Acute Myocardiac Infarctions and Type 2 Diabetes Mellitus (T2DM) : a Literature Review

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Abstract

Diabetes mellitus (DM) is known to be a metabolic disorder happened to be chronic and identified with persistent hyperglycemia. It might be due to insulin secretion, insulin resistance or both disorders. Coronary artery disease is known to be the top killer in the world. According to WHO, as much as 17.5 million people died of cardiovascular disease. Diabetes mellitus and its correlation with coronary artery disease have been acknowledge since ages ago and known to be separate entities. As one of the risk factors, the hyperglycemia caused by DM might affect patients by enhancing the process of early atherosclerosis that attach the vital organs. This study aims to review past literature and studies regarding type 2 diabetes mellitus and acute myocardial infarction

Keywords: Diabetes mellitus; acute myocardiac infarctions; literature review

1. Introdction

Diabetes mellitus (DM) is known to be a metabolic disorder happened to be chronic and identified with persistent hyperglycemia. It might be due to insulin secretion, insulin resistance or both disorders. Approximately, there were 415 million adults that was diagnosed with DM in 2015 by the age category of 20 to 79 years old (Zheng, 2018). By 2040, the number is predicted to rise by another 200 million (Zheng, 2018).

Coronary artery disease is known to be the top killer in the world. According to WHO, as much as 17.5 million people died of cardiovascular disease (WHO, 2019). ST-segment elevation acute myocardial infarction (STEMI) is known to be one of the most serious case of coronary artery disease.

Diabetes mellitus and its correlation with coronary artery disease have been acknowledge since ages ago and known to be separate entities. High prevalence of coronary artery disease was found in diabetic patients, followed by studies on necropsy revealing coronary atherosclerosis in diabetic patients (Gruberg, 2022).

As one of the risk factors, the hyperglycemia caused by DM might affect patients by enhancing the process of early atherosclerosis that attach the vital organs. Hence, this study will review past studies regarding STEMI on type 2 diabetes mellitus patients.

2. Overview on Type 2 Diabetes Mellitus

Diabetes is defined to be a chronic metabolic disorder, hypoglycemia as the main problem. It happened due to impaired insulin secretory or insulin resistance, or both causative. (Goyal, 2021). Type 2 diabetes is a more of a common type rather than type 2, happened due to the body not responding to the insulin. (Khan, 2020).

Patients with diabetes mellitus are increasing every year. Based on the International Diabetes Federation, it is estimated that at least 463 million people aged 20-79 years in the world have diabetes in 2019 (9.3% of the total population of the same age). Meanwhile, based on gender, the prevalence of diabetes in 2019 was 9% for women and 9.65% for men. It is known that the prevalence of diabetes increases with age to 19.9% or 111.2 million people aged 65-79 years. It is estimated that the number of people with diabetes will continue to increase, reaching 578 million in 2030 and 700 million in 2045 (International Diabetes Federation, 2019).

2.1. Pathophysiology

The pathophysiology of T2DM includes environmental triggers and genetic predisposition-related variables (Defronzo, 2009). Impairment of insulin secretion is the primary symptom of the illness. -cell dysfunction was a significant contributor to T2DM. Peripheral muscle tissues' ability to absorb glucose will be reduced, and as a result of enhanced gluconeogenesis, hepatic glucose production (HGP) would rise (Defronzo, 2009).

The beta cell will first respond by secreting more insulin in an effort to keep blood glucose levels within normal range. As the condition worsens, beta cells won't be able to keep up, and insulin production won't be able to keep the glucose level in check, leading to hyperglycemia (Goyal, 2021). T2DM showed an increase in pancreatic beta cells, glucagon output, and hepatic glucagon sensitivity. By counteracting the effect of insulin's reduction of hepatic glucose production (HGP), glucagon aids in the maintenance of glucose homeostasis. This procedure also has the effect of increasing sensitivity to the stimulatory effect of glucagon on HGP (Defronzo, 2009).

