Analysis Of Serum Cystatin C Levels In People With Type 2 Diabetes Mellitus As A Biomarker Of Early Detection Of Atherosclerosis

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Abstract.
Type 2 diabetes mellitus (DMT2) is associated with atherosclerosis, which causes the disease. cardiovascular and increased mortality. It is still difficult to detect ateroskelerosis in the early stages. Arterial stenosis often develops without symptoms in patients. DMT2, then causes cardiovascular disease. Therefore, development diagnostics to easily detect early-stage atherosclerosis are needed. In this study, we focused on cystatin C serum, an inhibitor of cysteine proteinase. Some research results, it has reported a significant correlation between serum Cystatin C levels and Arterial stiffness in a group of normal individuals. Cystatin C serum has a correlation strong with a value of elasticity of the carotid artery walls that reflect the degree of atherosclerosis subclinical. This is a new sign that is quite potential as a biomarker of early detection atherosclerosis. The purpose of the study is to know the picture serum Cystatin C levels as an early marker to determine the presence of possible complications of atherosclerosis in DMT2 patients, as well as the usefulness of Cystatin-C in predicting atherosclerosis of the early stages. Research methods are analytical research with use cross-sectional design. The study was conducted by calculating the value of Cystatin C blood serum with DMT2. The study subjects were people with DMT2 in RSUD.Labuang Baji Makassarand its network. Sum the sample in this study was 20 people. Determination of the research subject is done by conducting a search on medical records of DMT2 patients who meet the criteria of inclusion and exclusion to achieve minimum number of samples. The study subjects were classified into two groups based on medical record data searches are subclinical atherosclerosis group and nonclinical group ateroskelorosis. The research sample is a serum sample. Serum sample examination is carried out in the Clinical Prodia Laboratory using PENIA method. The results of this study reported the results that Cystatin-C Serum is closely correlated with subclinical atherosclerosis (arterial stiffness. Increase in serum cystatin-C levels indicates the risk of atherosclerosis in Patients with DMT2. The results of this study reported that serum cystatin C levels in dmt2 patients in the nonclinical atherosclerosis group (n = 10) showed normal cystatin levels (0.50 - 0.96 mg/L), while serum Cystatin-C levels in dmt2 group patients showed normal cystatin levels (0.50 - 0.96 mg/L), while serum cystatin-C levels in DMT2 group patients Subclinical atherosclerosis (n = 10) has an increase in serum cystatin-C levels (> 0.90 mg/L). Level cystatin C serum is associated with SA in DMT2 patients. Cystatin C was identified as a predictor of atherosclerosis risk, after adjusting for a variety of factors associated with diabetes.

Keywords: *Diabetes Mellitus, Cystatin-C, Ateroskelerosis*

I. INTRODUCTION

Diabetes Mellitus (DM) is an important public health issue of the four priority non-communicable diseases targeted by the Researchers World leader. The number of cases and prevalence of diabetes continued to increase over several years last decade. In 2015 Indonesia stood in the seventh position with the number of sufferers. As many as 10 million people. This number is expected to increase by 2040, which is as much as 16.2 million people, it can be interpreted that there will be an increase in sufferers as much as 56.2% from 2015 to 2040 [1,2].DM is a group of metabolic diseases with characteristic hyperglycemia that occurs due to secretion abnormalities and the work of insulin. More than 90% of all diabetic populations are type 2 diabetes mellitus (DMT2) which is characterized by decreased insulin secretion due to progressive reduction of pancreatic beta cell function caused by insulin resistance. DMT2 is associated with atherosclerosis, which causes cardiovascular disease and increased mortality [3]. Atherosclerosis is the narrowing and hardening of arterial blood vessels due to plaque buildup on the walls of blood vessels [4]. It is still difficult to detect atherosclerosis in the early stages. Arterial stenosis often develops without symptoms in patients DMT2, then causes cardiovascular events.

Therefore, development diagnostics to allow detecting early-stage Atherosclerosis are indispensable.Measurement of the elasticity value of the artery wall can be used as a diagnostic step for detect atherosclerosis in the early stages, so it takes serum markers that have strong relationship with the value of elasticity on artery walls. Some of the research results have been reported a significant correlation of Cystatin-C (CysC) levels with arterial stiffness in the a group of normal individuals. CysC has a strong correlation with elasticity values carotid artery walls reflecting degrees of subclinical atherosclerosis [5,6,7,8]. This is potential new markers as biomarkers of early detection of atherosclerosis. CysC is cysteine protease, a non glycosylated protein with a molecular weight of 13.36 kDa, is produced by almost all cells are in the human body. CysC increases in diabetes patients before the appearance of microalbuminuria, it was produced stablely unaffected by the process inflammation, gender, age, diet, and nutritional status [9].CysC reportedly linked to plaque morphology using computed tomography multi-detector and coronary angiography, even in patients without chronic kidney disease [10,11].

