Coronary Instent Restenosis following Bare Metal Stents in Prediabetic Patients

Thesis

Submitted for partial fulfillment of Master degree
in **Cardiology**

By

Hossam El din Abd El Khalek Rasmy

M.B., B.Ch

Under the Supervision of

Professor Doctor/ Mohamed Tarek Zaki
Professor of Cardiology
Faculty of Medicine –Ain Shams University

Professor Doctor/ Khaled Abdel Azeem Shokry
Professor of Cardiology
Medical Military Academy

Doctor/ Sherif Mansour Soliman
Lecturer of Cardiology
Faculty of Medicine –Ain Shams University

Faculty of Medicine
Ain Shams University
2012

Introduction

Diabetes mellitus has been associated with poor clinical outcome and higher restenosis rate after percutaneous coronary intervention using balloon dilatation alone and bare-metal stents ***(Carrozza et al., 1993).*** It is also an independent risk factor for instent restenosis ***(Abizaid et al., 1998).***

Several factors related to DM may be involved in the increased incidence of ISR including the duration of the disease, the sustained hyperglycemic state, the requirement of insulin for control of plasma glucose concentration, the hyper-insulinemic condition of patients whose pancreatic β cell reserve is still preserved, and the abnormal growth factors leading to neo-intimal proliferation ***(Aronson et al., 1996).***

Prediabetes also known as impaired Glucose hemostasis [IGH] is a condition that precedes type-II DM where the levels of blood glucose are higher than normal but are not high enough to be classified as diabetes mellitus. It is associated with obesity and dyslipidemia. The American Diabetic Association defined prediabetes in 2008 by two criteria; a fasting plasma glucose level between 100-125 mg/dl which is also called impaired fasting Glucose [IFG] and an oral glucose tolerance test between 140-199 mg/dl which is called impaired Glucose tolerance [IGT], however, they added in 2009 HbA1c level between 5.7% - 6.4% to these criteria ***(American Diabetic Association position statement, 2010).***

A strong correlation between pre-diabetic hyperglycemic states and increased cardiovascular risk has been demonstrated ***(Levitan et al., 2004).*** Meta-analyses of epidemiologic studies suggest that there is a continuous gradient of risk across blood glucose levels (fasting and post-load) for the incidence of diabetes, cardiovascular disease (CVD), and mortality. A 1-mmol/l lower fasting blood glucose level is associated with an approximately 20% lower risk of CVD ***(Asia Pacific Cohort Studies Collaboration, 2004).***

Amano et al studied a group of older individuals with prediabetes using intravascular ultrasound and noted a 4-fold increased odds of lipid-rich plaques in individuals with IGH, a magnitude of association similar to that for diabetes ***(Amano et al., 2008).*** The role of pre-diabetic hyper-insulinemic state in the development of restenosis after PCI is however less understood, although a direct correlation of neo-intimal hyperplasia after PCI and insulin resistance has been suggested ***(Nishio et al. 2005).***

In-stent restenosis is neointimal hyperplasia inside the implanted stent causing its blockage (≥ 50 % lumen diameter stenosis). It occurs in the first 3-6 months after stent implantation ***(Mehran et al., 1999)***. This study aims at studying coronary restenosis in prediabetic cases.

Aim of the Work

The aim of this work was:

A pilot study to assess the occurrence of in-stent restenosis in coronary bare metal stent [BMS] implantation in pre-diabetic patients.

In-stent Restenosis

Stent placement during percutaneous transluminal coronary angioplasty (PTCA) has been widely adopted for the treatment of coronary artery disease. The principal drawback of stent placement has been in-stent restenosis, which develops during the first few months after the procedure ***(Lowe et al., 2002).*** Typically, restenosis is viewed as a binary figure, defined by ≥ 50% lumen diameter stenosis at 6-month follow-up angiography (FU angio). This definition was based on early experimental animal data indicating that coronary flow reserve is diminished in ≥ 50% diameter stenoses ***(Gould et al., 1974).*** Since then, many trials evaluating new developments in coronary interventions have included 6-month FU angio as an integral part of the protocol. This allowed for detail quantitative assessment of the lesions and vessels treated, yielding the primary end point of many trials.

Definition:

In-stent restenosis is neointimal hyperplasia inside the implanted stent causing its blockage (≥ 50 % lumen diameter stenosis). It occurs in the first 3 - 6 months after stent implantation ***(Mehran et al., 1999).***

Classification of ISR:

The lesions are classified as follows: (Figure 1).