The kidney is also involved in the pathogenesis of T2DM. While in a hyperglycemic state, it is expected that the kidney will respond by excreting the excessively filtered glucose. However, the kidney retains glucose when glucose reabsorption in T2DM is improved. The term "septicidal septet" is widely used to refer to this kidney involvement in the development of T2DM. (Defronzo, 2014)

Last but not least, altered neurotransmitter dysfunction in the brain has an impact on etiology. In a healthy person, the brain would get instructions from insulin to stop eating and to quell the hunger. Despite having hyperinsulinemia, overweight people nevertheless consume more food than average. These events provide credence to the notion that the brain has insulin resistance (Defronzo, 2014). The terrifying octet is the name given to these eight T2DM diseases.

2.2. Clinical Manifestations

Patients are most commonly seen with increased thirst, frequent urination, malaise, bacterial and fungal infections, and slow wound healing. Some patients may complain of tingling or numbness in both the hands and the legs, as well as impaired eyesight (Goyal, 2021).

2.3. Complications

Diabetes is more than an elevation of blood glucose, it brings complications in organs like kidneys, systems such as cardiovascular, retina, nervous systems and liver organs (Schatz, 2010).

2.3.1. Diabetic Kidney Disease

A microvascular consequence of type 1 or type 2 diabetes, diabetic kidney disease (DKD), also known as diabetic nephropathy, has a prevalence rate of 30–40%. Both functional and structural alterations in the kidney

tissue accompany diabetic kidney disease, such as reduced podocyte function and its separation from the glomerular basement membrane (GBM). With the mesangial matrix expansion, the thickening of GBM will trigger glomerular sclerosis alongside with tubule-interstitial fibrosis, kidney function decreasing, presented in albuminuria and detoriating glomerular filtration rate (GFR) (Demir, 2021). It is becoming clear that excessive lipid buildup in the kidneys and the related lipotoxicity play a part in the onset of diabetic kidney disease as well (Thongnak, 2020).

2.3.2. Cardiovascular System

The most frequent cause of death and morbidity among diabetic people is cardiovascular disease (CVD). Nearly half of type 2 diabetes-related fatalities are caused by cardiovascular disease (CVD), and more than 30% of type 2 diabetes patients experience cardiovascular problems (Einarson, 2018). A wide range of cardiovascular system dysfunctions, such as atherosclerosis, myocardial infarction, heart failure, and cardiomyopathy, are covered under CVD. Despite the exponential growth in studies investigating the link between diabetes and CVD, the precise pathogenic processes are still unknown. We will include the recently discovered signaling molecules that may contribute to the emergence of CVD brought on by type 2 diabetes in this section (Demir, 2021).

One of the most prevalent types of CVD in people with type 2 diabetes is atherosclerosis, which is the process of plaque development inside the arteries. Atherosclerosis development is complex, including a wide range of pathogenic triggers and cell types. By encouraging endothelial cell dysfunction, which occurs early in the formation of atherosclerotic lesions, hyperglycemia acts as a significant risk factor for atherosclerosis. The synthesis of AGEs is triggered by high blood glucose levels, which disrupt the function of the proteins or lipids by nonenzymatically attaching to them. For instance, AGE-modified proteins or lipoproteins bind to and activate the AGE receptor (RAGE), increasing VCAM-1 expression and improving binding to monocytes that infiltrate into the ECM between endothelium and smooth muscle cells. (Borndfelt, 2009; Wang, 2016).

2.3.3. Diabetic retinopathy

Diabetes frequently leads to diabetic retinopathy. Nearly 20% of individuals have diabetic retinopathy at the time of diagnosis, and 40–45% of patients eventually acquire retinopathy as the illness progresses. Endothelial cells of the retinal microvasculature and the pericytes, which sit below the endothelial cells to support and control endothelial cell function, are the two primary cell types of the retina that are affected by diabetic retinopathy. In a nutshell, AGEs, oxidative stress, and hyperglycemia damage the tight connections between endothelial cells and cause pericytes to detach and undergo apoptosis (Demir, 2021).

