulation of mental stress can augment myocardial oxygen requirements and aggravate myocardial ischemia<sup>(13)</sup>.

6. Lifestyle risk factors, including: obesity ( $BMI \geq 30$  kg/m<sup>2</sup>), physical inactivity and atherogenic diet: in both men and women, exercise levels achieved with as little as 30 minutes of walking daily provide major cardiovascular benefits<sup>(15)</sup>. Regular exercise lowers glycosylated hemoglobin (HbA<sub>1c</sub>), CRP levels and improves coronary endothelial function.

7. Emerging risk factors (dysregulated coagulation or fibrinolysis

system, increase homocysteine and lipoprotein (a) level, prothrombotic factors, proinflammatory factors): as fibrinogen levels and CRP that correlate with coronary risk and provide information regarding coronary risk independent of the lipoprotein profile.

In CAD, the hypoxic stimulus of repeated bouts of ischemia characteristically induces formation of collateral vessels in the myocardium, by contrast, we now appreciate that many lesions that cause acute or unstable atherosclerotic syndromes, particularly in the coronary circulation, may arise from atherosclerotic plaques that do not produce a flow-limiting stenosis<sup>(20, 21)</sup>.

DM is an important modifiable risk factor for CVD, defines as a common, complex, and chronic metabolic disease characterized by hyperglycemia and associated disturbance in carbohydrate, fat, and protein metabolism according to American diabetes association (ADA)<sup>(24)</sup>.

T2DM is the most common form of DM and is associated with family history of DM, older age, obesity, and sedentary life style. T2DM account about 90-95% of DM cases in CAD population. The presences of T1DM or T2DM confer a marked increase the risk of CAD development. CAD account for 80 % of death among patients with DM compare with 30% in those without DM<sup>(25)</sup>.

HbA<sub>1c</sub> normally less than 6%, and provides accurate measure of glycemic control over a period of 3 months. HbA<sub>1c</sub> formed progressively and irreversibly in the red blood cell during its life and reflect the mean fasting and postprandial plasma glucose levels<sup>(26)</sup>.

Measurement of HbA<sub>1c</sub> as percent of total hemoglobin, provide a valuable method for assessing the long control of DM, since HbA<sub>1c</sub> level approach normal

values as diabetic respond to treatment<sup>(28)</sup>.

Currently, the ADA recommends a target HbA<sub>1c</sub> < 7% for most diabetic patients and < 6% for selected individuals<sup>(31)</sup>. Coronary artery lesion can be classified by using society of cardiovascular of angiography and intervention (SCAI) or American Heart Association (AHA) and American College of Cardiology (ACC) classification<sup>(32)</sup>.

After the inception of balloon angioplasty for the treatment of CAD, two major limitations become apparent; the first one was abrupt vessels closure which occurs in 5-8% of cases and result in significant morbidity including acute myocardial infarction (AMI) and emergency CABG. The second major limitation was restenosis, which occurred in up to 30-40% of cases<sup>(33)</sup>. Coronary stents were designed to address these limitations with baremetal stent (BMS) by scaffolding dissections as well as increasing acute gain, preventing elastic recoil, and reducing the rate of restenosis. While stents dramatically reduce the incidence of restenosis after balloon angioplasty, in-stent restenosis (ISR) remain a significant problem until introduction of drug eluting stent (DES)<sup>(34)</sup>.

ISR define as reduction in the lumen diameter after PCI as a result of neointimal tissue proliferation in response to arterial damage<sup>(36)</sup>. DM considered as a strong predictor for ISR.<sup>(37)</sup>

There are two types of restenosis: angiographic restenosis (AR) and clinical restenosis (CR).

AR defined as  $\geq 50\%$  luminal narrowing at follow up angiography. ISR

with BMS occur in approximately 20-30%, and 8-12% in DES<sup>(39)</sup>. CR is defined as recurrent angina or angina equivalent symptoms after PCI. Early restenosis due to elastic recoil while late is related more to remodeling. In contrast to ST, CR generally develops within the first 3 to 9 months after PCI & presents most commonly as stable angina, though if ignored may progress to unstable angina or (rarely) AMI<sup>(40)</sup>. Peak late lumen loss occurs between 6-9 months after stent implantation and then tends to decrease over long term.