- Class I: Focal ISR group. Lesions are ≤ 10 mm in length and are positioned at the unscaffolded segment (i.e.: articulation or gap),the body of the stent, the proximal or distal margin (but not both), or a combination of these sites (multifocal ISR)
- Class II: "Diffuse intrastent" ISR. Lesions are > 10 mm in length and are confined to the stent(s), without extending outside the margins of the stent(s).
- Class III: "Diffuse proliferative" ISR. Lesions are > 10 mm in length and extend beyond the margin(s) of the stent(s).
- Class IV: ISR with "total occlusion." Lesions have a TIMI flow grade of 0.

(Mehran et al., 1999)

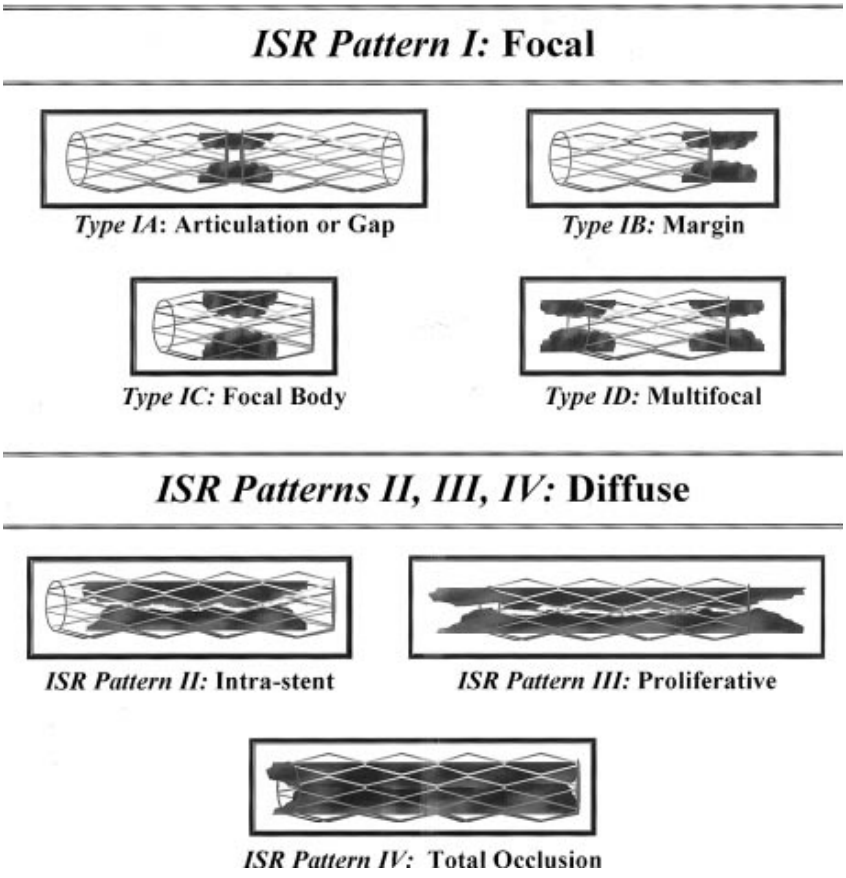

Figure (1): Schematic image of 4 patterns of introduced classification of ISR in relation to previous dichotomous description of focal vs diffuse ISR. Pattern I contains 4 types (A-D). Patterns II through IV are defined according to geographic position of ISR in relation to previously implanted stent ***(Mehran et al., 1999).***

Patterns and mechanisms of in-stent restenosis:

The mechanism of restenosis after stent placement was different from that after balloon angioplasty or atherectomy. Three distinct processes are involved, recoil of the vessel, neointimal proliferation, and early thrombus formation. The relative contribution of each of these depends on the type of injury. About three quarters of the lumen loss after balloon

angioplasty is due to vessel recoil and the rest to neointimal proliferation, whereas coronary stenting virtually eliminates vessel recoil, and restenosis is largely due to neointimal proliferation ***(Mintz et al., 1996)***.

In a study published by **Kimura et al** in **1997**, to evaluate the mechanism of restenosis after balloon angioplasty or atherectomy, they found that at 6-months follow up the decrease in lumen area, as assessed by intravascular ultrasound, correlated more closely with a decrease in vessel area, hence vessel remodeling, than the increase in plaque and media area. Thus they concluded that the mechanism of restenosis after balloon angioplasty or atherectomy was mainly due to negative remodeling of the target vessel at the site of intervention than due to intimal hyperplasia.