2.3.4. Diabetic neuropathy

Diabetic neuropathy, which affects the peripheral and autonomic nerve systems, affects almost half of diabetes patients. The peripheral sensory nerve endings in the hands and lower limbs are often affected by diabetic neuropathy, which results in pain, burning, tingling, and numbness. Motor nerve endings in the lower extremities are injured as the condition worsens, leading to loss of balance and a numb foot with sensory loss. There are instances where diabetic neuropathy occurs at the proximal areas, such as the thigh or pelvis, and exhibits a proximal-to-distal gradient, in addition to peripheral nerve loss (Schwarz, 2020).

New research reveals that the development of diabetic neuropathy may also be influenced by insulin resistance and insulin deficiency in sensory nerves. A neurotrophic hormone known as insulin is necessary to preserve healthy neuron activities. Diabetes-related mitochondrial dysfunction, limited ability to regenerate tissue, and impaired neurochemical production are all factors that may contribute to the onset of diabetic neuropathy (Grote, 2016).

2.3.5. Liver fibrosis

As late consequences of diabetes, non-alcoholic steatohepatitis (NASH) and liver fibrosis are also becoming more prevalent. When everything are normal, the liver can handle sudden stresses well and repair as needed. Damaged cells' apoptosis is a critical step in the regeneration process, which must be kept under control for normal liver function. On the other hand, persistent exposure to hyperglycemia, insulin resistance, and excessive lipid buildup provide a chronic inflammatory state where lipotoxicity and oxidative stress help to progress non-alcoholic fatty liver disease from a reasonably benign condition to NASH (NAFLD). In contrast to NAFLD, NASH is seldom reversible and, if untreated, advances into fibrosis and then cirrhosis. Since NASH and/or liver fibrosis are the most frequent reasons for liver transplants globally, there are currently no FDA-approved treatments for these conditions (Demir, 2021).

3. Acute Myocard Infarction

Mendis et al in their journal stated, The definition of myocardial infarction according to WHO is a cell death (necrosis) of the heart muscle caused by ongoing ischemia. MI usually originates from acute manifestations of atherosclerosis associated with coronary heart disease, causing blockage of the coronary arteries (Mendis et al, 2010).

Meanwhile, according to the European Society of Cardiology (ESC), a condition can be regarded as an acute myocardial infarction if there is an acute myocardial injury characterized by the occurrence of myocardial ischemia, changes in cardiac troponin values of at least one value from the upper limit of the 99th percentile, and at least one of the symptoms below this:

• Symptoms of myocardial ischemia
• Changes in ECG values are ischemic
• Pathological changes in Q waves
• Imaging evidence of recent loss of viable myocardium or new abnormalities of regional wall motion in a pattern consistent with an ischemic etiology
• Presence of coronary thrombus identified on the basis of angiography or autopsy results (ESC, 2018)

3.1. Epidemiology

Myocardial infarction spreads in various ways in the world. In the United States and United Kingdom, the incidence of myocardial infarction reaches 650,000 and 180,000 each year. A total of more than 3 million people suffer from STEMI and 4 million people suffer from NSTEMI in the world.

According to studies, India is 4 times more at risk of suffering from AMI than the rest of the world's population, this is due to a combination of genetics and lifestyle factors that lead to metabolic dysfunction. Research on 1000 population in India, <> attacked by AMI. The mortality rate for AMI reaches 30% or every 1 out of 25 people who get AMI who goes through the initial stages of hospitalization, dies in the first year after being diagnosed. The mortality rate reached 31.7% caused by IMA.

