



# Coronary arteries bypass grafting stenosis

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### ABSTRACT

Coronary artery disease (CAD) is a major global problem. In addition, it is higher risk of mortality for women more than men are when develop in female gender. Atherosclerotic plaques consist of deposits of fatty material in the tunica intima. The role of inflammatory process in CAD has been known from 1980's. Several studies investigated the innate immunity and adaptive immunity roles in atherosclerosis and they concluded that it plays a key role in atherosclerosis. Coronary artery bypass grafting (CABG) is a widely used method for the treatment of CAD. Based on the literature, CABG is the most common surgical operation done worldwide. In During the first 10 years after CABG, up to 50% of saphenous grafts will occlude. Graft restenosis is beginning with acute thrombosis, intima hyperplasia, and plaque formation. In this review, some molecular pathways of graft failure and restenosis such as apoptosis and nuclear factor kappa B (NF-κB) are described.

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## Introduction

Atherosclerosis is a chronic inflammatory blood vessels condition affecting some important great arteries, which is the principal pathophysiological pathway of coronary artery disease (CAD) and Cerebrovascular events. Several studies confirmed the existence of T cells, B cells, monocytes and dendritic cells (DCs) inside the atherosclerotic plaques of mice and men (1).

Atherosclerotic plaques consist of deposits of fatty material in the tunica intima, smooth muscle cells that form an overlying cap, and elaborated extracellular matrix molecules that together lead to luminal narrowing. There are also a significant population of activated inflammatory cells, particularly macrophages that secrete metalloproteinases that can degrade the matrix molecules and lead to plaque instability and rupture(2). Atherosclerosis is also

associated with innate and acquired immune responses, that start in the early years of life, but that becomes clinically apparent in later life (3-6).

The role of inflammation in CAD has been known from 1980's. Several studies investigated the innate immunity and adaptive immunity roles in atherosclerosis and they concluded that it plays a key role in atherosclerosis (7,8). It was shocking to refer to atherosclerosis as an inflammatory disorder in the arterial linings almost about a century ago. Furthermore, after 1850, which was the date of confirming the involvement of inflammatory processes in atherosclerosis, so many studies have been done proving this fact by verifying cellular structure of atherosclerotic lesions which is possible by particular monoclonal antibodies for each cell (9-12).

Several studies confirmed the existence of T

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cells, B cells, monocytes, and dendritic cells (DCs) inside the atherosclerotic plaques of mice and men (13-15). Atherosclerotic plaques could release different biomarkers such as proinflammatory cytokines, amyloid A, adhesion molecules, and C-reactive protein in plasma (16).

The role of Interleukin-2 (IL-2) in the process of atherosclerosis is yet ambiguous; nevertheless, its immunomodulatory role in the activation of immune cells such as lymphocytes and monocytes has been proven. Martins et al. in their study in 2006, mentioned a significant elevation in IL-2 concentrations in their CAD study group (17).

Atherosclerosis is thought to be initiated by damage to the endothelium resulting in altered endothelial function. The risk factors of CAD are generally the cause of this damage through one or more of the following pathways including high levels of oxidized low-density lipoprotein (LDL), free radicals (reactive oxygen species (ROS)), genetic variations, elevated plasma homocysteine concentrations, infectious microorganisms (herpes virus or chlamydia pneumonia), shear stress in the areas of turbulent blood flow, or endogenous inflammatory signals such as cytokines (18).

It is reported that 12 million people in United States have atherosclerosis-associated conditions (19,20). CADs cause about 30% of all global deaths. In 2008 approximately 17.3 million people died and about 23.3 million will die from CAD in 2030 (2).

In low- and middle-income countries, CAD leads to more than 80% of mortality; almost equally in men and women. It is estimated that by 2015, nearly 20 million people will die from CADs, main reasons are heart diseases and stroke. It is projected that these will remain the leading causes of death (21).

According to the Ebrahimi et al. review article, prevalence of CAD and coronary risk factors in Iran is higher than Western countries but similar to some Middle East countries (22).

The most prevalent clinical manifestations of CAD are myocardial infarction (MI), stable or unstable angina, and sudden death. Atherosclerosis, as a prominent predisposing factor, plays the major role in the pathogenic processes leading to CAD (23).

However, most cases of myocardial infarction occur due to thrombosis followed by plaque rupture (24).

### **Coronary arteries bypass grafting (CABG)**

Coronary artery bypass grafting (CABG) is a widely used method for the treatment of CAD. Based on the literature, CABG is the most common surgical operation done worldwide (25,26).

There are criteria because of which a patient will be considered as a CABG candidate including:

A) Extensive coronary artery diseases (CAD) including narrowing, atherosclerosis, and stenosis (in

general obstructive diseases) in the main left coronary artery or all three coronary arteries

B) Stable angina with persistent symptoms in patients who have taken adequate medication

C) Severe dysfunction of the left heart ventricle,

D) Having a high risk of future heart attack or any cardiac events diagnosed by exercise test or angiography

E) Unstable angina

F) Chronic or calcified arterial occlusions

G) Occlusive coronary disease in a patient with diabetes mellitus (27)

More than 300,000 CABG operations were performed in the North America annually (28) with about 467,000 CABG performed operations just in 2003 (29). Furthermore, it has been reported that over 10,000 patients require CABG every year in Iran (30). Many percutaneous coronary interventions were done in the patients with the history of CABG. Therefore, restenosis occurs more frequently in these patients, which may lead to new coronary events (31,32).

