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Subclinical Atherosclerosis in Young Adult Population with First Degree Relatives of Type 2 Diabetes Mellitus

Muhammad S. Abdaly, Mohamad S. Azizi, Ika P. Wijaya, Pringgodigdo Nugroho, Dyah Purnamasari

Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Dyah Purnamasari, MD., PhD. Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. email: dyah_p_irawan@yahoo.com.

ABSTRAK

Penyakit kardiovaskular (CVD) menjadi penyebab utama kematian secara global. Infark miokard akut pada orang dewasa muda jarang terjadi. Aterosklerosis adalah penyebab utama CVD, termasuk infark miokard, stroke, gagal jantung, dan penyakit arteri perifer. Kondisi ini dimulai sejak dini dan bersifat progresif. Faktor risiko CVD termasuk hipertensi, dislipidemia, dan obesitas berperan dalam proses aterosklerosis dan merupakan komponen dalam sindrom resistensi insulin.

Salah satu faktor risiko untuk terjadinya resistensi insulin pada orang sehat adalah first degree relative (FDR) dari pasien diabetes melitus tipe 2 (T2DM). Kelompok ini menunjukkan risiko resistensi insulin dan gangguan sel beta pankreas yang lebih tinggi bahkan pada masa remaja, walaupun asimtomatik. Manifestasi klinis dari gangguan metabolik dan aterosklerosis akan muncul lebih awal pada kelompok FDR T2DM yang memiliki pola hidup sedentari dan obesitas, jika dibandingkan dengan kelompok non-FDR. Beberapa penelitian sudah berusaha untuk mendeteksi gangguan metabolik dan aterosklerosis subklinis yang mungkin terjadi; oleh karena itu pencegahan dini dapat dilakukan pada kelompok berisiko tinggi ini. Sayangnya, faktor-faktor yang memengaruhi onset dan tingkat keparahan manifestasi klinis yang akan terjadi selanjutnya dari studi-studi sebelumnya masih belum jelas.

Kata kunci: *penyakit kardiovaskular, aterosklerosis, first-degree relative, diabetes melitus tipe 2.*

ABSTRACT

Cardiovascular disease (CVD) remain a leading cause of death globally. The concept of acute myocardial infarction in young adults was uncommon. Atherosclerosis is the leading cause of CVD, including myocardial infarction, stroke, heart failure and peripheral artery disease. This condition is initiated early in childhood and progressive in nature. CVD risk factors includes hypertension, dyslipidemia and obesity play a role in the development of atherosclerosis and components in insulin resistance syndrome.

One of many risk factors for insulin resistance in healthy individuals is a first-degree relative (FDR) of Type 2 Diabetes Mellitus (T2DM) patients. This group shows a higher risk of insulin resistance and pancreatic beta cells disruption even in adolescence, although they often remains asymptomatic. Clinical manifestations of metabolic disorders and atherosclerosis will appear earlier in the FDR T2DM group who have sedentary lifestyles and obesity, when compared to the non-FDR group. Several studies have attempted to detect metabolic disorders and subclinical atherosclerosis that might occur; therefore an early prevention can be carried out in these high-risk groups. Unfortunately, factors that affect the onset and the severity of the prospective clinical manifestations from the previous studies remained inconclusive.

Keywords: *cardiovascular disease, atherosclerosis, first-degree relative, type 2 diabetes mellitus.*

INTRODUCTION

Cardiovascular disease (CVD) remain a leading cause of death globally. In 2013, approximately 17.3 million out of 54 million of total death per year was caused by CVD.[1] Based on a WHO report in 2014, CVD ranked as the leading cause of death in Indonesia, at an approximate of 37% of all causes of death.[2] The concept of acute myocardial infarction in young adults was uncommon. A study by Mahle, et al.[3] reported that only 5% of total number of acute coronary syndromes constituted of individuals younger than 40 years. A study by Rithza, et al.[4] described that the number of patients younger than 45 years old who suffered from acute coronary syndrome were 101 cases.