CR describe as<sup>(38)</sup>:

Diameter stenosis  $\geq 50\%$  and one of the following:

1. Positive history of recurrent angina pectoris, presumably related to target vessels.
2. Objective signs of ischemia at rest (electrocardiographic changes) or during exercise test (or equivalent), presumably related to target vessels.
3. Abnormal result of any invasive functional diagnostic test [e.g., coronary flow velocity reserve, fractional flow reserve (FFR) < 0.80]; IVUS minimum cross sectional area  $4 \text{ mm}^2$  (and  $< 6.0 \text{ mm}^2$  for left main stem) has been found to correlate with abnormal FFR and the need for subsequent TLR.
4. TLR with diameter stenosis  $\geq 70\%$  even in the absence of the previously mentioned ischemic signs or symptoms.

Although the introduction of drug eluting stent (DES) has reduced the rates of restenosis and clinical events after PCI, the diabetes mellitus has been proved to be a strong risk factor for ISR<sup>(43)</sup>, ISR in diabetic still have poorer clinical outcomes compared with non-diabetics<sup>(45)</sup>.

**Aims of the study:**

To determine the influence of HbA<sub>1c</sub> level on the frequency of DES-ISR in diabetic patients after elective PCI.

**Patients and Methods:**

Between April 2013 and March 2014, (89) diabetic patients enrolled in this observational study with history of previous elective PCI and stented coronary artery with DES complaining of ischemic symptoms arrange for elective coronary catheterization with or without PCI who were admitted to the Iraqi Center for Heart Diseases. (26) Patients were excluded for many reasons. The remaining (63) patients were compatible with our selection criteria (type I SCAI lesion of native vessel, patent and not meet criteria of type C lesion according to AHA/ACC) after reviewing previous PCI reports and evaluated thoroughly. (29) Patients with patent stents. Assessment of (34) patients with ISR was done by interventional cardiologist (27 patients with HbA<sub>1c</sub>>7%, and 7 patients with HbA<sub>1c</sub>≤7%) . Patients with unavailable reports or computer disc of previous PCI and patients with PCI and stenting less than 3 months (not period of ISR) not involved in this study.

Exclusion criteria (predictors for restenosis) include:

1. AMI (primary or rescue PCI) at timing of previous PCI
2. Unstable angina (UA) at timing of previous PCI
3. Low body mass index (BMI)
4. Presence of overlapping stent
5. Prior restenosis
6. PCI of proximal left anterior descending artery (LAD)
7. Chronic total occlusion
8. Bifurcational lesion
9. Suboptimal result of previous PCI
10. Age ≥ 65 year
11. Chronic renal failure

12. Type II, III, IV SCAI lesion (native vessel)

**Definitions:**

DM was defined as the fasting blood sugar concentration ≥126 mg/dl, random blood sugar ≥200 mg/dl with suggestive symptoms or positive history of DM with diet control or use an oral hypoglycemic agent(s) or insulin therapy, HbA<sub>1c</sub> ≥ 6.5%<sup>(8)</sup>.

ISR was defined as ≥50% luminal narrowing at angiography after PCI<sup>(16)</sup>.

Good-control group was defined as diabetic patients with HbA<sub>1c</sub> ≤ 7% and poor-control with HbA<sub>1c</sub> > 7%<sup>(23)</sup>.

Proximal LAD start from origin of LAD to first septal branch and non-proximal LAD start from first septal branch to the end of artery. The consents of the patients and the official requirement were taken.

**Results:****1. Age and gender distribution of diabetic patients with DES-ISR:**

34 diabetic patients with ISR enrolled in this study, males were 19 (55.9%) and females were 15 (44.1%), the male to female ratio was 1.2:1. The mean age of males and females were 55.1±1.6 and 50.2±1.3 years respectively (Table 1).

**2. Distribution of ISR according HbA<sub>1c</sub> level and gender:**

HbA<sub>1c</sub> level ≤ 7% seen in 7 (20.6%) patients, and > 7% seen in 27 (79.4%) patients. The mean HbA<sub>1c</sub> level of the diabetic patients with ISR were high and poorly controlled (7.92% ± 1.3%) and P.value <0.005. The mean HbA<sub>1c</sub> level for diabetic males with ISR was (7.28±1.04%), 15 (78.9%) patients with HbA<sub>1c</sub> level > 7%, and 4 (21.1%) patients with HbA<sub>1c</sub> level ≤ 7%, P. value = 0.01. Otherwise mean HbA<sub>1c</sub> level in diabetic females with ISR was

(8.6±1.02%) and 12 (80.0%) patients with HbA<sub>1c</sub> level >7%, and 3 (20.0%) patients with HbA<sub>1c</sub> level ≤7%, P.value=0.02. The duration of stenting {mean ± SD (months)} of ISR for patients with HbA<sub>1c</sub> level ≤ 7% were 8±0.3 and patients with HbA<sub>1c</sub> level > 7% were 8.4±0.1, P.value > 0.05 (Table 2).

