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Review Article

Increase Cardiovascular Event in Patient with Diabetes Mellitus Undergoing Percutaneous Coronary Intervention

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ABSTRACT

Diabetes mellitus (DM) associated with increase major risk factors of cardiovascular disease, such as peripheral arteriopathy, ischemic heart disease, or cerebrovascular accident. The Framingham study showed that patient with DM considerably increase coronary artery disease (CAD), particularly in old patient and women. Prevalence of DM is rising and cardiovascular mortality associated with DM is the main problem in the world. Additionally, there is a higher death rate among DM patients following a myocardial infarction with complications, such as stent thrombosis, instent restenosis, and no reflow phenomenon can worse overall long-term prognosis with CAD. This review considers the mechanism for diabetes mellitus in CAD patient, expecially patient with DM can increase risk of major complication in patient CAD undergoing percutaneous coronary intervention (PCI).

1. Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia. It could be brought on by decreased insulin secretion, resistance to peripheral actions of insulin, or both. When combined with other metabolic abnormalities in DM patients, chronic hyperglycemia can damage organ systems and lead to life-threatening complications, the most prevalent of which are microvascular and macrovascular issues that increase the risk of cardiovascular diseases.[1]

2. Definition

Epidemiology

On a global scale, the occurrence of DM is escalating to epidemic levels. Patients with DM have clinical implications that are equally significant to those who are diagnosed with CAD. The incidence of cardiovascular disease and death is higher in those with DM or a previous myocardial infarction (MI), regardless of gender or age. Furthermore, DM is associated with an elevated susceptibility to risk factors that contribute to the development of cardiovascular disease (CVD). The prevalence of hypertension, high LDL serum levels, and obesity is higher in adults with DM, with rates of 75%, 70%, and 60% respectively. The main determinant of the likelihood of mortality due to heart disease is the existence of CAD. Additionally, individuals with DM experience an elevated mortality rate after experiencing a myocardial infarction (MI) event, and they also have a less favorable long-term outlook when it comes to CAD.[1]

Pathophysiology of CAD in Diabetes Mellitus

Diagnosis of DM based on fasting plasma glucose ≥126 mg/dL (7.0 mmol/L), 2-hour glucose after 75-g oral glucose load ≥200 mg/dL (11.1 mmol/L), random plasma glucose ≥200 mg/dL confirmed by repeat testing in the absence of signs or symptoms of hyperglycemia or hyperglycemic crisis, hemoglobin A1c (HbA1c) ≥6.5% (48 mmol/mol).[2]

The diabetic population present 90% of CAD is the main problem of death in these patients. Research has consistently demonstrated that women with diabetes have a 2- to 4-fold increased relative risk of CAD when compared to the general population. This is because women lose the hormone cycle-related protection against CAD. Patients with DM itself is a powerful independent risk factors that lead to cardiovascular events. Atherosclerosis has a several pathophysiologic factors that are related to its poor prognosis and unique reaction to coronary revascularization. The hematologic and metabolic problems related to DM include thrombophilia, insulin resistance, dyslipidemia, inflammation, and hyperglycemia. Platelets are prone to aggregation and exhibit a higher number of GPIIb/IIIa receptors, especially when hyperglycemia is present. Additionally, the abnormalities lead to the development of hypertension, abnormality of endothelial cell, accelerated atherogenesis and expecially coronary thrombosis. Diabetic nephropathy condition, reduce creatinine clearance and proteinuria can decrease survival after coronary revascularization.[3]

The architectural configuration of CAD in patients with DM is linked to their prognosis and how they respond to percutaneous coronary