Atherosclerosis is the leading cause of CVD, including myocardial infarction, stroke, heart failure and peripheral artery disease. This condition is initiated early in childhood and progressive in nature. Atherosclerosis remains asymptomatic for the first few decades before becoming clinically manifested. This condition is known as subclinical atherosclerosis.5 CVD risk factors includes hypertension, dyslipidemia and obesity play a role in the development of atherosclerosis and components in insulin resistance syndrome.[6]

One of many risk factors for insulin resistance in healthy individuals is a first-degree relative (FDR) of Type 2 Diabetes Mellitus (T2DM) patients. This group shows a higher risk of insulin resistance and pancreatic beta cells disruption even in adolescence, although they often remains asymptomatic.[7] Clinical manifestations of metabolic disorders and atherosclerosis will appear earlier in the FDR T2DM group who have sedentary lifestyles and obesity, when compared to the non-FDR group. Several studies have attempted to detect metabolic disorders and subclinical atherosclerosis that might occur; therefore an early prevention can be carried out in these high-risk groups. Unfortunately, factors that affect the onset and the severity of the prospective clinical manifestations from the previous studies remained inconclusive.

ATHEROSCLEROSIS AND INSULIN RESISTANCE

Atherosclerosis is a chronic systemic inflammatory process that is related to the elasticity of a blood vessel. It remains as the main cause of cardiovascular diseases such as coronary heart disease and stroke. Blood vessels that are often affected include large blood vessels (aortic, carotid, iliac arteries) and moderate blood vessels (coronary arteries and popliteal arteries).[8]

The cause of atherosclerosis is not fully established yet. Several previous studies have shown that atherosclerosis arises due to endothelial dysfunction that causes structural changes in the arterial wall which result in thickening and stiffening of blood vessels.[9] Endothelial dysfunction occurs due to several factors, such as hypertension, increased low density lipoprotein (LDL) concentration, toxic effects of cigarette, high density lipoprotein (HDL) transportation dysfunction, and insulin resistance. This process will reduce the production of nitric oxide (NO) ultimately resulting in endothelial dysfunction.[10]

In T2DM, the process of atherosclerosis has occurred in the phase of insulin resistance, which precedes the onset of hyperglycemia, thus resulting in advanced cardiovascular complications. Insulin resistance is a condition of the inability of insulin to produce biological effects, including effects on glucose metabolism, protein, and lipids and to regulate blood vessel function. Hyperinsulinemia is the body's compensation mechanism to prevent hyperglycemia. Hyperinsulinemia increases the individuals' risk to develop glucose intolerance, increase triglyceride levels, decrease HDL cholesterol levels, and hypertension.[11] Hyperinsulinemia accompanied by hyperglycemia and dyslipidemia will increase the progression risk of atherosclerosis, which in turn will increase the risk of CVD.[12] The pathophysiology of insulin resistance and atherosclerosis can be seen in **Figure 1**.

