INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

DIFFERENCES IN INTERLEUKIN 18 LEVELS IN DIABETIC NEPHROPATHY AND NON-DIABETIC NEPHROPATHY PATIENTS

Rizka Sari Anggawaty Hrp[*1], Alwi Thamrin Nst[2] & Ratna Akbari Ganie[1]
[1]Department of Clinical Pathology, Faculty of Medicine, Universitas Sumatera Utara /H. Adam Malik Hospital Medan
[2]Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara / H. Adam Malik Hospital Medan

DOI: https://doi.org/10.29121/ijrsm.v7.i11.2020.9

Keywords: Type 2 diabetes, diabetic nephropathy, Interleukin 18.

Abstract

Background: Diabetic nephropathy is a common complication in diabetics. In this disease damage to the kidney filter or known as glomerulus. Therefore causing glomerular damage, the amount of blood protein is excreted into the urine abnormally. IL-18 is a proinflammatory cytokine produced from activated macrophages, serum IL-18 levels are produced to increase in patients with diabetic nephropathy. IL-18 which affects the production of other proinflammatory cytokines, endothelial apoptosis, ICAM-1 certification enhancement. Thus, IL-18 may be an important factor not only in the process of atherosclerosis but also in the development of diabetic nephropathy.
Aim: Knowing the IL-18 levels in diabetic nephropathy and non-diabetic nephropathy patients.
Methods: The study was conducted using the Cross Section method. This study took blood samples from 60 diabetic patients, of which 30 patients with nephropathy and 30 patients with type 2 diabetes. Then took 5 ml of blood from a vein and assessed serum IL-18 levels in all patients.
Results: The study was conducted for 3 months, 41 men (68.3%) 19 women (37.1%). Serum IL-18 levels were significantly increased in patients with diabetic nephropathy compared with patients with type 2 diabetes (362.7 vs 55.7 pg / ml, p <0.001)
Conclusions: Increased IL-18 levels in diabetic nephropathy patients can be used as prognostic events for diabetic nephropathy.

Introduction

Type 2 diabetes mellitus is a metabolic disease characterized by hyperglycemia while this disease can cause interference with other organs of the body due to insulin deficiency or inadequate increase in insulin performance (Dipiro *et al*, 2005; PERKENI, 2015).

The World Health Organization (WHO) estimates that the global prevalence of type 2 diabetes mellitus will increase from 171 million people in 2000 to 366 million in 2030. This report shows an increase in the number of people with Diabetes Mellitus by 2-3 times in 2035. According to World Health Organization (WHO), Indonesia ranks 4th in the world in terms of the number of sufferers of Diabete Mellitus after China, India and the United States. (WHO, 2016)

While based on data from the International Diabetes Federation (IDF) in 2013, there were 382 million people in the world suffering from type 2 Diabetes Mellitus with 4.6 million deaths. In 2011, Indonesia ranked tenth in the world with 6.6 million people with Diabetes Mellitus type 2 and in 2030 it was projected to occupy the 9th position with an estimated 10.6 million people with the most sufferers in the age range of 45-65 years. This illustrates that type 2 diabetes mellitus is a serious problem and has a negative impact on quality of life (PERKENI, 2015).

The condition of chronic hyperglycemia in patients with diabetes mellitus can cause various complications both microvascular and macrovascular. Microvascular complications in Diabetes Mellitus patients include nephropathy, neuropathy and retinopathy. (Fowler, 2008)

Diabetic nephropathy is a complication of diabetes mellitus in the kidney which can end up as kidney failure. This situation is found in 35-45% of people with DM. (Foster DW, 2000) Based on annual research taken in 2002 by Bethesda of the National Institutes of Health, the prevalence rate for diabetic nephropathy is close to 40% for terminal renal failure. Currently 25% of patients with kidney failure undergoing dialysis are caused by DM especially DM type 2 because DM is more often found. (Bethesda, 2010)

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

IL-18 is a proinflammatory cytokine produced from activated macrophages, serum IL-18 levels have been reported to be elevated in patients with diabetic nephropathy.

IL-18 is known to cause the production of other proinflammatory cytokines, endothelial apoptosis, increased regulation of ICAM-1. Thus, IL-18 may be an important factor not only in the process of atherosclerosis but also in the development of diabetic nephropathy (Moriwaki Y, 2003)

Method

This research uses descriptive-analytic research design with Cross Sectional approach. A total of 60 patients with type 2 diabetes consisted of 30 people with diabetic nephropathy and 30 people with diabetes who did not experience diabetic nephropathy. blood samples were taken to determine levels of IL-18.

