

Interferon gamma concentration in Diabetes Mellitus and Dyslipidemia patient

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Abstract

Introduction: Patient with diabetes mellitus (DM) and dyslipidemia occurs chronic inflammation characterized by changes in the concentration of various cytokines. This causes changes in the body's immunity so that can be easier in having an infection. One of the most important cytokines against infection is IFN- γ . This study aimed to determine IFN- γ concentration in DM and dyslipidemia patients.

Metode: An amount 234 people who received treatment at the health center in Banda Aceh in 2019 were included in this study. From each respondent, 5 ml of blood was taken to check fasting blood glucose, triglycerides, high-density lipoproteins (HDL), and interferon-gamma (IFN- γ). Test of fasting blood glucose, triglycerides, HDL was carried out using the colorimetric enzymatic method. The IFN- γ protein concentration was examined using the sandwich enzyme-linked immunosorbent assay (ELISA) technique.

Result: IFN- γ concentration in the non-DM group was higher than in the DM group. There was a significant difference between the average IFN- γ concentration in the non-DM group compared with the DM group ($p = 0.000$). All DM patients had increased fasting blood glucose, most had hypertriglycerides, but HDL levels were normal. The fasting blood glucose group <126 mg / dl had a higher IFN- γ concentration than the group with fasting blood glucose levels ≥ 126 mg / dl. There was a significant difference in the concentration of IFN- γ between the two groups ($p = 0.000$). The group with triglyceride levels <150 mg / dl had lower IFN- γ levels than the group with triglyceride levels ≥ 150 mg / dl. There was a significant difference between the average IFN- γ concentration between those groups ($p = 0.000$). The fasting blood glucose levels ≥ 126 mg / dl and triglycerides levels ≥ 150 mg / dl had higher IFN- γ concentration than the group who had fasting blood glucose levels ≥ 126 mg / dl and triglycerides levels < 150 mg / dl.

Conclusion: There are differences in IFN- γ concentrations in people with DM, increased fasting blood glucose and dyslipidemia compared to normal people. (*Health Science Journal of Indonesia 2021;12(2):74-80*)

Keywords: IFN- γ , diabetes mellitus, dyslipidemia

Abstrak

Pendahuluan: Penderita diabetes mellitus (DM) dan dyslipidemia mengalami inflamasi kronik yang ditandai dengan perubahan konsentrasi berbagai sitokin. Hal ini yang menyebabkan perubahan imunitas tubuh sehingga mudah mengalami infeksi. Salah satu sitokin yang paling berperan terhadap infeksi adalah interferon gamma (IFN- γ). Penelitian ini bertujuan untuk memeriksa konsentrasi IFN- γ pada penderita DM dan dislipidemia.

Metode: Sebanyak 234 orang yang melakukan pengobatan di puskesmas di Kota Banda Aceh pada tahun 2019 diikutsertakan dalam penelitian ini. Dari setiap responden dilakukan pengambilan darah sebanyak 5 ml untuk dilakukan pemeriksaan kadar gula darah puasa (KGD P), trigliserida, high density lipoprotein (HDL), dan interferon-gamma (IFN- γ). Pemeriksaan KGD P, trigliserida, HDL dilakukan dengan metode enzimatik kolorimetrik. Pemeriksaan konsentrasi protein IFN- γ menggunakan teknik sandwich Enzyme-linked immunosorbent assay (ELISA).

Hasil: Konsentrasi IFN- γ pada kelompok non-DM lebih tinggi dibandingkan dengan kelompok DM. Terdapat perbedaan bermakna antara rata-rata konsentrasi IFN- γ pada kelompok non-DM dibandingkan dengan kelompok DM ($p=0,000$). Semua penderita DM mengalami peningkatan KGD P, sebagian besar mengalami hipertrigliserida, namun kadar HDL normal. Pada kelompok KGD P <126 mg/dl memiliki konsentrasi IFN- γ yang lebih tinggi dibandingkan dengan kelompok dengan KGD P ≥ 126 mg/dl. Terdapat

perbedaan bermakna perbedaan konsentrasi IFN- γ antar kedua kelompok tersebut ($p=0,000$). Kelompok dengan kadar trigliserida <150 mg/dl memiliki kadar IFN- γ lebih rendah dibandingkan dengan kelompok dengan kadar trigliserida ≥ 150 mg/dl. Terdapat perbedaan bermakna antara rata-rata konsentrasi konsentrasi IFN- γ antar kedua kelompok tersebut ($p=0,000$). Pada kelompok KGD $P \geq 126$ mg/dl dan trigliserida ≥ 150 mg/dl memiliki kadar IFN- γ yang lebih tinggi dibandingkan dengan kelompok KGD $P \geq 126$ mg/dl namun trigliserida <150 mg/dl. Terdapat perbedaan bermakna antara rata-rata konsentrasi konsentrasi IFN- γ antar kedua kelompok tersebut ($p=0,000$).

Kesimpulan: Terdapat perbedaan konsentrasi IFN- γ pada orang dengan DM, peningkatan KGD P dan dislipidemia dibandingkan dengan orang normal. (Health Science Journal of Indonesia 2021;12(2):74-80)

Kata kunci : IFN- γ , diabetes mellitus, dislipidemia.