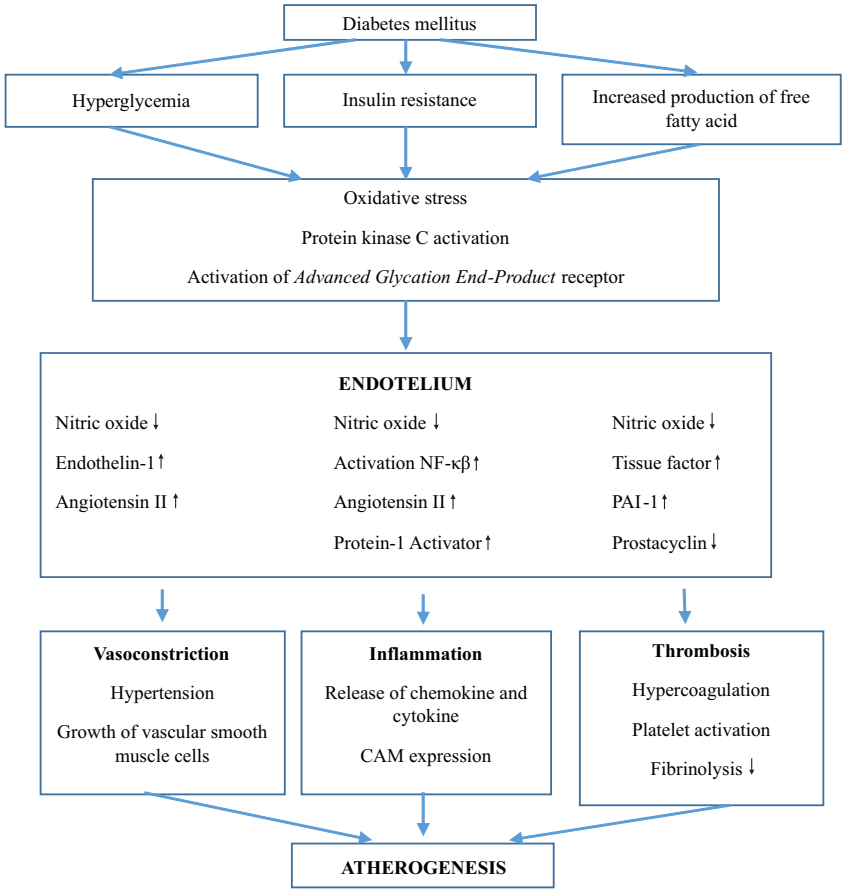

Figure 1. The pathophysiology of atherosclerosis in diabetes mellitus[12]

INSULIN RESISTANCE IN POPULATION WITH FIRST-DEGREE RELATIVES OF TYPE 2 DIABETES MELLITUS

Studies in twins indicate that insulin resistance is influenced by genetic and environmental factors but insulin secretion is mainly influenced by genetic factor.[13] The role of genetics has been studied extensively but much less when compared to studies regarding the role of environmental factors in T2DM. Genetic studies are challenging, considering that interethnic and interracial marriages are not uncommon, therefore it is difficult to conduct a study in a certain group of race. Studies in siblings of T2DM in one European ethnic group showed that phase 1 and 2 insulin secretion was decreased with normal insulin sensitivity, whereas in African-American ethnic groups it showed that insulin resistance was the first clinical manifestation that was observed, without the presence of pancreatic beta cell secretion dysfunction.[14] A study by Rosenbaum, et al.[14] in 2004 also reported a significant association between the family history of T2DM with impaired pancreatic beta cell function (not affected by body fat composition) without the presence of insulin resistance. In the study it was also reported that insulin resistance was mainly affected by increased in body fat composition.

The offspring of individuals with T2DM is a high-risk population for insulin resistance and has more severe cardiovascular risk factors, such as thicker intra-abdominal fat, higher systolic blood pressure, higher blood triglyceride and total cholesterol levels, lower HDL cholesterol levels and higher endothelium dependent vasodilatation (EDV), when compared with populations without family history of T2DM.[15]

Relatives (siblings and biological children) of T2DM subjects who are still normoglycemic also have higher insulin concentrations, lower peripheral glucose uptake and more accumulation

of fat tissue in the muscle compared to subjects without a history of T2DM.[15,16]

Studies regarding the prevalence of insulin resistance in T2DM-FDR population are still limited in Indonesia. Purnamasari, et al.[17] have conducted a study in Jakarta and showed that the prevalence of insulin resistance in siblings of patients with T2DM by 26,67%. Kumar, et al.[18] in India also conducted a study regarding the prevalence of insulin resistance in the FDR population and the results were 37.8%. However, prevalence of insulin resistance syndrome based on National Cholesterol Education Criteria Adult Treatment Panel III (NCEP ATP III) criteria in the adult general population in the United States is slightly lower at an approximate of 24%.[19]

SUBCLINICAL ATHEROSCLEROSIS DIAGNOSIS

Subclinical atherosclerosis is a manifestation of endothelial dysfunction and the onset of CVD. In these conditions, there has been an alteration in the blood vessel walls without any significant symptoms; therefore, at this stage an early intervention is expected to prevent cardiovascular events in the future.[20]

Several approaches are used to detect atherosclerosis as early as possible, both non-invasive and invasive techniques. Invasive techniques have the advantage of a higher levels of precision and the ability to directly see abnormalities that occur in blood vessels. The disadvantages of this technique include discomfort for patients, higher costs, and higher risks of complication. While the non-invasive technique has relatively affordable cost and more convenient for patients.[21]

