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DIFFERENCE OF FETUIN-A LEVEL IN TYPE 2 DIABETES MELLITUS WITH CORONER HEARTH DISASE AND WITHOUT CORONER HEART DISEAS

Tetty Wahyuni Panjaitan*[1], ZulfikarLubis[2] & Santi Syafril[3]
[*1]Resident of Clinical Pathology, Faculty of Medicine, University of North Sumatra Medan
[2]Department of Clinical Pathology, Faculty of Medicine, University of North Sumatra Medan
[3]Department of Internal Medicine, Faculty of Medicine, University of North Sumatra Medan

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Abstract

Background

FetuinFetuin- A a glycoprotein that forms in the liver and has a strong relationship with the occurrence of type 2 DM. FA inhibits the autophosphorylation process of insulin receptors, suppresses adiponectin and inhibits vascular calcification. Increased levels of FA with decreased levels of adiponectin cause insulin resistance. Insulin resistance causes hyperglycemia. Continuous hyperglycemia will cause inflammation and impaired blood fat metabolism resulting in accumulation of fat in blood vessels known as atherosclerosis.

Method

A cross sectional study design was carried out at the Clinical Pathology Unit of RSUP. H. Adam Malik (HAM) Medan in January 2018. Subjects were patients with type 2 diabetes mellitus who were treated at the Cardiology Polyclinic and Endocrinology Polyclinic of the Department of Internal Medicine Haji Adam Malik General Hospital, Medan. As many as 20 people with type 2 diabetes mellitus (male12, female 8) and type 2 DM sufferers without CHD as many as 20 people (male 9, female 11). Data is processed and analyzed on a computer program. To see the difference in FA levels in type 2 DM with CHD and without CHD used t-test when paired with normal distribution, if not normally distributed, the Man Whitney test is used. The value of $p < 0.05$ was stated as significant.

Result and Discussion

There was a significant difference in FA levels between groups of type 2 DM patients with CHD (207.07 ± 16.01) and type 2 DM patients without CHD (294.85 ± 10.97) with P = 0.000 (P <0.05).

Conclusion and Suggestion

FA can be used as an initial marker of the occurrence of vascular calcification in patients with type 2 diabetes. It is necessary to screen the FA examination in patients with type 2 diabetes mellitus in order to find out the process of vascular calcification has occurred since the beginning.

Introduction

Fetuin-A (FA) is a multifunctional plasma that was first discovered in 1944 by Kai O. Pedersendari. [1] It is a glycoprotein formed in the liver. [1] FA has many functions such as regulating bone remodeling, calcium metabolism, inhibiting phosphorylation of insulin tyrosine kinase, inhibiting transformation of growth factor-β (TGF-β) and as an inhibitor of calcification of arterials.[2] FA also plays a role in inducing the function of cytokines which are markers of inflammation (pro-inflammatory cytokines or provocation cytokines).[3] Adiponectin which is atheroprotective.[4]

FA and Adiponectin are key regulatory proteins in the liver. Increased FA levels are proven to suppress Adiponectin. Higher FA levels and lower Adiponectin levels can cause insulin resistance induced by obesity and develop into type 2 diabetes mellitus (DM). Under normal beta cell conditions, insulin resistance induced by FA and the effect of subclinical inflammation on β cells can be compensated; However, with the disruption of β cell function, increased levels of FA can cause DM type 2.[6,7]