The initial effect of balloon dilatation is to produce endothelial desquamation, dissection and splitting of the atheromatous plaque and rupture of fibrous tissue. This leads to the release of tissue factor, a glyco-protein which initiates the cascade of thrombus formation (thrombin release, thromboxane A, prostaglandin, responsible for the deposit of activated platelets), and the release of serotonin which leads to vasoconstriction and recoil phenomena ***(Kearney et al., 1997).***

The amount of underlying vessel wall damage, and the length and depth of the dissection are factors which influence the magnitude of deposition of activated platelets. Stents are

therefore commonly deployed at sites where the thrombotic process has already been activated ***(Komatsu et al., 1998).***

Some minutes or hours following implantation of a metallic stent, the wire becomes covered by a thin layer of fibrinogen and activated platelets. Different factors will determine the degree of platelet deposition and thrombus adhering to the stent wires ***(Baron et al., 1998).***

The degree of smoothness of the struts surface achieved by electropolishing, modifications of the ionic charge or the coating of the stent with a thin film, of biocompatible material, or ionic bound heparin, or c7E3 Fab (abciximab) have been shown to significantly reduce activated platelet adhesion ***(Baron et al., 1998).***

It has been shown that a particular metal is more or less thrombogenic than another. ***Scott et al.*** in ***1995*** found no difference in platelet deposition and fibrin accumulation between identical coil stents made of tantalum or stainless steel. However, the structure of the stent does seem to be important. The properties of wire crossing-points and the amount of turbulence induced by the profile of the struts were suggested as a possible mechanism leading to higher platelet accumulation; stent configuration can therefore influence vascular response independent of deep wall injury ***(Garasic et al., 1997).***

In an experimental study using two different coiled-wire stents of identical material that differed only in the presence or

absence of a gap between the coils, a significantly greater proliferative response was noted in arterial segments treated with the stents with gaps than in those without ***(Edelman et al., 1996).***

Low-profile struts appear to be desirable and the stent filament diameter should be reduced to the minimum needed for adequate support to tackle back intimal flaps and seal the dissected vessel wall.

This activated platelet deposit induces a thrombus which will migrate into the damaged area and fill in the space between the stent wires and the ruptured plaque.

The process of platelet deposit and thrombus formation represents **the initial response** to violation of endovascular continuity and the addition of a metal stent into the vascular milieu, and may serve as a nidus for subsequent cell proliferation and resultant neointimal hyperplasia.

The next stage is the migration and accumulation of inflammatory cells (including lymphocytes, eosinophils, histiocytes and multinucleated giant cells), around the stent wires, extended from the luminal surface into the intima.

Kornowski et al. in ***1998*** found inflammatory infiltrates with granuloma formation surrounding stented wires implying a foreign-body reaction in response to the stent. In pig models, granuloma formation had a pivotal role in cell proliferation and neointimal formation after coronary stenting.

Kearny et al in ***1997*** who retrieved tissue specimens by directional atherectomy from 10 patients presented with in-stent restenosis. By analyzing their cellular composition, they found that all the specimens contained extensive foci of hypercellularity composed predominantly of smooth muscle cells (SMCs) (59.3±3.0 %), with evidence of ongoing proliferation activity. Macrophages and leukocytes were identified in all the specimens but accounted for a proportional smaller number of cells (14.5±1.9 % and 9.5±1.4 % respectively). And finally organized thrombus was also observed in 6 of the 10 specimens. These findings support that in-stent restenosis resulted from SMCs hyperplasia and suggested the role of platelets and other inflammatory cells, macrophages and leukocytes, as triggers for neointimal tissue proliferation.

The depth of arterial laceration, as well as stent material and design has been shown to impact upon the degree of inflammatory response. ***Kormowski et al.*** in ***1998*** had found a significant positive correlation between the degree of injury to the various anatomic structures of the vessel wall induced by the stent struts and the extent of inflammatory reaction.

The third stage involves proliferation of vascular smooth muscle cells in the media and neointima, starting on the 5^{th} day and lasting about 20 days. Smooth muscle cells migrate to and proliferate within the neointima; the rate of proliferation and subsequent neointimal size is proportional to the severity of early

inflammatory cell recruitment. Both arterial injury and inflammation are able to contribute to neo-intimal cellular proliferation independently, each even in the absence of the other.