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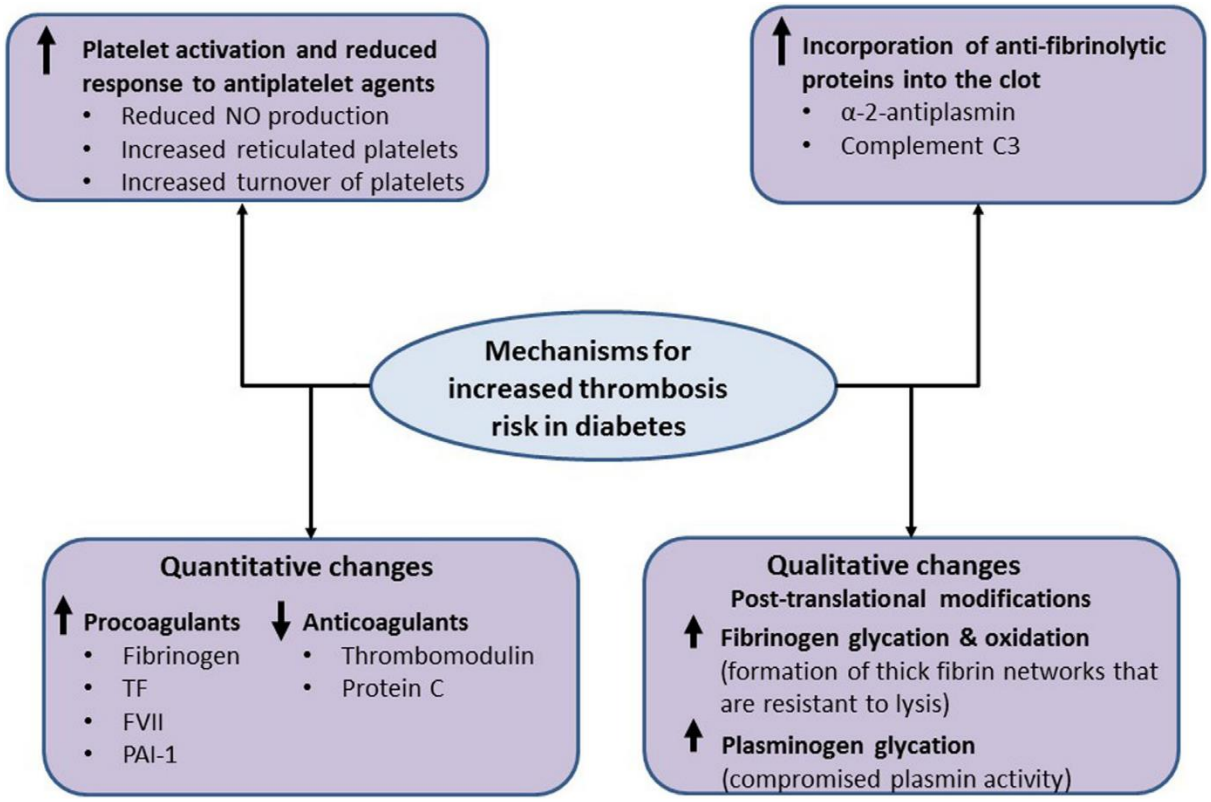

Figure 1. Mechanism pathways for thrombosis risk in diabetes (Adapted from Pechlivani N and Ajjan RA).[8]

intervention (PCI). Individuals diagnosed with DM exhibit a higher prevalence of fully blocked coronary segments and narrower inner diameters in segments neighboring obstructive coronary lesions. Additionally, individuals with diabetes have an increased amount of plaques that are rich in lipids. These plaques are more susceptible to rupturing, perhaps due to a greater load of atherosclerosis. Individuals diagnosed with diabetes mellitus may have less flexibility in their coronary artery profile when faced with significant obstructive lesions. Individuals diagnosed with diabetes mellitus exhibit a diminished ability to develop coronary collaterals. Remodeling, or the process of early compensatory enlargement at areas affected by atherosclerosis in order to maintain the size of the inner area and blood flow, is frequently observed in coronary arteries.[3]

Hyperglycemia causes many dysfunctions in the vascular system that greatly contribute to the development of atherosclerosis. The pathogenic changes observed in the vasculature of DM are primarily driven by three primary processes: non-enzymatic glycosylation of lipids and proteins, activation of protein kinase C (PKC), and oxidative stress. Coronary artery disease arises from a range of cellular and molecular pathophysiologic pathways. Patients with DM exhibited elevated levels of atherosclerotic plaques, increased volumes of atheroma, and reduced widths of the coronary artery lumen, in comparison to individuals without diabetes.[2]

Coronary patients with DM had a higher chance of developing more severe CAD and experiencing greater morbidity and death compared to those without DM. Diabetes mellitus is connected to the process of atherogenesis through various mechanisms, such as abnormalities in the composition and concentration of lipoproteins, their association with hypertension, insulin resistance, and hyperinsulinemia, a state of inflammation and increased blood clotting, protein glycosylation in the plasma and arterial wall, lipid oxidation, and dysfunction of the endothelium.[4]

Some studies show that glycosylated hemoglobin, especially in women, may be a independent risk factor for CAD. It is unknown if there is a glycemia threshold for atherogenesis in DM. Nonetheless, some research designates preprandial blood glucose levels of less than 126 mg/dL and a HbA1c of less than 7% as objectives. Of glucose intolerance, DM and coronary artery disease, insulin resistance it can have the strongest association with other atherogenic factors. Insulin resistance is the first sign of DM in genetically predisposed populations, appearing 15–25 years before the disease manifests clinically. Insulin resistance is more common in persons with DM in their family history.[5]