### 3. Distribution of patent stent according HbA<sub>1c</sub> level and gender:

HbA<sub>1c</sub> level ≤ 7% seen in 22 (75.9%) patients and > 7% seen in 7 (24.1%) patients. The mean HbA<sub>1c</sub> level of the diabetic patients with patent stent were good controlled (6.8±1.20%) and P.value <0.005. The mean HbA<sub>1c</sub> level for diabetic males with patent stent was (6.9±1.03%), 13 (72.2%) patients with HbA<sub>1c</sub> level ≤ 7%, and 5 (27.8%) patients with HbA<sub>1c</sub> level > 7%, P. value = 0.02. Otherwise mean HbA<sub>1c</sub> level for diabetic females with patent stent was (6.6±1.01%), 9 (81.8%) patients with HbA<sub>1c</sub> level ≤ 7%, and 2 (18.2%) patients with HbA<sub>1c</sub> level > 7%, P. value = 0.04. The duration of stenting {mean ± SD (months)} of patent stent for patients with HbA<sub>1c</sub> level ≤ 7% were 7.6±0.4 and patients with HbA<sub>1c</sub> level > 7% were 7.8±0.2%, P.value > 0.05 (not significant), (Table 3).

### 4. Distribution of ISR according to HbA<sub>1c</sub> level and type of artery:

ISR in all patients were more frequent in non-proximal LAD artery followed by right coronary artery (RCA) and circumflex coronary artery (Cx) arteries; 23 (67.6%), 7 (20.6%) and 4 (11.8%) patients respectively. HbA<sub>1c</sub> level > 7% were more frequent in LAD artery,

followed by RCA and Cx; 20 (87.0%) patients, 6 (85.7%) patients and 1 (25.0%) patients respectively. HbA<sub>1c</sub> level ≤ 7% in LAD, Cx and RCA arteries were 3 (13.0%) patients, 3 (75.0%) patients and 1 (14.3%) patients respectively, (P.value < 0.005), (Table 4).

### 5. Distribution of ISR in males according to HbA<sub>1c</sub> level and type of artery:

ISR in male patients were more frequent in non-proximal LAD artery followed by RCA and Cx arteries; 11 (57.9%), 6 (31.6%) and 2 (10.5%) patients respectively. HbA<sub>1c</sub> level > 7% were more frequent in LAD artery, followed by RCA, and Cx; arteries were 9 (81.9%) patients, 5 (83.4%) patients and 1 (50.0%) patients respectively. HbA<sub>1c</sub> level ≤ 7% in LAD, Cx and RCA; were 2 (18.1%) patients, 1 (50%) patients and 1 (16.7%) patients respectively, (P.value < 0.005), (Table 5).

### 6. Distribution of ISR in females according to HbA<sub>1c</sub> level and type of artery:

ISR in female patients were more frequent in non-proximal LAD artery followed by Cx and RCA arteries; 12 (80.0%), 2 (13.3%) and 1 (6.7%) respectively. HbA<sub>1c</sub> level > 7% were more frequent in LAD artery and RCA; were 11 (91.7%) patients, 1 (100%) patient respectively and no patient with Cx artery. HbA<sub>1c</sub> level ≤ 7% in Cx and LAD; were 2 (100%) patients, 1 (8.3%) patients respectively and no patient with RCA artery, (P.value < 0.005), (Table 6).

**Table 1. Age and gender distribution of diabetic patients with DES- ISR**

Variable	Total no. (%)	Age, mean $\pm$ SD
Male	19 (55.9)	55.1 $\pm$ 1.6
Female	15 (44.1)	50.2 $\pm$ 1.3
Total no. (%)	34 (100.0)	
Male to female ratio	1.2:1	

Table 2. Distribution of ISR according HbA<sub>1c</sub> level and gender

Gender	Total no. (%)	$\leq 7\%$	$> 7\%$	Mean HbA <sub>1c</sub>	<i>p</i>
Male no. (%)	19 (55.9)	4 (21.1)	15 (78.9)	7.28 $\pm$ 1.04	0.01
Female no. (%)	15 (44.1)	3 (20.0)	12 (80.0)	8.6 $\pm$ 1.02	0.02
Total no. (%)	34 (100.0)	7 (20.6)	27 (79.4)	7.92 $\pm$ 1.30	< 0.005
Duration of stenting mean $\pm$ SD (months)	8.2 $\pm$ 0.2	8 $\pm$ 0.3	8.4 $\pm$ 0.1		