There are several non-invasive modalities that can be used to detect subclinical atherosclerosis including B-mode ultrasound examinations that can determine the thickness of the arterial intima-media arteries; high resolution magnetic resonance imaging (MRI) that is capable of evaluating the volume, plaque composition, and integrity of fibrous cap; and electron-beam computed tomography (EBCT) which can measure coronary artery calcification but cannot ascertain the tendency of plaque to rupture. Whereas invasive techniques include coronary angiography which is able to directly assess the coronary stenosis and intravascular ultrasound examination which is able to identify plaque size and composition that cannot be done through coronary angiography.[21]

The assessment of tunica intima media thickness of carotid artery by carotid ultrasound has been approved by the American Heart Association as a diagnostic tool for atherosclerosis.[21] In addition, the measurement of the thickness of the carotid artery is an examination that can be performed quickly, without radiation exposure, non-invasive and at affordable costs.[22] Carotid ultrasound examination had a sensitivity of 93.4% and a specificity of 94% to assess vascular calcification, blood vessel diameter, thickness of tunica intima media, assessing the presence of plaque and its expansion.[23]

THE CAROTID INTIMA MEDIA THICKNESS AS CARDIOVASCULAR DISEASE PREDICTOR

The carotid intima-media thickness (CIMT) assessment is an examination of the thickness of the carotid artery wall, where atherosclerotic lesions in the common carotid artery depicted systemic atherosclerosis. This non-invasive procedure is relatively easy to perform and the results are comparable to other imaging techniques.[23] Compared with coronary angiography, CIMT examination has a sensitivity and specificity in predicting coronary artery disease of 89.7% and 86.7%, respectively.[24]

The measurement carotid artery thickness has the prognosis to predict the incidence of stroke and coronary heart disease in the future. Hazard ratio of the risk of coronary artery disease between the mean thickness of CIMT ≥1 mm and <1 mm was 5.07 (in women) and 1.85 (in men). While the hazard ratio of stroke in the ratio of CIMT thickness ≥1 mm and ¸0.6 mm was 8.5 (in women) and 3.6 (in men).[25] A meta-analysis study involving 8 studies with a total of 37,197 subjects showed that a 0.1 mm increase in the CIMT thickness of the carotid artery would increase the risk of myocardial infarction from 10 to 15% and the risk of stroke from 13 to 18%.[26] Thus a thicker CIMT increases the risk

for cardiovascular events, such as myocardial infarction and stroke.

THE GENETIC ROLE OF ATHEROSCLEROSIS IN FIRST DEGREE RELATIVE OF TYPE 2 DIABETES MELLITUS PATIENTS

In atherosclerosis, a prospective study in Caucasian ethnicity, which involved biological offsprings of patients with T2DM, who were normoglycemic and normotensive showed a more severe endothelial vasodilation and carotid artery thickening when compared to subjects without a family history of T2DM. This endothelial dysfunction is mediated by conditions of insulin resistance.[27]

Insulin resistance affects the renin angiotensin aldosterone system (RAAS). Therefore, the development of atherosclerosis is also be affected by the RAAS. Although there were several studies that has reported this relationship between RAAS and atherosclerosis in high-risk populations (hypertension, diabetes, cerebrovascular disease and arterial artery disease) and normal populations, the effect of RAA systems on atherosclerosis in the FDR of T2DM patients remain unclear.[28,29]

A study by Goldfine, et al. compared endothelial dysfunction and insulin resistance between 38 non-DM subjects with a history of T2DM in both parents and 38 control subjects. The study showed that the groups with family history of T2DM had a decreased endothelial dependent vasodilatation (EDV) response and further multiple regressions analysis showed that family history of DM was a significant determinant of EDV.[30]

Several studies have shown that mitochondria play an important role in the development of atherosclerosis. Mutations in mitochondrial DNA (mtDNA) at the nucleotide position 3243 A to G (A3243G) are the main genetic causes of diabetes.[31] Mitochondrial DNA has a somatic mutation rate of 5 to 20 times greater than nuclear DNA (nDNA), as mtDNA is located close to the respiratory chain that has the potential to produce reactive oxygen species (ROS). ROS is the main source of oxidative stress at cellular levels.[32] Damage to mtDNA by ROS will result in the dysfunction of protein synthesis for the respiratory chain, in turn resulting in ATP production dysfunction and increased ROS leakage, which causing a vicious cycle because further mtDNA mutations will occur.