Results

A total of 60 people with diabetes mellitus were included as subjects in this study, consisting of 30 people with diabetic nephropathy and 30 people with diabetes who did not experience diabetic nephropathy. The characteristics of the subjects in this study can be seen in the following table 1:

Table 1 Characteristics of Research Subjects

Characteristics		n	%
Gender	Male	41	68.3
	Female	19	31.7
Age	<50 years old	13	21.7
	50 - 59 years old	31	51.7
	60 - 69 years old	11	18.3
	>= 70 years old	5	8.3
Diabetic nephropathy	Nephropathy	30	50.0
	Non nephropathy	30	50.0
	Normal	30	50.0
	Stage III	12	20.0
	Stage IV	13	21.7
	Stage V	5	8.3
		60	100.0

From all research subjects, as many as 68.3% of the sufferers were male and only 31.3% were female. Patients with diabetes mellitus who were the subjects in this study were mostly in the age range under 50-59 years (51.7%). The patients who were under 50 and 60-69 years old were 21.7% and 18.3%, respectively.

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

Table 2 Characteristics of Laboratory Results for Research Subjects

	Nephropathy		Non Nephropathy		*p-value*
	Mean ±SD	Median (Min - Max)	Mean ±SD	Median (Min - Max)	
GDP	189.1 ±87.8	168 (107 - 487)	218 ±82.5	208 (114 - 430)	0.06 [a]
GD2PP	266 ±123.7	237.5 (140 - 741)	292.6 ±111.3	269 (148 - 526)	0.21 [a]
Creatin	3.13 ±1.18	2.65 (1.47 - 6.42)	0.88 ±0.21	0.82 (0.58 - 1.34)	<0.00[a]
eGFR	25.6 ±8.49	26.5 (9 - 40)	87.9 ±18.9	85 (61 - 121)	<0.00[b]
HbA1c	8.6 ±2.5	8.4 (1.47 – 6.42)	9.7 ±2.8	9.4 (5.8 – 15.2)	0.14 [a]

a.Uji Mann Whitney
b.Uji T independent

Table 2 shows that there is a significant difference in serum creatinine levels and glomerular filtration rate between subjects with diabetic nephropathy and those without diabetic nephropathy. DM patients who experienced diabetic nephropathy had a serum creatinine level of 3.13 mg / dl, which was much higher than DM patients who did not experience diabetic nephropathy which was only 0.88 mg / dl ($p < 0.001$).

Likewise with the value of the glomerular filtration rate, where diabetic nephropathy patients have a glomerular filtration rate of 25.6 ml / minute / 1.73m2, where this value is much lower than DM patients who do not experience diabetic nephropathy, namely 87.9 ml / minute / 1.73m2 ($p < 0.001$).

Table 3 Comparison of IL-18 levels in DM patients with and without diabetic nephropathy

	Nephropathy	**Non Nephropathy**	**p-value**
	Median (Min - Max)	Median (Min - Max)	<0.001*
IL-18	362.7 (190.5 – 1064.5)	55.7 (5.2 – 184.5)	

*) Significant with the Mann Whitney Test

Based on table 3, it can be seen that the IL-18 levels of DM patients who experience diabetic nephropathy are much higher than DM patients who do not experience diabetic nephropathy (362.7 vs 55.7 pg / ml, $p < 0.001$).

Table 4 Correlation of Severity of Diabetic Nephropathy and Serum IL-18 Levels

Diabetic Nephropathy	**IL-18 (pg/ml)**	**p-value**
	Mean ±*SD*	

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

stage 3	259.3 ± 40.7	<0.001*
stage 4	399.3 ± 49.7	
stage 5	786.4 ± 257.2	

*) Significant with the One Way Anova Test

Table 4 shows that there is a significant difference in IL-18 levels among patients with stage 3, 4 and 5 diabetic nephropathy. It can be seen that the IL-18 levels in stage 3 nephropathy are the lowest (259.3 pg / ml), and the levels are increasing. with increasing severity of diabetic nephropathy. Patients with stage 4 diabetic nephropathy had IL-18 levels of 399.3 pg / ml, while in stage 5 patients, the levels were even higher, reaching 786.4 pg / ml and this difference was statistically significant (p <0.05).

