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Influence Engulfment Cell Motility-1 (ELMO-1) Protein and Matrix Metalloproteases-9 (MMP-9) in Diabetic Nephropathy Patients

Elfiani Elfiani and Huntari Harahap

Abstract

Engulfment and Cell Motility-1 (ELMO-1) are well-known genes in Asia that can cause diabetic nephropathy in people with Diabetes Mellitus type-2. The increase in ELMO-1 protein affects Matrix Metalloproteases-9 (MMP-9) levels, both of which can cause chronic glomerular injury through dysregulation of Extra Cellular Matrix metabolism and decreased adhesive properties of endothelial cells to kidney structures. This study aims to prove differences in ELMO-1 and MMP-9 protein levels in type-2 Diabetes Mellitus (DM) patients with Diabetic Nephropathy compared to those without Diabetic Nephropathy. This study is a comparative observational study with venous blood samples taken from 60 patients with type-2 DM patients without Diabetic Nephropathy as a control and type-2 DM group with Diabetic Nephropathy cases diagnosed based on the criteria of Glomerular Filtration Rate and Albumin-to-Creatinine Ratio. In this study, the levels of ELMO-1 and MMP-9 proteins were checked by ELISA (Enzyme-linked Immunosorbent Assay). The results showed that the mean plasma ELMO-1 value was higher in the Diabetes Mellitus type-2 group with Diabetic Nephropathy than without the Diabetic Nephropathy group (t-test, p = 0.025). The mean plasma MMP-9 value was higher in the DM with Diabetic Nephropathy group rather than in the DM without Diabetic Nephropathy group (t-test, p = 0.032). Conclusion ELMO-1 and MMP-9 levels were higher in Diabetes Mellitus type-2 with diabetic nephropathy.

Keywords: Diabetic Nephropathy, Diabetes Mellitus, Engulfment and Cell Motility-1, Matrix Metalloproteases-9, chronic glomerular injury, dysregulation of ECM metabolism, Albumin to Creatinine Ratio, Glomerular Filtration Rate

1. Introduction

The prevalence of Diabetes Mellitus (DM) increases globally; in 2011, about 366 million people experienced Diabetes, and it is estimated to continue to grow to 522 million people in 2030 [1]. Diabetes Mellitus will cause damage and failure of various

organs; one of these organs is the kidney. This complication of DM in the kidney is called Diabetic Nephropathy. The prevalence of Diabetic Nephropathy occurs in 20–40% of all type-2 DM patients [2]. Kidney damage in Diabetic Nephropathy is irreversible and causes an increase in morbidity, mortality, and the burden of health financing in most countries [3].

The principal risks of Diabetic Nephropathy are modifiable, namely blood pressure, blood sugar, and dyslipidemia. Meanwhile, factors that cannot be modified include age, race, and genetic profile [4]. However, the pathogenesis that contributes to Diabetic Nephropathy incidence is not fully understood, especially the role of genetics [5]. So that efforts to obtain genetic information in type-2 DM patients who are susceptible/at risk of Diabetic Nephropathy provide an opportunity to predict and diagnose this complication early [6].

The ELMO-1 gene is a functional gene that codes for the formation of the ELMO-1 protein, located on chromosome 7 of mammalian cells. ELMO-1 protein helps engulf "eating" or clean apoptotic cells and plays a role in cell motility and cell shape changes [7, 8].

ELMO-1 protein increases in hyperglycemic conditions and TGF-β1 (Tumor Growth Factor Beta-1), collagen type-1, fibronectin expression, and Extra Cellular Matrix (ECM) in the kidneys. MMP-9 also plays a vital role in diabetic nephropathy. Increased secretion of MMP-9 destroys the podocyte diaphragm, which is an essential component in maintaining the standard barrier of glomerular filtration [10].

2. Diabetic nephropathy

2.1 Research methods and study design

This study is an observational study with a cross-sectional comparative study design. This study was conducted at three hospitals in Jambi Province, Indonesia, with a total sample of 60 people. Control this research is Diabetes Mellitus type 2 group without Diabetic Nephropathy patients diagnosed with type-2 Diabetes without impaired kidney function and two times the value examination, Albumin to Creatinine Ratio (ACR) <30 mg/g for 2–3 months mild/normal albuminuria levels. Diabetes mellitus with nephropathy diabetes has hemodialysis, decreased Glomerular Filtration Rate, and or persistent albuminuria.