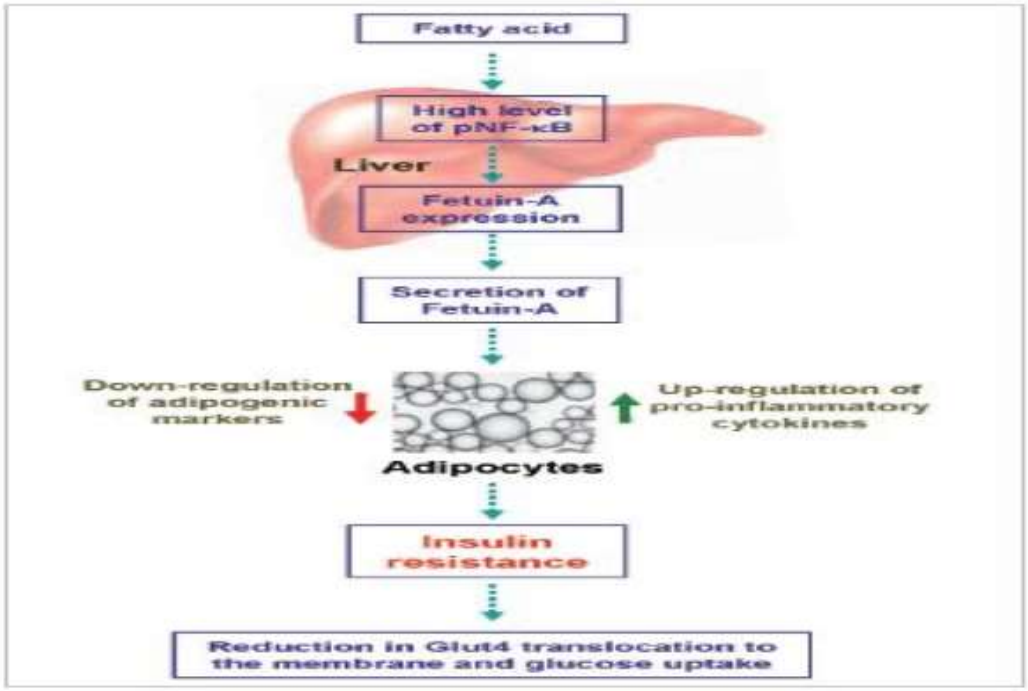

Figure 1. Fetuin-A regulation of adipocytes and insulin resistance, Samir, 2012

In figure 1, the accumulation of fatty acids in the liver will stimulate an increase in the nuclear factor-kappa B (pNF-Kb) protein, which is a protein complex that controls DNA transcription, cytokine production and cell survival. The increase in pNf-Kb stimulates the expression of the gene it regulates. Expression of FA genes aroused an increase in FA levels in the liver. Increased levels of FA will increase the inflammatory response by stimulating pro-inflammatory cytokines and suppressing Adiponectin. Increased levels of FA with a decrease in Adiponectin levels will cause insulin resistance. Insulin resistance will cause Glut4in to be active and Glut4 cannot be transplanted to the membrane so that it cannot carry glucose into cells and impaired glucose absorption. [8,9]

Insulin resistance which is characterized by hyperglycemia, in the long run can cause complications that can affect the eyes, kidneys and nerves, as well as increase the risk of cardiovascular disease.

- Thickening of the basal membrane of small blood vessels, as a result of a decrease in blood supply and oxygen
- Damage to the structure of blood vessels; damage at the molecular level. mainly caused by vascular endothelial dysfunction. Endothelial dysfunction causes blood vessels to be unable to dilate.
- Insulin resistance causes abnormalities such as lipoprotein glycosylation, which increases the Atherogenic potential of blood vessels.
- Increased C-reactive protein (CRP) and interleukin-6, a sign of inflammation and dyslipidemia which also stimulate the process of atherosclerosis,

The relationship between FA with various parameters both physiological and pathological makes FA currently widely studied in order to be an early marker of a disease diagnosis. There are ten relationships between Fetuin-a with various conditions explained in the figure below.[11]