Table 5. Correlation of IL-18 levels with HbA1c and e-GFR

	IL-18 levels	
	koefisien (r)	p value
HbA1c levels	-0.14	0.26
e-GFR	-0.77	< 0.001*

*) significant with Pearson Correlation

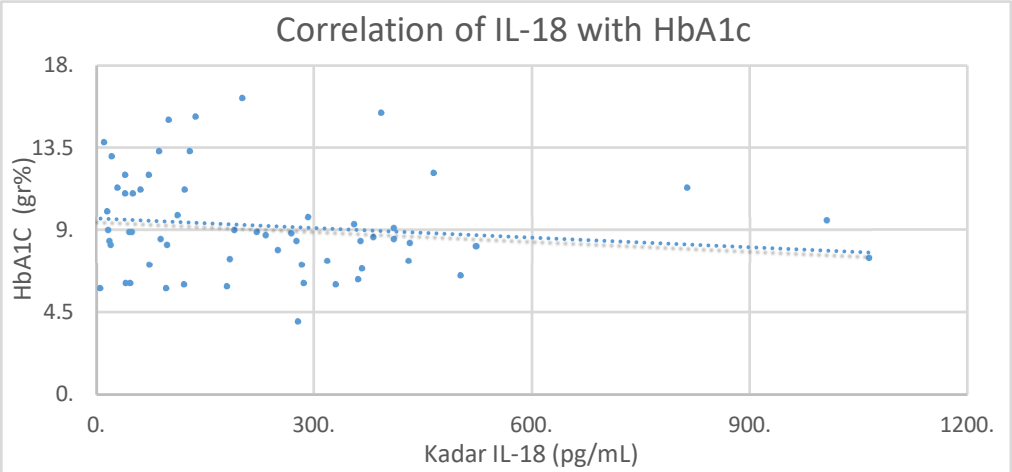

Figure 1 The scatter plot between IL-18 and HbA1c correlation

Based on table 5, it can be seen that there is no significant correlation between IL-18 levels and HBA1c levels in DM patients (p> 0.05).

However, table 5 also shows that there is a significant correlation between IL-18 levels and the e-GFR value of type 2 DM patients.To further clarify the form of correlation between the two variables, the following is a scatter plot between IL-18 levels, HBA1c values and e-GFR values.

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

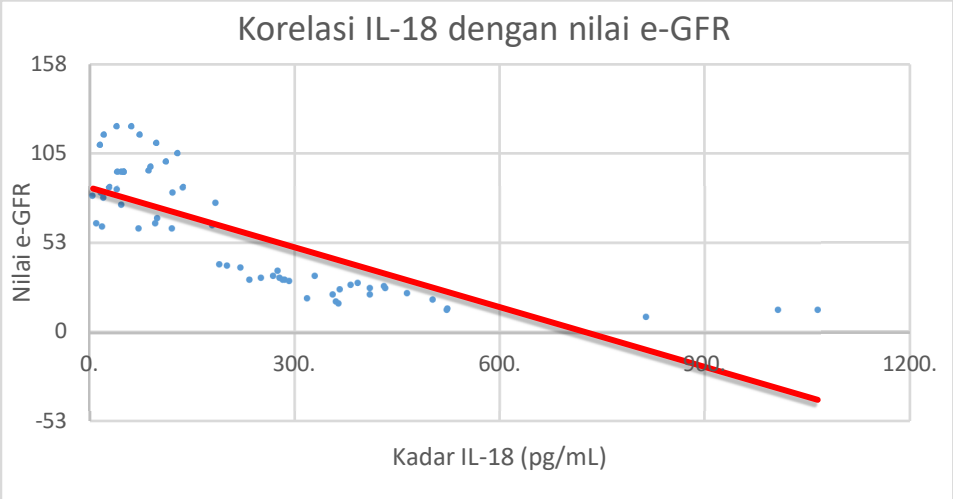

Figure 2 The scatter plot between IL-18 and e-GFR correlation

Based on Table 5 and Figure 2, it can be seen that the correlation between IL-18 levels and e-GFR values is negative, which means that the relationship between IL-18 levels and eGFR values goes in the opposite direction. In other words, the higher the IL-18 level of the DM patient, the lower the e-GFR value of the patient and means more potential for diabetic nephropathy. This is in line with the findings in table 4 which states that the IL-18 levels in stage 5 diabetic nephropathy patients are much higher than those with stage 4 and stage 3 patients.