Insertion and deletion polymorphism of the angiotensin converting enzyme (ACE) is one of the polymorphisms associated with atherosclerosis.[33] A study also found that p22phox, the NAD (P) H-oxidase subunit that produces ROS, also has polymorphisms that is associated with polymorphism in atherosclerosis.[34]

The population of FDR T2DM has earlier endothelial dysfunction and subclinical atherosclerosis when compared to non-FDR T2DM, despite remaining normotensive and normoglycemic. The role of genetics in atherosclerosis has been studied extensively through genetic polymorphisms studies, for example mtDNA polymorphism that has a protective role against atherosclerosis.

CAROTID INTIMA-MEDIA THICKNESS IN FIRST DEGREE RELATIVE OF TYPE 2 DIABETES MELLITUS

In 2003, Pannacciulli, et al[35] conducted the first study regarding the presence of atherosclerotic lesions in the population with FDR of T2DM. The study was conducted in Italy involving a total of 401 subjects aged 18-45 years with normal blood glucose concentrations. The results in the FDR group had a greater thickness of media intima than the non-FDR group. The study also showed a positive correlation between the thickness of the carotid media intima with age, BMI, abdominal circumference, triglyceride levels, systolic blood pressure, fasting blood glucose, 1-hour and 2-hour post prandial blood glucose and HOMA-IR, while the HDL showed a negative correlation.

Ahmad, et al.[36] in 2006 studied a total of 76 subjects who had normal blood glucose levels and were not obese in North India (38 subjects who had a family history of T2DM, 38 other subjects without a family history of T2DM). The results also indicate the same thing as the research conducted by Pannacciulli, et al. in 2003. Besides the thickness of the intima media, which was significantly different between the two groups, the CRP levels and BMI in the FDR

of T2DM group were higher than the non-FDR group. The thickness of tunica intima media in this study had a positive correlation with systolic blood pressure, LDL cholesterol, post-prandial insulin levels and HOMA-IR.

In 2017, Kumar, et al.[37] conducted similar study as Ahmed et al. in India. The difference was that they differentiated subjects with a history of parents (father or mother or both) who suffer from type 2 diabetes in relation to inflammation, insulin resistance, body mass index and thickness of the intima media. The result showed that individuals who have a history of both parents suffering from type 2 DM had worse glycemic status, higher CIMT compared to individuals who only have one parent suffering from type 2 DM.

An unpublished study in Indonesia by Abdaly, et al.[38] showed that the average CIMT of the FDR group was 0.44 mm with a standard deviation of 0.06 mm. While the mean CIMT of non-FDR group was lower than FDR subject, which was 0.38 mm with a standard deviation of 0.05 mm (p=0.005). The results of this study are in line with previous studies that examined the thickness of the CIMT in the subject of FDR T2DM. This study shows that CIMT in FDR and non-FDR group in Indonesia have the lowest average when compared to subjects in Brazil, Italy, and India. This might be due to the higher body mass index of the Caucasians and Indians when compared to Malays.[39,40]

The body mass index (BMI) has been shown to be a positively correlated factor with carotid artery intima-media thickness. BMI and waist circumference have a relationship with the occurrence of insulin resistance. In obese subjects with insulin sensitivity, insulin plays a role in inhibiting the up-regulation of inflammatory markers circulating in the blood. Conversely, high levels of inflammatory markers due to impaired insulin inhibitory effects were found in obese subjects with insulin resistance.[41] The increase in acute phase protein as a result of insulin resistance will later lead to endothelial dysfunction and atherogenesis.[42]

CONCLUSION

Family history of the first degree of T2DM play an important role in the occurrence of subclinical atherosclerosis, especially at a young age in addition to other conventional factors for the occurrence of cardiovascular diseases such as hypertension, diabetes mellitus, dyslipidemia, smoking and obesity. Thickness of the carotid artery intima media as the surrogate marker of atherosclerosis has been shown to be thicker in the FDR group when compared to non-FDR group.

CONFLICTS OF INTEREST

None of the authors have any conflict of interest to declare.

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