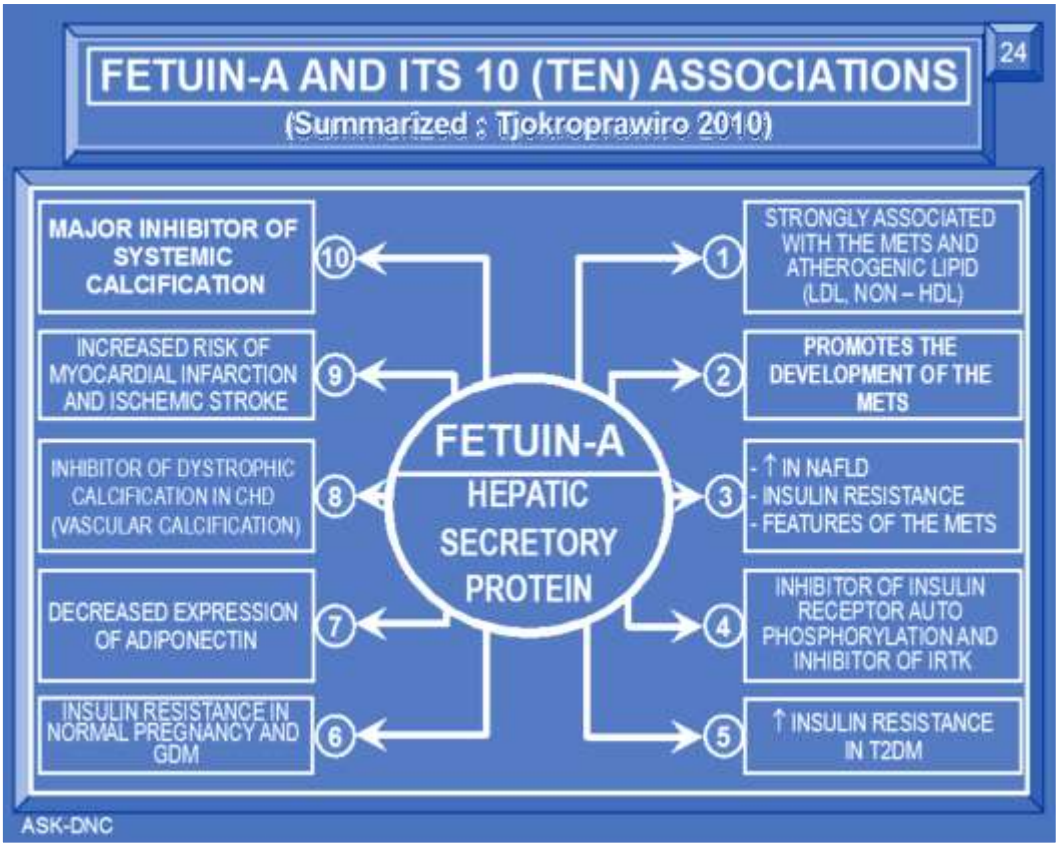

Figure 2. Fetuin-A Effect (Summarized: Tjokroprawiro 2010)

In figure 2, FA which is a protein produced in the liver has a strong relationship with metabolic syndrome and LDL as a cause of atherosclerosis. FA also plays a role in the development of metabolic syndrome. Increased levels of FA are found in NAFLD, insulin resistance, and metabolic syndrome. FA inhibits the autophosphorylation process of insulin receptors and also inhibits insulin receptor tyrosine kinase. High FA levels cause insulin resistance in DM type 2.[12] FA can also cause insulin resistance in normal pregnancy and Gestational DM. FA also functions in reducing adiponectin levels and FA also functions as an inhibitor of vascular calcification. Increased levels of FA can cause an increased risk of myocardial infarction and ischemic stroke. FA also has a major role as an inhibitor of systemic calcification.[13]

The mechanism of action of insulin and FA is well known in the process of insulin resistance which has been identified as a major cause of type 2 diabetes. On the one hand, higher FA levels in the blood than normal can cause insulin resistance but these high levels also function as protectors from the process of atherosclerosis in the arterial.[14] On the other hand, low levels of fetuin-A in the blood can cause vascular calcification and worsen atherogenic conditions. Therefore, FA levels can be used as an early marker of atherosclerosis in patients with type 2 DM.[15]

Material and Methods

The study was conducted by observational analytic method by cross sectional method. The study was conducted in January 2018 to March 2018 at the Department of Clinical Pathology of the USU FK / H. Adam Malik Hospital Medan in collaboration with the Endocrinology Division and the Division of Cardiology at the Department of Internal Medicine FK-USU / RSUP. H. Adam Malik Medan. Subjects were type 2 DM patients who went to the Cardiology and Endocrinology Polyclinic of the Department of Internal Medicine Department of Haji Adam Malik Hospital Medan who met the criteria of the research subjects.