Abnormality of HbA1c serum predicted an increased risk of all causes of mortality in patients with CAD undergoing PCI. There are several impacts of abnormal HbA1c levels, including abnormal of HbA1c can lead to impair of vascular endothelial cell, increased cellular proliferation, and extracellular matrix formation. According to coronary angiography, the HbA1c levels were an independent factor influencing the severity of CAD; abnormal HbA1c levels are linked to a higher cardiovascular risk and an adverse baseline feature, which explains the increase in long-term death in CAD patients.[6,7]

a. Hypercoagulability in Diabetes Mellitus

The return of atherosclerosis is more prevalent in individuals with diabetes mellitus. Hyperglycemia and hyperinsulinemia cause an elevation in prothrombotic proteins and the activity of circulating tissue factor, which promotes blood clot formation. Inadequate management of blood sugar levels in patients with diabetes mellitus (DM) leads to increased blood clotting and elevated levels of fibrinogen, von Willebrand factor-antigen, and plasminogen activator inhibitor-1 antigen. There is a correlation between lower levels of anticoagulants (protein C) and higher concentrations of coagulation factors (II, V, VII, VIII, X) in individuals with elevated blood glucose serum levels. Within the diabetic population, these prothrombotic processes can lead to the development of atherothrombosis.[2]

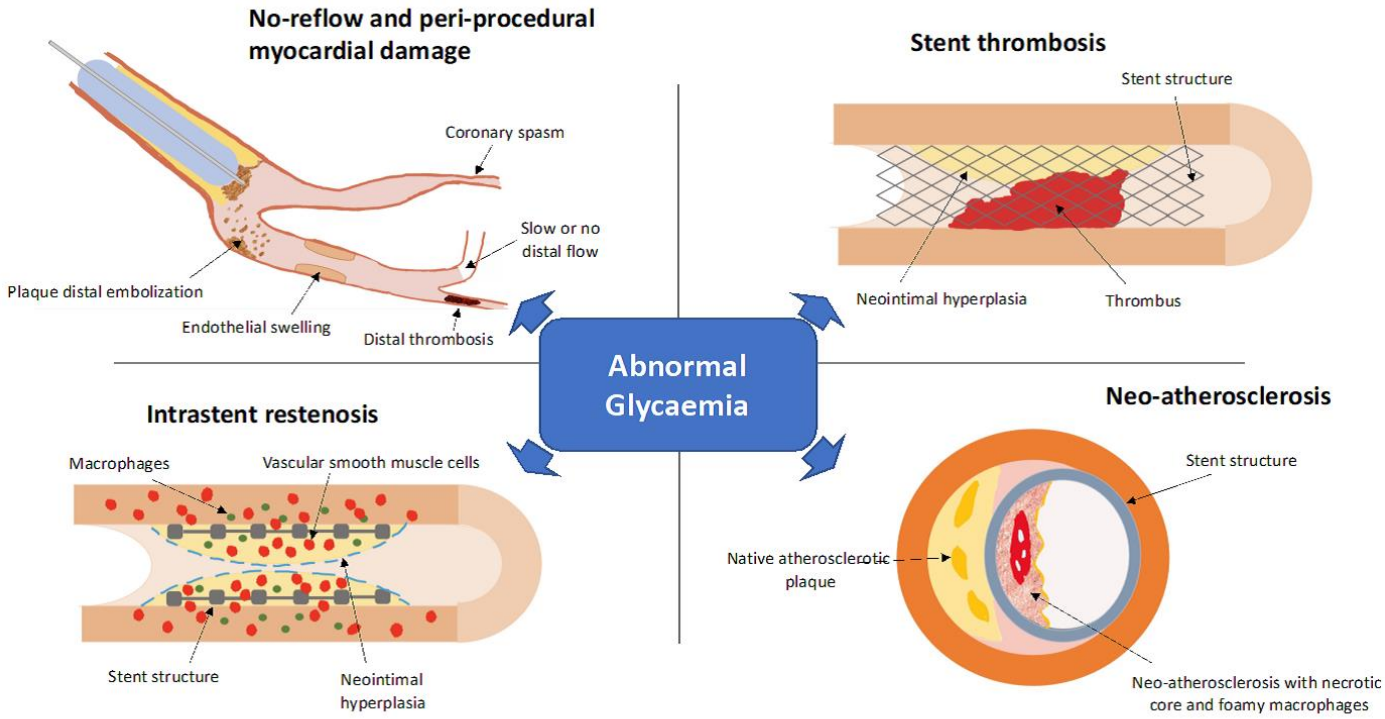

Figure 2. Effect of abnormal gycaemia incude stent-related complication (Adapted from Nusca A, Piccirillo, et al).[10]