*P. value < 0.05 considered significant*

Table 3. Distribution of patent stent according HbA<sub>1c</sub> level and gender

Gender	Total no. (%)	$\leq 7\%$	$> 7\%$	Mean HbA <sub>1c</sub>	<i>p</i>
Male no. (%)	18 (62.7)	13 (72.2)	5 (27.8)	6.9 $\pm$ 1.03	0.02
Female no. (%)	11 (37.3)	9 (81.8)	2 (18.2)	6.6 $\pm$ 1.01	0.04
Total no. (%)	29 (100.0)	22 (75.9)	7 (24.1)	6.8 $\pm$ 1.20	< 0.005
Duration of stenting mean $\pm$ SD (months)	7.7 $\pm$ 0.3	7.6 $\pm$ 0.4	7.8 $\pm$ 0.2		

Table 4. Distribution of ISR according to HbA<sub>1c</sub> level and type of artery

	Total no. (%)	$\leq 7\%$	$> 7\%$	P.value
LAD no. (%)	23 (67.6)	3 (13.0)	20 (87.0)	< 0.005
Cx no. (%)	4 (11.8)	3 (75.0)	1 (25.0)	> 0.05
RCA (%)	7 (20.6)	1 (14.3)	6 (85.7)	> 0.05
Total no. (%)	34 (100.0)	7 (20.6)	27 (79.4)	< 0.005

*LAD= non-proximal LAD*

Table 5. Distribution of ISR in males according to HbA<sub>1c</sub> level and type of artery

	Total no. (%)	≤ 7%	> 7%	P.value
<b>LAD no. (%)</b>	11 (57.9)	2 (18.1)	9 (81.9)	< 0.005
<b>Cx no. (%)</b>	2 (10.5)	1 (50.0)	1 (50.0)	> 0.05
<b>RCA (%)</b>	6 (31.6)	1 (16.7)	5 (83.4)	> 0.05
<b>Total no. (%)</b>	<b>19 (100.0)</b>	<b>4 (21.1)</b>	<b>15 (79.0)</b>	<b>0.01</b>

**Table 6. Distribution of ISR in females according to HbA<sub>1c</sub> level and type of artery**

	Total no. (%)	≤ 7%	> 7%	P.value
<b>LAD no. (%)</b>	12 (80.0)	1 (8.3)	11 (91.7)	< 0.005
<b>Cx no. (%)</b>	2 (13.3)	2 (100.0)	0 (0.0)	> 0.05
<b>RCA (%)</b>	1 (6.7)	0 (0.0)	1 (100.0)	> 0.05
<b>Total no. (%)</b>	<b>15 (100.0)</b>	<b>3 (20.0)</b>	<b>12 (80.0)</b>	<b>0.02</b>

### Discussion:

DES-ISR is mainly caused by the effects of vascular smooth muscle cell proliferation, migration and neointimal hyperplasia. Immediately after DES deployment and as part of response to mechanical injury, the endothelium is damaged and deposition of platelets and fibrin occur at the site of injury<sup>(48)</sup>. DES-ISR occurs lately over months at the location around stent struts by chronic inflammatory phase with neointimal proliferation and hyperplasia that increasing after 3 up to 6-9 months after deployment (sometime extending beyond), and a gradual decrease thereafter. An exaggerated vascular proliferation is observed in patients with DM<sup>(49)</sup>.

Our study analyzed post-procedural HbA<sub>1c</sub> level within period between 3-9 months after elective previous PCI with DES in diabetic patients.

A. This study revealed that diabetic patients with poor glycemic control are at high risk of developing ISR for both gender while good glycemic controlled

diabetics showed less rates of ISR depend on new results.

Our explanatory causes for ISR in poor glycemic control are related to impairment of many metabolic, biochemical aspects and chronic hyperglycemia that affect the degree of inflammation and increasing vascular response resulting in renarrowing of implanted DES.

Our findings are supported by results of many studies including:

✓ Study done by Lindsay J, Sharma AK et al<sup>(50)</sup> that showed DES-ISR increase in diabetic patients who had a history of elective PCI with implantation of BMS or DES with poor glycemic control, but with lower frequency of ISR in DES than BMS.