Discussion

A research has been conducted which aims to determine the differences in levels of interleukin 18 in the blood of patients with type 2 diabetes with nephopathy and non-nephropathy. A total of 60 people with type 2 DM were included as subjects in this study grouped according to the patient's glomerular filtration rate. Of all research subjects, as many as 68.3% of sufferers were male and only 31.3% were female. Patients with diabetes mellitus who were the subjects in this study were more in the age range under 50-59 years (51.7%). The sufferers who are in the range of under 50 years and 60-69 years respectively amounted to 21.7% and 18.3%.

In line with the study conducted by Duan et al 2019, out of 635 participants who experienced a decrease in eGFR <60 mL / min / 1.73m2, most were found in 262 male participants (41.3%). Of 3958 patients with albuminuria, 1505 (38%) were male. Their results also showed that of 962 participants suffering from diabetic nephropathy, 369 (38.4%) were male participants.

In a study conducted by Takasaki et al 2016, they conducted a cross sectional study of 2212 patients with type 2 diabetes (mean age 60.9 years) 928 patients were women; 1838 patients were men with type 2 diabetes. They obtained the results of the study, the average age of stage 1 diabetic nephropathy patients was 59.0 ± 13.9, the average age of stage 2 diabetic nephropathy patients was 64.0 ± 12.2, the average age of stage 3 diabetic nephropathy patients was 62.5 ± 14. the average stage 4 diabetic nephropathic patient was 66.7 ± 13.3, the mean age of the stage 5 diabetic nephropathic patient was 60.4 ± 12.0.

In another study conducted to test the role of IL-18 by AKIHIKO NAKAMURA et al in 2013. "Combination therapy with enzyme inhibitors and angiotensim II receptor antagonists improves microinflammation and oxidative stress in patients with diabetic nephropathy", indicating that increased levels of IL-18 leads to the development of diabetes nephropathy and describes it as a poor prognosis.

In line with the study conducted by Mir et al 2017. Comparison of serum levels of IL-18 in peripheral blood of patients with type II diabetes with nephropathy clinical protests and patients with type II diabetes without nephropathy clinical protests. They conducted a study of 69 diabetic patients who had documented files at two centers (Ali Asghar Hospital and Imam Ali Hospital Dialysis Center). They found that serum IL-18 levels were significantly increased in patients with diabetic nephropathy compared to diabetic without nephropathy (serum IL-18 261.29 ± 20.25 vs 167.20 ± 13.48 pg / ml, P <0.001, so they concluded that serum IL-18 levels in

nephropathic patients increased significantly and serum IL-18 levels might be a predictor factor development of diabetic nephropathy

Conclusion

Based on the results of the study stated earlier, there is a significant difference between serum IL-18 levels in diabetic nephropathy and diabetic nephropathy patients with p <0.001. IL-18 levels in diabetic nephropathy patients with a median value of 55.7 pg / mL and nephropathy with a median value of 362.7 pg / mL. IL-18 examination is expected to be added as one of the parameters examined in determining the prognostic incidence of diabetic nephropathy.

References

[1] American Diabetes Association (ADA). Standards of medical care in diabetes. Diabetes Care. 2015 ; 38 (1) : SI-S88

[2] Fowler M.J.,2008. Microvascular dan Macrovascular Complications of Diabetes. Diabetes Foundation. 26: 77 - 82

[3] Gonzalez,JFN and Fernandez,CM. 2008. The role of Inflammatory cytokines in diabetic nephropathy. J Am Soc Nephrol. America 19:433-442

[4] World Health Organization. (2016). Global Report on Diabetes. 1st ed. Geneva : World Health Organization, pp. 21-31

[5] Bawazier LA. Proteinuria. Dalam : Buku Ajar Ilmu Penyakit Dalam FKUI. Edisi keempat jilid I. Pusat Penerbitan Departemen Ilmu Penyakit Dalam, Jakarta 2009: 519

[6] PERKENI. Buku Pedoman Konsensus Pengendalian dan Pencegahan Diabetes Melitus Tipe 2 di Indonesia. Jakarta : PERKENI, 2015

[7] Murray RK, Granner DK, Rodwell VW. Harper's illustrated biochemistry. 27ed. USA: The McGraw-Hill Companies. 2006

[8] Moriwaki Y, Yamamoto T, Shibutani Y, et al: Elevated levels of interleukin-18 and tumor necrosis factorβ in serum of patients with type 2 diabetes mellitus: Relationship with diabetic nephropathy. Metabolism 52:605-608, 2003

[9] Gerdes N , Sukhova GK , Libby P , Reynolds RS , Young JL , Schonbeck U.Expression of interleukin (IL)-18 and functional IL-18 receptor on human vascular endothelial cells, smooth muscle cells, and macrophages: implications for atherogenesis.J Exp Med 195: 245-257, 2002.