However, it is the combination of inflammation and injury that has shown to cause the greatest amount of neo-intimal formation ***(Kornowski et al., 1998).***

Hoffman et al in **1996** studied the mechanism of late lumen loss and restenosis after stent implantation by studying 142 stents placed in 115 lesions, using serial intravascular ultrasound studies. They tried to illustrate the mechanism of restenosis after stent implantation, whether primarily induced by hyperplasia of neointimal tissue or by the process of remodeling (chronic stent recoil). They found that, late lumen loss within the stent was correlated strongly with tissue growth (neointimal tissue accumulation) and weakly with chronic stent recoil. This was true for native coronary and vein graft, for coronary as well as biliary stents and overlapping versus non-overlaping stents. On the contrary, late lumen loss distal to the edge of the stents was correlated mainly to arterial remodeling than to tissue growth. Thus it appeared from the previous study that:

- Chronic stent recoil is minimal.
- Late lumen loss and in-stent restenosis were the result of neointimal tissue proliferation.
- The pattern of restenosis was the same for native arteries as well as for vein graft, biliary as well as coronary stents.

- Stents appeared to affect the adjacent vessel segments, causing a combination of arterial remodeling and tissue proliferation.

Intimal hyperplasia is the main mechanism of in-stent restenosis (ISR), other contributing factors include elastic recoil, arterial remodeling, tissue prolapse through struts and inadequate coverage of the initial lesion ***(Homels et al., 1998)***. ***Haude et al*** in ***1993*** demonstrated that, elastic recoil accounts for an average 31% loss of the maximal achievable vessel diameter, whereas after stenting, this average loss in vessel diameter was only 3.5%.

Mudra et al in ***1997*** studied 68 consecutive patients with 72 lesions who received Palmaz-Schatz coronary stents. After 5 month follow-up, the restenosis rate was 15.3%. serial intravascular ultrasound analyses revealed that lumen renarrowing within the stent was exclusively due to neointimal ingrowth, and no stent compression was observed. It was also found that the maximal neointimal tissue burden was at the mid-portion of stent, at the site of articulation. Thus, it appeared that neointimal hyperplesia was the sole mechanism of in-stent restenosis and that vessel remodeling does not play part in that phenomenon.

As restenosis after stent implantation has been confirmed, in several studies, to be secondary to neointimal hyperplasia, subsequently other investigators have studied the sequence of events that happened after stent implantation and hence aggravating the proliferation of neointimal tissue.

Komatsu et al. in ***1998*** investigated 11 stented coronary arteries obtained from 11 patients who had died 2 days to 21 months after stenting. The aim of their study was to examine the histopathological events after coronary stenting, for a better understanding of the sequence of events leading to neointimal tissue proliferation and whether or not it differed in restenotic versus non-restenotic stents. They found that at 6 days after stenting, the site of the struts showed thrombus formation and an accumulation of macrophages around the struts. At 9 days after stenting, an early proliferation of neointimal tissue composed of abundant macrophages and smooth muscle cells (SMCs) mixed with the mural thrombus. One month after stenting, the areas around the struts contained remnants of thrombus, but there was distinct proliferation of SMCs, with occasional macrophages. At 2 months, all lesions showed a distinct layer of neointimal tissue, composed predominantly of SMCs with scattered macrophages, little fibrin and newly formed microvessels.

This study suggested that the sequence of events leading to a neointima formation after stent implantation is basically local thrombus formation followed by a gradual invasion of cellular components such as macrophages and SMCs accompanied by the deposition of extracellular matrix components. It appears that platelets in concert with macrophages, through the release of a variety of growth factors, like platelet derived growth factors and other cytokines, are crucial for the recruitment of SMCs to the site of the stents for neointimal tissue proliferation ***(Komatsu et al., 1998).***

This study showed also, that neointimal tissue proliferation started to appear as early as 9 days after stent implantation and the histopathological events were the same whether restenosis had developed or not. Thus, it appeared that the difference between restenosis and non-restenosis is quantitative rather than qualitative pattern of tissue ***(Komatsu et al., 1998).***

The coating of the stent surface with bonded heparin has been shown to reduce amount of mural thrombus and inflammatory response whilst coating with polymer alone had no effect. Nevertheless intimal thickening was not reduced by the use of heparin coating suggesting a need to look elsewhere than on the stent surface to reduce in stent restenosis ***(Bettrand et al., 1998)***.

Predictors of In-Stent Restenosis:

Several factors were studied as possible predictors for in-stent restenosis. These factors were either demographic or clinical variables or related to the angiographic characteristics of the patients.

I- Diabetes mellitus:

The benefits of intracoronary stenting are well established, with a reduction in restenosis rates and clinical events most pronounced in diabetics. Despite these improvements, the main limitation of PCI in diabetics continues to be the high rate of restenosis.