The inclusion criteria in this study were over 20 years ago, had suffered from type-2 Diabetes for at least five years, had a medical record with routine laboratory examination data in the form of blood sugar and urinalysis, assessment of kidney function (urea levels and creatinine), ultrasound, and ACR examination at least two times in 3–6 months and were willing to participate in this study by signing the informed consent. Exclusion criteria in this study were patients with urinary tract infections, other kidney diseases such as kidney stones and kidney cysts (from medical records), pregnancy, and patients with autoimmune or immunocompromised diseases.

ELMO-1 and MMP-9 levels were examined using ELISA (Enzyme-linked Immunosorbent Assay). Sample this research from blood plasma; then carried out according to the ELISA kit instructions for human ELMO-1 from MyBioSource catalog number MBS9321199 and MMP-9 from RayBioR catalog number ELH-MMP9.

This research has passed ethics from the Faculty of Medicine's research ethics commission team, Andalas University, and received ethical clearance number 706/KEP/FK/2019. Data analysis used a t-test because the data distribution was normal.

2.2 Results

2.2.1 Basic characteristics of research subjects

The basic characteristics of the assessed research subjects are shown in **Table 1**. Based on the essential characteristics of research subjects, it is known that Type-2 Diabetes with Diabetic Nephropathy has systolic and diastolic blood pressure, fasting blood sugar levels, and blood sugar levels 2 hours after eating. Albumin to creatinine ratio (ACR) in urine is higher than non-diabetic nephropathy. And statistically significant. In contrast, the mean value of glomerular filtration rate (GFR) was lower in the Diabetic Nephropathy group and statistically significant.

2.2.2 Levels of plasma protein ELMO-1 and MMP-9

ELMO-1 and MMP-9 protein levels between DM subjects with Diabetic Nephropathy and without Diabetic Nephropathy are presented in **Tables 2** and **3** below.

Table 2 shows that the mean ELMO-1 plasma value was higher in the DM group with Diabetic Nephropathy and without Diabetic Nephropathy group, statistically significant ($p < 0.05$).

Table 3 shows that the mean plasma MMP-9 value was higher in the DM group with Diabetic Nephropathy than the without Diabetic Nephropathy group. And this difference was statistically significant ($p = 0.032$).

2.3 Discussion

The Genome-Wide Association Studies in Japan in 2005 identified the part of Engulfment and cell motility-1 (ELMO-1) in diabetic nephropathy. A study using

Characteristics	Diabetes with Diabetic Nephropathy (n = 30)	Diabetes without Diabetic Nephropathy (n = 30)	p-value
Age	51,17 ± 7,88	49,87 ± 8,42	0,539[a]
Gender			
Male, n	15 (57,7%)	11 (36,7%)	0,297[b]
Female, n	15 (44,1%)	19 (55,9%)	
Fasting blood sugar levels	160,40 ± 60,32	138,90 ± 35,54	0,249[a]
Blood sugar levels 2 hours after eating	245,87 ± 59,57	237,27 ± 84,56	0,428[a]
Systolic blood pressure	139,33 ± 17,21	122,43 ± 14,47	**<0,001[a,*]**
Diastolic blood pressure	83,33 ± 9,59	78,00 ± 8,87	**<0,033[a,*]**
Urine creatinine	95,64 ± 72,65	89,59 ± 71,53	0,887[a]
Urine albumin	618,83 ± 876,23	12,67 ± 9,65	**<0,001[a,*]**
Albumin to creatinine ratio	1387,67 ± 2743,37	14,21 ± 6,6	**<0,001[a,*]**
Glomerular filtration rate, mL/min	69,76 ± 36,10	92,91 ± 23,76	**0,005[a]**

[a]*t-test.*
[b]*Chi-square test.*
[*]*Statistically significant; p-value < 0,05.*

Table 1.
Basic characteristics of research subjects.