3.2. Etiology

3.2.1. Classification of myocardial infarction

There are several types of myocardial infarction classified by Thygesen et al. (2013) in the Fourth Universal Definition of Myocardial Infarction based on pathological conditions, clinical differences, and prognosis, as well as differences in treatment strategies, including:

- Type 1 Myocardial Infarction
  Type 1 myocardial infarction is necrosis of heart muscle cells due to ischemia in blood vessels caused by atherosclerosis, ulceration, fissure, erosion or dissection which produces intraluminal thrombus in one or

more coronary arteries. MI type 1 may occur in the presence of severe CHD, 5-20% in non-obstructive patients or in the absence of CHD an MI can be found by angiography. (Tygesen et al., 2018).

- Type 2 myocardial infarction
  Type 2 myocardial infarction is caused by an imbalance between the supply of oxygen and the oxygen needed by the myocardium, not due to cases of myocardial necrosis caused by CHD. In patients with suspected CAD, acute stressors such as acute gastrointestinal bleeding with decreased hemoglobin, or tachyarrhythmias that may be clinically manifest myocardial ischemia also occur in myocardial injury and type 2 myocardial infarction. ST elevation in type 2 myocardial infarction varies from 3-24%. (Thygesen et al., 2018)
- Type 2 Myocardial Infarction and Myocardial Injury
- Type 2 myocardial infarction and deep non-ischemic myocardial injury occur together. The clinical difference that distinguishes it is that myocardial infarction requires changes in cardiac troponin (cTn) values while acute myocardial injury also finds the same thing, but the injuries experienced are more related to structural heart disease, changes in cardiac troponin (cTn) values are also more stable. (Thygesen et al., 2018)
- Myocardial Infarction Type 3
  Type 3 myocardial infarction caused by sudden cardiac death with symptoms suggestive of myocardial ischemia accompanied by suspected EKG changes due to recent ischemia or recent Left Bundle Brunch Block (LBBB) represents a dubious diagnostic group. Often patients who experience events like this die before the blood sample is examined for cardiac biomarkers, or even if there has not been an increase in cardiac biomarkers identified. (Thygesen et al., 2018)
- Type 4a Myocardial Infarction associated with Percutaneous Coronary Intervention (PCI) and 4b Myocardial Infarction due to stent thrombosis
  Type 4a is a myocardial infarction that arises due to an increase in cardiac troponin levels above 5 times the upper limit of the 99th percentile in patients with normal values or increased troponin levels to above 20% if normal values are increased or decreased. Whereas in Type 4b, is a myocardial infarction accompanied by stent thrombosis. This can be detected by angiography or autopsy in which myocardial ischemia is found and is accompanied by an increase or decrease in cardiac biomarker values from normal levels of at least one value above the upper limit of the 99th percentile normal. (Thygesen et al., 2018).
- Type 5 Myocardial Infarction Associated with Coronary Artery Bypass Grafting (CABG)
  Defined as a 10-fold increase in cardiac biomarker levels. The increase in this biomarker is associated with CABG insertion. (Thygesen et al., 2018).

Myocardial infarction with ST elevation vs non-ST elevation

Myocardial infarction with ST-elevation (STEMI) is an event of transmural myocardial ischemia that will result in myocardial injury or necrosis. NSTEMI is myocardial infarction without S-segment enhancement. T on the EKG. Myocardial infarction based on etiology and pathogenesis is divided into 5, in type 1 myocardial infarction, STEMI and NSTEMI include this category (Akbar H et al., 2022).

Classification of Acute Myocardial Infarction based on morphology

Divided into 2:

a. Transmural infarction
   Transmural infarction is associated with atherosclerosis in the major coronary arteries. In transmural infarction, it is also divided into anterior, posterior, or inferior infarction. Transmural infarction is thorough in the thickness of the heart muscle and eventually causes total blockage in the area of the blood vessel supply (Reznik A G, 2010).
b. Subendocardial infarction

Muscles located in the subendocardium have a high frequency of infarction even in the absence of evidence of infarction on the outer surface of the heart, which includes small areas of the subendocardial wall of the left ventricle, interventricular septum, or papillary muscles (Reznik A G, 2010) .