The results of Rei Kaneko et al (2018) show that CysC, but not eGFR, is related with cardiovascular disease in subjects with mild kidney disorders [5]. Findings similarly reported by Yu Kyung et al (2017), CysC is superior to eGFR for predict cardiovascular events in diabetics with complications or no complications of cardiovascular disease[7]. Alexandr Ceasovsch et al (2020), also reported that CysC has significant value for the diagnosis of peripheral artery disease (PAD), and has accuracy as a biomarker in predicting PAD [12]. Based on this, the problem formulation can be presented as follows "Whether cysc can be used as an early marker to determine the presence of complications atherosclerosis in people with DMT2?". The specific

purpose is to know the correlation CysC serum with ateroclerosis in people with DMT2. By knowing the correlation of Cys Serum with atherosclerosis in DMT2 then adds knowledge about the role of CysC serum in detecting atherosclerosis in DMT2 patients, and can be used as basic data for future research, especially related to the development of serum CysC as a biomarkerdiagnostics in the treatment of atherosclerosis in DMT2 patients.

II. METHODS

This type of research is analytical research using cross-sectional design (latitude cut study). The study was conducted by calculating the value of Cystatin C in the blood serum of people with DMT2. The study population is people with DMT2 in Poli Internal Medicine and Heart Poli RSUD Labuang Baji Makassar and its network. Determination the study subject is conducted by conducting a search on the patient's medical record DMT2 meets the selection criteria until it reaches a minimum sample number. Sum the sample was 20 people using the Consecutive Sampling Technique. Inclusion Criteria : DMT2 patients with negative urine protein test results, DMT2 patients with the results of examination of serum creatinine levels are still in normal value, DMT2 patients willing to be the subject of research by signing a letter of approval (informed consent). Exclusion Criteria : serum samples that are hemolysis, lipemic or icterus.

Determination of the research subject is done by conducting a search on medical records of DMT2 patients who meet the criteria of inclusion and exclusion to achieve Minimum number of samples. The study subjects were classified into two groups based on medical record data searches are subclinical atherosclerosis group and nonclinical group ateroskelorosis. DMT2 - Sub Clinical Atherosclerosis : medical record of pulse wave speed examination results brachial ankle (baPWV) $\geq$ 1700 ms. DMT2 –Non Clinical Atherosclerosis : medical record of pulse wave speed examination results brachial ankle (baPWV) $<$ 1700 ms. The research sample is a serum sample. Serum sample examination is carried out in the Clinical Prodia Laboratory using PENIA method (Particle-Enhanced Immuno Nephelometry).

III. RESULT AND DISCUSSION

Research entitled Analysis of serum cystatin-C levels in people with type 2 diabetes mellitus (DMT2) as a biomarker of early detection of atherosclerosis, has been carried out with a total of 20 test samples. Test sample in the form of venous blood sample of DMT2 patients showing symptoms of atherosclerosis subclinical (SA) as many as 10 people (n = 10), and who showed no symptoms of subclinical atherosclerosis/non-subclinis atherosclerosis (NSA) as many as 10 people (n = 10). Only the results of the patient's medical record data that meet the inclusion criteria of the study are used as subject of research. The results of the study of DMT2patient medical record data that was subjected to the study it is as follows :

Table 1. Characteristics of study subjects (patients with DMT2) subclinical atherosclerosis (SA) and Non-Subclinical Atherosclerosis (NSA) based on medical record search results.

Sample Code	Gender (F/M)	Age (years)	Diabetes duration (Years)	Smooking (Y/N)	Hypertention (Y/N)	baPWV/ ABI	Group
01	F	62	11	N	Y	Hiigh	SA
02	F	65	7	N	Y	Normal	NSA
03	F	56	6	N	Y	Normal	NSA
	M	67	10	Y	Y	High	SA
04	F	63	11	N	Y	High	SA
	F	61	5	N	Y	Normal	NSA
	M	57	6	Y	Y	Normal	NSA
05	M	70	11	Y	Y	High	SA
	F	65	10	N	Y	High	SA
06	M	52	4	Y	Y	Normal	NSA
	F	62	5	N	Y	Normal	NSA
07	F	66	12	N	Y	High	SA
	F	54	5	N	Y	High	SA
08	F	57	4	N	Y	Normal	NSA
	F	49	2	N	Y	Normal	NSA
	F	47	2	N	Y	Normal	NSA
09						High	SA
	M	51	4	Y		High	NSA
10	F	50	3	N	Y	High	SA
		56	5	Y		Normal	NSA
11	M	58	7	N	Y	lNormal	NSA
	F				Y		
12							SA
					Y	Normal	NSA
13							
14						Normal	NSA
						High	NSA
15							
16							NSA
							NSA
17							