b. Vascular Calcification in Diabetes Mellitus

Diabetic patients exhibit an increased presence of calcified atherosclerotic lesions, particularly in complex atherosclerotic lesions. The coronary calcium score, evaluated by electron-beam computed tomography, is a risk factor for cardiovascular events and death rate in both individuals with and without DM. Individuals with DM have higher levels of coronary artery calcification (CAC) scores and a greater load of calcified plaque, compared to individuals without diabetes mellitus.[2]

c. Endothelial Dysfunction in Diabetes Mellitus

Endothelial function can occur in DM resulting in exposure to high blood glucose concentrations. Endothelial dysfunction is an important risk factor marker for CVD events. Dysfunctional endothelium leads to leukocyte and platelet adhesion, thrombosis, and inflammation process via the PI3-kinase/Akt pathway, insulin stimulates endothelial NO synthase-induced NO production by endothelial cells. Defects in the insulin signaling pathway, which are observed in insulin resistance and DM, lead to decreased endothelial NO synthase activity and NO production, which in turn promotes endothelial dysfunction.[2]

Diabetes Mellitus and Percutaneous Coronary Intervention

Multiple trials and clinical investigations have indicated that aberrant glucose levels before to PCI are associated with procedural problems and long-term outcomes. This situation might result in several complications during the procedure, such as the no-reflow phenomena, Preprocedural MI, Stent Thrombosis (ST), Intra-Stent Restenosis (ISR), and neoatherosclerosis.[9]

Vascular smooth muscle cells migration and proliferation play a major risk factor in the pathogenesis of restenosis in diabetic patients. Restenosis can occur in over 55% of individuals with diabetes mellitus within six months of a successful PCI, according to multiple studies. Neointimal hyperplasia (NIH), which is defined as the thickening of a tunica intima, is mostly responsible for restenosis after angioplasty and stenting. There are several processes can describe the restenosis incident higher rate in diabetic patients, such as, They are more likely to develop vascular thrombosis because of their hematological abnormalities. Patients with diabetes have higher coagulation activity, increased spontaneous and induced platelet aggregation, enhanced platelet synthesis of thromboxane A2, increased platelet activation (platelet factor 4 and thromboglobulin) with procoagulant factor (fibrinogen, factor VII, and von Willebrand factor). Furthermore, Patients with DM may experience decreased prostacyclin synthesis and impaired fibrinolysis due to elevated levels of plasminogen activator inhibitor type 1 and dysfunctional vascular endothelium are associated with vasospasm and coronary thrombosis.[11–13]

The no-reflow phenomenon refers to the impairment of blood flow to the heart muscle, even after the epicardial coronary arteries have been reopened. This condition is linked to a state of high blood sugar through various mechanisms. One of these mechanisms involves the increased levels of intercellular adhesion molecule-1 (ICAM-1) and P-selectin, which promote the adhesion of white blood cells to capillaries. This leads to an increased obstruction of the capillary bed. Additionally, high blood sugar levels increase the risk of micro-thrombi formation, which is associated with a phenomenon called "no-reflow".[9]