Inclusion Criteria

- Men or women aged 18 - 70 years
- Type 2 DM sufferers without CHD
- Type 2 DM sufferers with CHD
- Give consent to participate in this research

Exclusion Criteria

- Patients with acute and chronic kidney disease
- Patients with impaired liver function
- Hypertension
- Dyslipidemia
- Obesity
- Inflammation / Infection

Research subjects numbered 40 people who were divided into 2 groups, namely type 2 DM patients with 20 people with CHD and 20 people with type 2 DM without CHD and had fulfilled the inclusion criteria. The sample of the study was carried out examination of Fetuin-A. This examination method uses the ELISA technique. Data is processed and analyzed in a computer program, presented in tabular form.

The materials used in this study include, Serum and Fetuin-A reagent. FA levels are tested simultaneously after a number of materials have been collected. The frozen material is thawed at room temperature, then homogeneous using vortex. Calibrator and control solutions are also equated with room temperature (20-25^{o} C). How it works: Add the standard, tested sample and FAP antibodies labeled HRP to the enzyme well that has been coated with FA antibodies then incubate and wash to remove the non-binding enzymes. After adding the chromogen solutions A and B, the color of the liquid will turn blue, and the reaction with the acid will cause the color to turn yellow. Color levels and FA concentration. the sample is positively correlated with the color formed

Results

The results of the normality test showed that the data of Fetuin levels both in the type 2 DM group with CHD and type 2 DM groups without CHD had a P value = 0.200 (P> 0.05). This value indicates that the two data are normally distributed so that further tests can be performed using the unpaired T-test (Parametric).

Karakteristik	Satuan	DM Tipe 2		Nilai *p*
		Dengan PJK (n=20)	Tanpa PJK (n=20)	
Fetuin-A (mean)	pg/mL	207,07 ± 16,01	294,85 ± 10,97	<0,000

The difference was significant when p <0.05, the difference test used the unpaired T-test
Based on the unpaired T-test can be concluded:
There was a significant difference in levels of Fetuin-A between groups of patients with type 2 DM and CHD (207.07 ± 16.01) and patients with type 2 DM without CHD (294.85 ± 10.97) with P = 0.000 (P <0, 05).

Discussion

The mechanism of action of insulin and FA is well known in the process of insulin resistance that has been identified as a major cause of type 2 diabetes. The occurrence of insulin resistance due to the expression of stimulated FA genes results in increased levels of FA in the liver. Increased levels of FA will increase the inflammatory response by stimulating pro-inflammatory cytokines and suppressing adiponectin. Increased levels of FA with a decrease in adiponectin levels will cause insulin resistance. Insulin resistance will cause Glut4in to

be active and Glut4 cannot be transplanted to the membrane so it cannot carry glucose to delam cells and impaired glucose absorption.

Fetuin-A is a glycoprotein produced in the liver, has a strong relationship with metabolic syndrome and LDL as a cause of atherosclerosis. There is a biphasic relationship of Fetuin-A with vascular disease, depending on the stage of atherosclerosis. FA is considered as one of the early markers of atherosclerosis in type 2 DM patients. Low levels of FA in the blood can cause vascular calcification and worsen atherogenic conditions. The relationship between FA levels and the risk of cardiovascular disease depends on its glycemic status. Other studies have also shown that elevated levels of Fetuin-A as a sensitive marker of macrovascular complications in diabetics such as atherosclerosis.

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