The cause of this is due to the blood vessels in the subendocardium experiencing systolic compression of the heart, so that, in the subendocardial layer under normal circumstances it is more difficult to obtain a stronger blood flow. Therefore, the first thing to be damaged in any interruption of the supply of blood flow to the heart is the subendocardial layer, then it spreads towards the epicardium (Guyton and Hall, 2015).

3.3. Risk factors

IMA risk factors are divided into 2, risk factors that can be changed and risk factors that cannot be changed.

- Modifiable risk factors
  - Smoking

    Smoking is known to be a strong predictor of myocardial infarction, premature atherosclerosis, and sudden cardiac death. A person can suffer a myocardial infarction 7 years earlier and is 2 times more likely to have an infarction than a non-smoker (Huma et al., 2012).
  - Physical Activity

    A person is at risk of having heart disease, especially myocardial infarction, one of which is caused by lack of physical activity. It is best if this condition is treated by starting exercise with moderate or not too heavy frequency (Huma et al., 2012).
  - LDL and triglyceride levels

    Increased LDL levels and the density of triglycerides are also important predisposing factors for myocardial infarction. as a measuring tool to identify high-risk individuals, one of the determining markers can use increased triglyceride levels (Huma et al., 2012).

    Dyslipidemia is a risk factor for AMI. There is evidence to suggest that LDL cholesterol is primarily atherogenic. Several studies have shown that reducing LDL cholesterol levels can reduce the incidence of AMI. Increased levels of LDL cholesterol are associated with the formation and growth of atherosclerotic plaques, instability and thrombosis (Gaziano et al., 2010).
  - Obesity or Body Mass Index (BMI)

    Increasing the measurement value to determine a person's nutritional status based on weight and height or better known as Body Mass Index (BMI) can directly increase the incidence of myocardial infarction due to infarction due to extreme obesity (Huma et al., 2012).
  - Diabetes mellitus
  - Hypertension

    Apart from DM, hypertension is known to have a close relationship with myocardial infarction. Hypertension is a very strong risk factor for MI. Hypertension is a major risk factor that causes atherosclerosis in the coronary arteries which can cause heart attacks (Huma et al., 2012).
  - Psychological stress

    Chronic life stress, social isolation and anxiety are psychosocial factors that can increase the risk of heart attack and stroke. (Huma et al., 2012).
- Risk factors that cannot be changed
  - Age

In terms of age, around 80% of the population of patients with heart disease die at the age of 65 years or more (Huma et al., 2012). As a person gets older, the risk also increases sharply for coronary heart disease.

- Gender
  When viewed from gender, men are more at risk of having more heart attacks and having heart attacks earlier. However, it does not rule out that women are also at risk for heart disease, the risk of women having a heart attack increases in post-menopausal conditions (Huma et al., 2012).
- Family or hereditary history of disease
- A person's risk of developing heart disease will increase if they have parents or siblings with a history of coronary heart disease (CHD) or stroke before the age of 55 for male family members, and 65 years old for female members.
- Genetic factors
  A comprehensive analysis study using molecular genetics showed that the myocardial infarction gene locus actually has its own unique locus and does not overlap with the chromosomal loci associated with the risk factors previously mentioned. (Huma et al., 2012).

3.4. Pathophysiology

The condition of acute myocardial infarction mostly comes from acute manifestations of atheromatous plaques in coronary arteries that have ruptured. This condition is related to type 1 myocardial infarction which is usually triggered by atherosclerotic plaques. These events are related to changes in plaque composition and thinning of the fibrous cap covering the plaque. This is followed by the process of platelet aggregation and activation of the coagulation pathway. Until a thrombus is formed with lots of platelets in it. This thrombus can clog the coronary arteries by becoming emboli which will clog the distal coronary arteries. Also, vasoactive substances will be excreted, causing vasoconstriction of blood vessels. Reduced coronary blood flow will cause myocardial ischemia. If the oxygen supply stops for 20 minutes, myocardial necrosis will occur (ESC, 2018., Santoso et al., 2009).