				SA
18				SA
19				
20				

Source: Secondary data, 2021

Description: SA = Subcyclical atherosclerosis
NSA = Non-Subclinical Atherosclerosis
F/M = Female / Male
Y/N = Yes / No

Venous blood sampling is performed on DMT2 patients who meet the inclusion criteria, as much as 5cc. The sample is then given the patient's identity code and sent to the prodia clinic laboratory for treatment examination of serum cystatin-c levels using the PENIA method. Cystatin-C test results serum in people with Diabetese Mellitus Type 2 subclinical atherosclerosis (SA) and non-subclinical Atherosclerosis (NSA) can be seen in table 2.

Table 2. Results of examination of serum Cystatin-C levels in people with Diabetese Mellitus Type 2 Subclinical Atherosclerosis (SA) and Non-Subclinical Atherosclerosis (NSA).

No.	Sampel Code	Group (SA/NSA)	Cystatin-C (mg/L)	Result (High / Normal/Low)
1.	01	SA	1,23	Tinggi
2.	02	NSA	0,91	Normal
3.	03	NSA	0,87	Normal
4.	04	SA	1,13	Tinggi
5.	05	SA	1,17	Tinggi
6.	06	NSA	0,94	Normal
7.	07	NSA	0,76	Normal
8.	08	SA	1,8	Tinggi
9.	09	SA	1,18	Tinggi
10.	10	NSA	0,89	Normal
11.	11	NSA	0,92	Normal

12.	12	SA	1,03	Tinggi
13.	13	SA	1,21	Tinggi
14.	14	SA	1,27	Tinggi
15.	15	NSA	0,64	Normal
16.	16	NSA	0,72	Normal
17.	17	NSA	0,87	Normal
18.	18	NSA	0,56	Normal
19.	19	SA	1,16	Tinggi
	20	SA	1,08	Tinggi
20.				

Source: Primer data, 2021

Description: Nilai rujukan normal = 0,50 – 0,96 mg/L
SA = Subcyclical atherosclerosis
NSA = Non-Subclinical Atherosclerosis

The results of the study entitled Analysis of Serum Cystatin-C levels in people with DMT2 as this biomarker of early detection of atherosclerosis reports results that Cystatin-C Serum is closely correlated with subclinical atherosclerosis (arterial stiffness. Increase in serum cystatin-C levels indicates the risk of atherosclerosis in Patients with DMT2. And Cystatin C is more sensitive to subclinical atherosclerosis than other indicators of kidney function such as sCr, GFR and microalbuminuria in diabetics (Moon, S.J., et al., 2017).It has been reported in the results of previous studies that the increase in serum cystatin C accompanied by decreased kidney function is directly relevant to the stiffness of large to small arteries (Ozkok A, et al.2014; Song SH, et al., 2008). And in patients with normal or mild renal dysfunction, there was a significant correlation between serum cystatin C levels of arterial stiffness. arterial stiffness has been shown to be significantly related (Madero M, et al., 2009).

The results of this study show that cystatin C is an independent risk factor for atherosclerosis, especially in people with diabetes. These results emphasize the efficiency of serum cystatin C as a replacement marker, predicting additional CVD risk in DMT2 patients. However, clinical application studies of the causal relationship between serum cystatin C and SA are still needed, through prospective tracking observations for the next few years.Level cystatin C serum is associated with SA in DMT2 patients. Cystatin C was identified as a predictor of atherosclerosis risk, after adjusting for a variety of factors associated with diabetes and the risk increased by 1-2 times with each 1 mg/L increase in cystatin C levels. These results suggest that serum

cystatin C will be a useful replacement marker for predicting atherosclerosis risk in people with DMT2.

IV. CONCLUSION

The results of the study entitled Analysis of Serum Cystatin-C levels in people with DMT2 as this biomarker of early detection of atherosclerosis, reports results that Cystatin-C Serum is closely correlated with subclinical atherosclerosis (arterial stiffness. Increase in serum cystatin-C levels indicates the risk of atherosclerosis in Patients with DMT2. In conclusion, this preliminary study provides information about the relationship of serum cystatin C levels with early-stage atherosclerosis in people with DMT2.

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