✓ Two important studies<sup>(51)</sup>, done by Corpus RA et al and Briguori C et al, they examined the effect of glycemic control on occurrence of ISR in diabetic patients undergoing elective PCI with DES. They observed lower rates of ISR, cardiac rehospitalization and recurrent angina in good glycemic controlled

patients with increase the rate of MACE in poorly glyceemic control patients.

✓ A cohort study done by Ueda H et al on 206 asymptomatic diabetic patients with DES implantation showed that post-procedural HbA<sub>1c</sub> level is an independent predictor of ISR after follow up<sup>(53)</sup>.

✓ Study done by Cutlip et al also demonstrated that post procedural HbA<sub>1c</sub> concentration of 7% to 8% is associated with a significantly higher risk of ISR and cardiovascular mortality following elective PCI with DES in diabetic patients<sup>(54)</sup>. However, conflicting findings exist on the impacts of intensive glucose control with aggressive HbA<sub>1c</sub> goals on cardiovascular events<sup>(55)</sup>.

✓ Clinical UKPDS trial have already demonstrated that therapies improve glyceemic control decrease the risk of microvascular disease, including retinopathy, nephropathy, and neuropathy<sup>(57)</sup>.

Some studies have results differ than our findings:

❖ Previously published studies done by Hasadai D, Rizza RA et al reporting that post-procedural HbA<sub>1c</sub> level are not considered as a predictor for cardiovascular events and DES-ISR in diabetic patients following successful PCI<sup>(58)</sup> assuming neurohormonal disturbances and coronary endothelial dysfunction in DM.

❖ Ike A, Nishikawa and colleagues<sup>(59)</sup> have recently published a study on the effect of glyceemic control after PCI with DES in diabetic patients with pre-procedural poor glyceemic (HbA<sub>1c</sub> ≥ 6.9 %), they observed that glyceemic control when started at time of PCI and continued afterward for approximately 300 days was not associated with improvement of clinical and angiographic outcomes including ISR. The authors suggested that a so-called “metabolic memory legacy effect” which is a complex of factors increasing the

MACE due to chronic hyperglycemia and adversely affected the clinical and angiographic outcomes in all diabetic patients with pre-procedural poor glyceemic control irrespective to their post-procedural control.

Currently data regarding the impact of insulin therapy on DES-ISR after elective PCI are controversial as reported by Malberg K et al study<sup>(60)</sup> while Abizaid et al<sup>(61)</sup> found an increased rate of DES-ISR and TLR in poorly glyceemic controlled insulin-treated diabetic patients compared with non-diabetic patients.

B. Our study also reveal that DES-ISR in poorly glyceemic controlled diabetic patients have a significant predilection for occurrence after PCI of non-proximal LAD artery for both gender.

The explanatory reasons are related to specific morphological and physiological characteristics of polygonal-shaped endothelial cells of LAD arterial wall and their effects on vascular inflammatory response to DES with exaggerated form.

This finding is supported by results of:

1. Study done by Feinglos MN, Bethel MA et al<sup>(62)</sup>, showing that PCI of LAD artery acts as an important predictor for DES-ISR in poorly glyceemic controlled diabetic patients.

2. Study done by Van den Berghe et al<sup>(63)</sup> proves that intervention of LAD artery play a role in occurrence of DES-ISR in diabetic (irrespective to HbA<sub>1c</sub> level) and nondiabetic patients.

Otherwise, in recently published study done by Lemesle G et al on 952 diabetic patients undergoing PCI of LAD (proximal and non-proximal) with stent implantation, reveal no significant relationship was observed between post-procedural HbA<sub>1c</sub> level and AR<sup>(64)</sup>. The investigators attributed such conflicting finding to usage of DES in their study (70%).

### Conclusions:

In conclusion, our data suggest that good glycemic control (HbA<sub>1c</sub> levels  $\leq 7\%$ ) in diabetic patients who underwent previous elective PCI is beneficial in reducing the risk of DES-ISR. In addition to, poorly glycemic controlled diabetic patients are more liable for DES-ISR of non-proximal LAD artery after elective PCI intervention.

### Recommendations:

Interventional recommendations for diabetic patients undergoing PCI and stenting with DES:

- ❖ Closely follow up diabetic patients undergoing PCI with DES in order to improve glycemic control and achieve normal HbA<sub>1c</sub> level (goal <7 %).
- ❖ This was a single-center experience and larger multi-center studies with large number of patients should confirm our findings.
- ❖ Potential biochemical and serological predictor risk factors for ISR cannot assess in our country and need to be taken in consideration (e.g. DD type of ACE gene, CRP and prior cytomegaly virus).

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