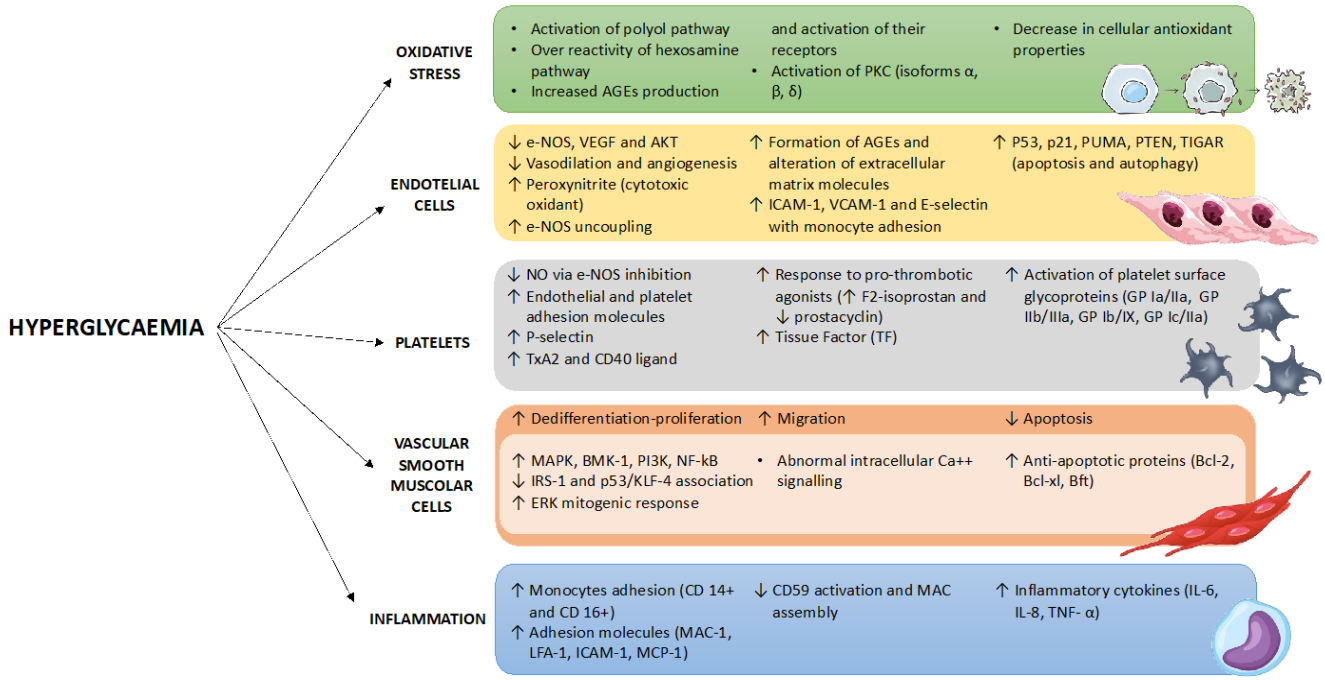

Figure 3. Pathophysiological of hyperglycaemia-induced vascular damage (Adapted from Nusca A, Piccirillo, et all). [10]

Intra-stent restenosis (ISR) is defined as the re-narrowing of a coronary artery lumen after intervention like PCI and coronary artery bypass graft surgery (CABG). It is an important problem in clinical practice because can lead to an increase in poor prognosis in patients. Patients with DM is an independent factor of ISR because they have an accelerated rate of late loss of lumen diameter of coronary arteries and increase of ISR, particularly associated with endothelial dysfunction, production of reactive oxygen, and formation of glycation end-production. Glycemic control before the PCI procedure showed to be associated with lower ISR events in comparison with uncontrol patients. A retrospective study analyzing glycemic control based on HbA1c measurements before PCI procedure to 6 months follow-up suggested that glycemic control is showed better clinical outcomes in patients with DM after PCI procedure. This condition can be affected by the management of both underlying DM treatment and intervention in the occluded coronary arteries.[14,15]

Diabetic arteriopathy can be caused by DM in the population. Microcalcifications, the development of tiny hydroxyapatite mineral deposits, can occur in the intima or media layers during the early stages of atherogenesis when cholesterol is present. Regardless of hypercholesterolemia, medial calcification can lead to the formation of calcific deposits that hinder vascular compliance. Hyperglycemia can lead to medial calcification by a process called glycosylation, in which serine and threonine residues of vascular proteins bind to N-acetylglucosamine (O-GlcNAc).[16]

Patients diagnosed with diabetes mellitus exhibit a diminished response to antiplatelet medications. Multiple trial results indicate that the platelet-membrane P2Y12 receptor is either increased in expression or has altered metabolic activity in individuals with DM. Angiolillo et colleagues conducted a thorough analysis of the pharmacokinetics and pharmacodynamics of clopidogrel. They found that in patients with diabetes, the active metabolites of clopidogrel were significantly lower compared to non-diabetic patients, even when a 600 mg load of clopidogrel was administered. The results suggested that a modification in the functional status of the P2Y12 signaling pathway is responsible for the decreased responsiveness to clopidogrel in patients with DM.[16]