Meanwhile, the pathophysiology that leads to type 2 myocardial infarction is ischemic myocardial injury, namely a mismatch between oxygen supply and demand. By definition, atherothrombotic plaques are not a feature of type 2 acute myocardial infarction. However, the results of angiography in several conditions found coronary atherosclerosis in type 2 myocardial infarction (ESC, 2018).

3.5. Diagnosis

The European Society of Cardiology (ESC) has divided the diagnosis of acute myocardial infarction into 2, STEMI and NSTEMI.

- Diagnosis of STEMI
  Consistent symptoms in STEMI patients are consistent chest pain and abnormalities in the EKG examination. Specific signs found were history of CAD, neck pain and lower jaw or left arm. In some patients, unusual symptoms such as shortness of breath, nausea/vomiting, dizziness, palpitations, syncope were also found
- Diagnosis NSTEMI
  Clinical Presentation
  Criteria for acute chest pain experienced by NSTEMI patients:
  - Prolonged acute chest pain
  - New onset angina (<3 months)
  - Crescendo angina

- Post-myocardial infarction angina

Physical examination

In patients with suspected NSTE-ACS, a normal physical examination is common, auscultatory examination reveals a systolic murmur due to ischemic regurgitation. Often also found causes of chest pain that are non-coronary (eg pulmonary embolism, acute aortic syndrome, myopericarditis, aortic stenosis) or abnormalities outside the heart (eg pneumothorax, pneumonia, or musculoskeletal disease).

Additional examination

- ECG
  The characteristics of the ECG examination found in patients suspected of NSTE-ACS are ST segment depression, transient ST segment elevation, and T-wave changes. However, in 30% of cases, NSTE-ACS patients have normal ECG results.
- CTN biomarkers
- Algorithm 'rule in' and 'rule out'(ESC, 2018).

4. Type 2 Diabetes Mellitus and Acute Myocardiac Infarction

Prevalence of DM in AMI patients varied from 20-30% (Arnold, 2014), but it keeps increasing (Gandhi, 2006). Based on a study in 2021 between two cohorts from American and Chinese, the result showed DM is often find in critical AMI patients (almost half and one-third) (Chen, 2021). According to a study in Qatar, as much as 54% prevalence of DM was shown in critical AMI patients (El-Menyar, 2009).

DM used as a good predictor for prognostic in AMI patients. In patients with AMI, DM contribute to 2 until 9 times higher risk of death (Chen, 2021). During a study in Italy, the death of DM patients with STEMI was also trigger by the predominant factors of the patients who have cardiorenal dysfunction (Marenzi, 2019).

Patients with DM always have bigger risk to atherosclerosis, with a more diffuse and more of multivessel coronary artery disease (Kim, 2011). Additionally, individuals with DM and AMI display micro- and macrovascular problems more quickly, which may be a factor in their worse prognosis. A number of pathophysiological explanations have been put forth to explain how DM adversely affects patients with AMI, including abnormalities in endothelial, vascular smooth muscle cell, and platelet function; decreased bioavailability of nitric oxide; increased oxidative stress; and a pro-inflammatory/thrombotic state (Paneni, 2013).

5. Summary

Diabetes mellitus is one of the risk factors for acute myocardial infarction. Prevalence of DM in AMI patients increasing by each year. It is a good finding that DM will be a good predictor for AMI prognostic. Patients of AMI with DM usually have worse prognosis and bigger chance leading to death. DM could affect abnromalities in endothelial, vascular smooth muscle cell, and platelet function; decreased bioavailability of nitric oxide; increased oxidative stress; and a pro-inflammatory/thrombotic state.

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