Artery bypass grafting failure is an unfavorable outcome of CABG operation (33) and leads to morbidity and mortality (34). Diabetes, plasma fibrinogen, creatinine, and high-density lipoprotein are as potential biomarkers of graft failure (33, 35). In the first 10 years after CABG, up to 50% of saphenous grafts will occlude (36,37).

Plasma anticardiolipin antibody is related to artery bypass grafting failure and it shows that an autoimmune pathway is activated in graft failure (38).

Endothelial injury is an important factor in atherosclerosis progression (18,19) which can influence the graft failure as well. Therefore, vein harvesting is one of the risk factors for graft failure (34). Endoscopic greater saphenous vein harvesting (EVH) is a minimally invasive technique for vein harvesting (39) and may reduce endothelial injury (40). Allen KB et al. in a five-year follow-up of a prospective RCT, displayed that use of EVH does not influence event-free survival (41). Some other scientists believe that EVH is independently associated with vein graft failure (42). Cellular proliferation and cell migration of smooth muscle cells are the main causes of graft failure after CABG in saphenous vein graft (43).

Graft restenosis is beginning by acute thrombosis, intima hyperplasia (IH), and plaque formation (34). Five years after grafting, the signs and symptoms of restenosis appear (44). Leukocyte endothelial interactions are increased by the adhesion molecule overexpression (45) due to abnormal blood flow in saphenous graft (46).

Apoptosis occurs in early-stage vein grafts. Mayr et al. also reported that IH is increased in the vein graft of P53 transgenic mice vein wall (47). Mitogen-activated protein kinase P38-MAPK is the main

apoptosis signaling pathway that might be activated by mechanical stretch (stretch-induced injury) in high blood pressure aorta (48). These stresses of graft wall, change the blood flow, transmural pressure, shear stress, and radial stress and they can activate a lot of apoptosis and inflammation intercellular pathways (49).

Apoptosis could be a potential strategic target for inhibiting graft restenosis and graft failure (34). Another mechanism of graft failure is the activation of NF kappa B (NF- $\kappa$ B) signaling pathway, which involve in cytokines and adhesion molecule secretion pathways (50). On the other hand, ischemia of graft due to vasa vasorum occlusion in graft harvesting procedures could increase danger signals of apoptosis (51). Inhibition of P38 kinase could be another pharmacological target for decreasing graft failure after CABG (48). For example 4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole (SB 203580) can inhibit P38 $\alpha$  and P38 $\beta$  in animal model, which it has been used for graft apoptosis and myocardial reperfusion apoptosis (51).

### **Graft atherosclerosis and risk factors**

Triglyceride-rich lipoproteins such as very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) could be great risk factors and strong predictors of graft lesion (52).

Bourassa et al. in 1984, mentioned that post-CABG graft occlusion during 10-12 years, made them to limit CABG indication into patients with very severe 3 vessels disease (VD) or left main CAD (53).

Diabetes mellitus (DM) is one of CAD risk factors but Singh SK et al. in 2008, showed that DM was very important in graft occlusion at 1-year angiography follow-up (54).

Type of the graft for CABG is another factor in graft occlusion. Most of the time, saphenous graft has been used but in one meta-analysis, in 2011, radial artery had less potency for early and mid-term graft occlusion (55). Graft age is another most important factor in graft occlusion. Therefore, graft age can also predict graft obstruction risk following graft type (56).

Elevated serum lipid profile may lead to total graft occlusion (57) and lipid reducing agents especially gemfibrozil are recommended (52); Some researchers suggested LDL tight control (less than 90 mg/dL) (58). Lp(a) may influence graft obstruction in normolipidemic patients (59).

Serum level of homocysteine is a risk factor for graft occlusion especially in saphenous graft. In Iwama Y et al. study, a positive correlation was found between plasma level of homocysteine and graft occlusion (60).

Smoking is a risk factor for CAD and post-CABG

graft occlusion (61). It seems that apoptosis and inflammation intercellular pathway are involved in smoking.

Hypertension has indirect correlation with graft occlusion. HTN can lead to intima hyperplasia in graft. So, hyperplasia is a trigger for graft obstruction (62,63).

### **Graft occlusion management**

5-10% of percutaneous coronary intervention (PCI) are performed in USA due to graft occlusion annually (64). Some other suggested that managements of graft occlusion therapy are repeated CABG and medical control (62).

Asymptomatic ischemia testing after graft occlusion is the worst and dangerous method for a cardiologist. It could confuse patients and cardiologists, but in some cases recurrent angina could be detected (65).

Favorable conditions for PCI management of graft occlusion:

1. Single graft lesion
2. Focal graft lesion
3. Patent indicates left internal mammary artery (LIMA) graft
4. Patent LAD graft

Some other patients should undergo repeated CABG:

1. Multiple graft lesions
2. Diffuse graft lesions
3. Adequate pulmonary and renal function, life expectation >5 yr (62)

### **Conclusion**

During first decay after CABG with saphenous grafting, 50% of patients have signs and symptoms of graft restenosis and graft failure. Therefore, inhibition of molecular pathway of apoptosis in graft tissue is very important. Apoptosis and NF- $\kappa$ B signaling pathway are the most involved pathways in graft failing. Therefore, minimally invasive graft harvesting, pharmacological anti-apoptosis medications, life style, diet, smoking cessation, and any modern molecular inhibitors are considerable.

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### **Conflict of Interest**

The authors declare no conflict of interest.

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