Management of Type II Diabetes Mellitus in CAD

Lifestyle

Physical activity is a therapeutic intervention for individuals with diabetes mellitus. Implementing a physical exercise regimen, consisting of 3-5 sessions per week lasting 30-45 minutes each, has proven to be an effective approach for enhancing insulin sensitivity and promoting weight loss in individuals with diabetes mellitus. Furthermore, this practice has been linked to better management of blood glucose levels. The suggested physical activity for individuals with DM is aerobic exercise with a moderate intensity level, ranging from 50% to 70% of their maximum heart rate. Examples of suitable activities are walking, cycling, running, and swimming. Proper nutrition plays a crucial role in the prevention of CVD and DM on an individual basis. There is a clear association between smoking and death from cardiovascular disease. It is estimated that tobacco use is responsible for up to 10% of adult cardiovascular deaths worldwide among those aged 30 years or older.[17]

Lipid-Lowering Therapy

Individuals diagnosed with diabetes mellitus experience heightened secretion of unbound fatty acids from adipose cells that are resistant to the effects of insulin. This elevated release of fatty acids significantly raises their susceptibility to developing dyslipidemia. Hyperglycemia causes elevated levels of oxidation and glycosylation, which in turn decrease vascular compliance and promote the development of severe atherosclerosis. The desired LDL-C target for patients with DM at moderate cardiovascular risk is below 100mg/dL, for those at high cardiovascular risk it is below 70mg/dL, and for those at very high cardiovascular risk it is below 55mg/dL. The ESC 2023 Guideline recommends initiating or continuing high-dose statin therapy in patients with ACS as soon as possible. The goal is to attainan LDL-C level of less than 1.4 mmol/L (55 mg/dL) and to lower LDL-C by at least 50% from the baseline (Recommendation Class IA).[18,19]

Antiplatelet Therapy

The role of antithrombotic therapy for DM with CAD events is well established. Aspirin inhibits platelet cyclooxygenase-1 enzymes irreversibly and prevents the conversion of arachidonic acid to bioactive prostanoid thromboxane A2 which is produced by activated platelets during the hemostasis process. From AHA 2020 guidelines recommend aspirin can be routinely administered early in patients with ACS, which showed similar benefits in patients with and without DM. The P2Y12 receptor antagonists can improve the profile of coronary arteries in patients with DM. This agent are two main clasess of oral administrated: thienopyridines (clopidogrel, ticlopidine, and prasugrel) and non-thienopyridines (ticagrelor). In patients with CAD and DM insulin-dependent, ticagrelor may benefit a more potent platelet inhibitor agent than prasugrel.[20]

Glycemic Control During Percutaneous Coronary Intervention

A target HbA1c of less than or equal to 6.5% is the ESC 2023 Guidelines recommendation to lower the risk of microvascular or macrovascular consequences. Additionally, this recommendation may be benefit for diabetic patient, such as those with a short duration of diabetes, a long life expectancy, and a lower risk of CVD.[18]

Metformin as biguanide agent inhibit the gluconeogenesis process and glucose output in hepar. The DPP4 inhibitor (gliptin) often combined with metformin to control of glucose in DM patients. GLP-1 RAs agent (liraglutide, semaglutide, albiglutide, dulaglutide) can lead to vasodilation and improves endothelial function. Besides that, this agent GLP-1 independently prevent the progression of the atherosclerotic process by inhibiting the formation of macrophage foam cell by downregulation of Acyl-CoA (ACAT1), a decrease of inflammation process and pro-atherogenic by reduction of cytokine levels. Some studies showed that GLP-1 reduce infarct size in STEMI patients undergoing PCI. SGLT2 inhibitors (Gliflozin) function through a mechanism of renal proximal tube to inhibit glucose reabsorption. This agent also promotes to increase excretion of urinary glucose, reduced blood glucose and plasma volume. By this mechanism, SGLT2 inhibitors useful in reducing CVD risk in DM population.[15,21]

3. Conclusion

Diabetes mellitus related to increase major risk factors of cardiovascular event. The mechanism for diabetes mellitus in CAD patients were complex, expecially patient with DM can increase risk of major complication in patient CAD undergoing percutaneous coronary intervention (PCI).

4. Declaration

4.1 Ethics Approval and Consent to participate
Not applicable.

4.2. Consent for publication
Not applicable.

4.3 Availibility of data and materials
Data used in our study were presented in the main text.

4.4 Competing interests
Not applicable.

4.5 Funding Source
Not applicable.

4.6 Authors contributions
Idea/concept: IP, MSR, BS. Design: HAY, IP. Control/supervision: IP, MSR, BS. Data collection/processing: HAY. Analysis/interpretation: HAY, IP. Literature review: IP, MSR, BS. Writing the article: HAY, IP. Critical review: IP, MSR, BS. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

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