Protein	Diabetes with Diabetic Nephropathy (n = 30)	Diabetes without Diabetic Nephropathy (n = 30)	p-value
Plasma ELMO-1 (ng/mL)	623,83 ± 940,73	211,21 ± 209,98	0,025[a,*]

[a]t-test.
[*]p-value <0,05; statistically significant (p < 0,05).

Table 2.
ELMO-1 plasma levels between DM subjects with diabetic nephropathy and without diabetic nephropathy.

Protein	Diabetes with ND (n = 30)	Diabetes with ND non-ND (n = 30)	p-value
Plasma MMP-9 (pg/mL)	1800,14 ± 1871,18	981,79 ± 758,49	0,032[a,*]

[a]t-test.
[*]p-value <0,05; statistically significant.

Table 3.
Plasma levels of MMP-9 between DM subjects with ND and non-ND.

diabetic rats found that increased ELMO-1 protein levels were in diabetic kidneys compared to normal rats [9]. Functions ELMO-1 proteins were phagocytosis of apoptotic cells and cell motility in mammals [7]. Failure to clear apoptotic cells can cause inflammation and autoimmunity damage [8].

In this study, there was no difference in age and gender. Because due to the nine samples' consecutive sampling technique, where there is a balanced age range between the case and control groups. There is a difference in age characteristics in the literature, stating that diabetic nephropathy is more common in old age. Because it is associated with a longer duration of disease in old age, and diabetes mellitus has been more than five years [11].

Based on patient characteristics, it is known that the mean value of glomerular filtration rate is lower in the diabetic group with Diabetic Nephropathy compared without Diabetic Nephropathy. This situation is because, in diabetic nephropathy, there is a more severe decrease in kidney function. The reduction in glomerular hydration rate in type-II DM patients is proportional to the degree of albuminuria. The more significant the reduction in glomerular filtration rate, the heavier the degree of albuminuria [11, 12].

In this study, the Diabetic Nephropathy group had a higher average blood pressure than non-ND Diabetes Mellitus. Blood pressure decreases the rate of glomerular psychopathy and albuminuria in Diabetic Nephropathy [13, 14]. The elevated blood pressure in diabetic nephropathy occurred due to disruption of the Renin-Angiotensin-Aldosterone System (RAA's) and decreased renal blood flow [13, 14].

In the study, ELMO-1 protein levels were higher in patients with diabetic nephropathy. ELMO-1 protein contributed to chronic glomerular injury progression through the increased accumulation of the extracellular matrix and decreased cell adhesion [14]. The extracellular matrix accumulation causes thickening of the glomerulus and renal tubules, a marker of advanced diabetes nephropathy [13].

This study reported higher plasma ELMO-1 and MMP-9 levels in diabetic patients with ND and was statistically significant (**Tables 2** and **3**). Functional studies on cultured cells and experimental animals show the role of the ELMO-1 protein in ND. Previous research has shown an increase in ELMO-1 signal with the

in situ hybridization (FISH) method in the kidney of rats with nephropathy compared to those without nephropathy.

MMP-9 protein is a protein involved in the degradation of the extracellular matrix and glomerular turnover. Changes in MMP-9 expression are associated with the development of diabetic nephropathy. Hyperglycemia, an increase in advanced glycation end products, and oxidative stress that occurs in people with Diabetes increase the expression of MMP-9. MMP-9 protein cause of disrupts the integrity and increases the permeability of podocytes to albumin, and increases protein synthesis, which is involved in forming the extracellular matrix. All of these are processes that occur in Diabetes nephropathy [10, 15, 16].

3. Conclusion

Engulfment and Cell Motility-1 (ELMO-1) and Matrix Metalloproteases-9 (MMP-9) protein levels were higher in Diabetic Nephropathy compared to Diabetes Mellitus without Diabetic Nephropathy and difference was statistically significant. Required a larger number of samples and performed prospectively.

Acknowledgements

Appendix and nomenclature

ACR	Albumin-to-Creatinine Ratio
ACEI	Angiotensin Enzyme Inhibitor
ADA	American Diabetes Association
DM	Diabetes Mellitus
ECM	Extra Cellular Matrix
ELISA	Enzyme-linked Immunosorbent Assay
ELMO-1	Engulfment and cell motility-1
IDF	International Diabetes Federation
MMP	Matrix Metalloproteases

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