[10] Hirata K, Shikata K, Matsuda M, Akiyama K, Sugimoto H, Kushiro M, Makino H: Increased expression of selectns in kidneys of patients with diabetic nephropathy. Diabetologia 41:185–192, 1998

[11] Sugimoto H, Shikata K, Hirata K, Akiyama K, Matsuda M, Kushiro M, Shikata Y, Miyatake N, Miyasaka M, Makino H: Increased expression of inter- cellular adhesion molecule-1 (ICAM-1) in diabetic rat glomeruli: glomerular hyper- filtration is a potential mechanism of ICAM-1 upregulation. Diabetes 46:2075– 2081, 1997

[12] Kundhar Ravinder N. Interleukin-6 & 18 and C-reactive protein in pathogenesis of diabetic nephropathy. IJKD 2008;272–9.

[13] Tolba Mohamed Shaban. Study of serum inter leukin-18 level in association with nephropathy in patients with type2. . p. 33–190.

[14] Morel JC, Park CC, Woods JM. A novel role for interleukin-18 in adhesion molecule induction through NF kappaB and phosphatidylinositol (PI) 3- kinase-dependent signal transduction pathways. J Biol Chem 2001;276 (10):37069–75.

[15] Gracie J Alastair, Robertson Susan E, McInnes Iain B. Interleukin-18. J Leukoc Biol 2003;73(February):151–67.

[16] Foster DW. Diabetes Mellitus in Horison Prinsip – Prinsip Ilmu Penyakit Dalam 13 ed. Jakarta: EGC: 2000

[17] Kundhar Ravinder N. Interleukin-6 & 18 and C-reactive protein in pathogenesis of diabetic nephropathy. IJKD 2005;272–9.

[18] Sundoyo, Ari W, dkk, buku ajar ilmu penyakit dalam edisi IV jilid II, pusat penerbitan departemen ilmu penyakit dalam, FKUI, Jakarta,2006;545 – 547

[19] Hendromartono. Nefropati Diabetik. Dalam : Buku Ajar Ilmu Penyakit Dalam FKUI. Edisi keempat jilid III. Pusat Penerbitan Departemen Ilmu Penyakit Dalam, Jakarta 2006: 1920-1923

[20] Sukandar Enday. Tinjauan Umum Nefropati Diabetik. Dalam : Nefrologi klinik. Bagian Ilmu Penyakit Dalam Fakultas UNPAD/RS. Dr. Hasan Sadikin Bandung. Edisi 3, 2006 : 331

[21] Kim S-H, Eisenstein M, Reznikov L, et al. Structural requirements of six naturally occurring isoforms of the interleukin-18 binding protein to inhibit interleukin-18. Proc Natl Acad Sci U S A 2000;97:1190 –5
[22] SiegmundB,SennelloJA,LehrHA,SenaldiG,DinarelloCA,Fantuzzi G. Interferon regulatory factor-1 as a protective gene in intestinal in- flammation: role of TCR gamma delta T cells and interleukin-18- binding protein. Eur J Immunol 2004;34:2356 – 64.
[23] Gatti S, Beck J, Fantuzzi G, Bartfai T, Dinarello CA. Effect of interleukin-18 on mouse core body temperature. Am J Physiol Regul Integr Comp Physiol 2002;282:R702–9.
[24] Li S, Goorha S, Ballou LR, Blatteis CM. Intracerebroventricular interleukin-6, macrophage inflammatory protein-1 beta and IL-18: py- rogenic and PGE(2)-mediated? Brain Res 2003;992:76 – 84
[25] M. Mir A. Rostami. Hormozi. Comparison of serum levels of IL-18 in peripheral blood of patients with type II diabetes with nephropathy clinical protests and patients with type II diabetes without nephropathy clinical protests. 2016; 246-250.