Diabetes mellitus (DM) is a chronic disease that greatly affects the quality of life. Based on data from the International Diabetes Federation prevalence of DM sufferers in the world reached 9.3%. In Indonesia, the estimate of DM sufferers at the age of 20-79 years reach 10-20 million people.¹ Based on the RISKESDAS 2018 data, the prevalence of DM in Indonesia reached 1.5%. In Aceh, this rate reached 1.7%, 0.2% higher than the national rate.²

Blood sugar level control in DM patients is extremely concerned. Ramadhan in her research which involved 85 DM patients stated that there were 92% of patients with uncontrolled fasting blood sugar levels, and 88% of DM patients with uncontrolled blood sugar levels 2 hours post-pandrial.³ Increased blood sugar levels are closely related to fat blood, mainly cholesterol and triglycerides.⁴

There is chronic inflammation in DM, which is marked by increased pro-inflammatory markers.^{5,6} Due to chronic inflammation, there is a decrease in the immune response in DM patients.⁷ Chronic hyperglycemia also causes impaired cytokine secretion.^{8,9} DM patients are also frequently accompanied by dyslipidemia. Increased adipose tissue in people with dyslipidemia will increase various proinflammatory cytokines such as TNF- α , IL-1, IL-6, and TGF- β .¹⁰

IFN- γ is a proinflammatory cytokine that plays a major role in infection. In its functions as an immunomodulator, IFN- γ will activate macrophages, NK cells, and play a role in the migration process of various types of other leukocyte cells.^{11,12} People with DM and dyslipidemia will easily be having other infectious diseases.^{13,14} Patients with DM who are accompanied with tuberculosis (TB) have decreased TNF-alpha and IFN- γ concentration, which can be interpreted as a decrease in the immune response so that they are easily infected with other

diseases.¹⁵ This function disorder may occur in DM sufferers make them easier to have other infection. This condition attracted the interest of researchers to study the changes IFN- γ concentrations in patients with diabetes mellitus and nonDM, the changes in IFN- γ concentrations in dyslipidemia and normal person, and the changes in IFN- γ concentrations in hyperglycemia and hypertriglycerides, and hyperglycemia without hypertriglycerides.

METHODS

Respondents

This research was conducted for 1 year, located in Banda Aceh. The sample in this study was patients undergoing treatment at public health facility at Banda Aceh in 2019 with the criteria aged 30-60 years and not in a pregnant condition. The respondents who participated in this study were 234 people. All respondents who participated in the study had signed informed consent. From each respondent, 5 ml of blood was taken to check fasting blood sugar level, triglycerides, HDL, and IFN- γ . This research has received approval from the Health Research Ethics Commission, National Health Research and Development Department with No: LB.02.01 / 2 / KE.171 / 2019.

Fasting blood glucose, triglycerides and HDL cholesterol examination.

Measurement of fasting blood glucose, triglycerides and HDL cholesterol was carried out by the colorimetric enzymatic method.^{16,17} The glucose examination was using glucose kit (cat. No. 112191), triglycerides was using triglycerides kit (cat. No.116392), HDL was using HDL kit (cat. No.108495). An amount of 1000 μ l of glucose reagent or triglyceride or HDL cholesterol were filled into three test tubes, each tube will be used as

standard, sample and blank. To the two tubes were added 10 μ l of sample or standard. Subsequently incubated for 10 minutes at a temperature of 25°C. Then the fasting blood sugar/triglycerides/HDL levels are valuable with a photometer 5010 V5+ at a wavelength of 546 nm.

IFN- γ Protein examination

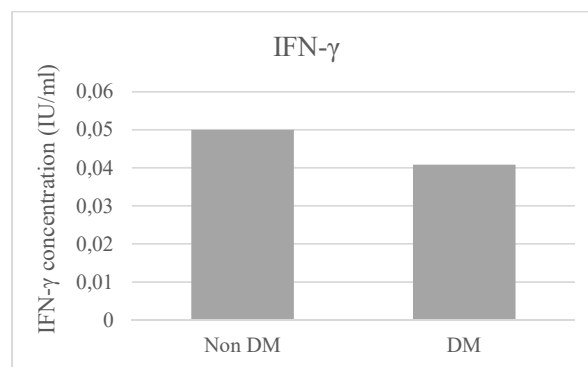
Measurement of IFN- γ protein concentration was using the sandwich enzyme-linked immunosorbent assay (ELISA) technique.¹⁸ The examination was performed by usage IFN-gamma ELISA kit (cat. No. 622120). An amount of 50 μ L of working strength conjugate was put into the ELISA well, then 50 μ L samples of standard or serum were added and incubated for 120 minutes at 22° C. Then, wash for around 6 cycles. Then 100 μ L of substrate was added and incubated for 30 minutes at 22°C. Finally, a stop solution of 50 μ L was added and it was read using Thermo Scientific Multiscan GO microplate spectrophotometer at a wavelength of 450 nm.

Statistic analysis

Respondents were divided into DM and nonDM groups. The DM group was obtained based on the doctor's diagnosis. Univariate analysis was performed on the DM and nonDM groups to obtain the average IFN- γ concentration data, the frequency distribution of DM and nonDM patients based on fasting blood glucose, triglycerides and HDL. For all respondents, bivariate analysis was carried out to obtain data on the average concentration of IFN- γ based on fasting blood glucose, triglyceride and HDL categories. Furthermore, the Mann-Whitney test was performed to obtain differences in the concentration of IFN- γ in each of these groups.

RESULTS

From the research results obtained 234 respondents consisted of 70 people diagnosed with DM by doctor and 164 people without diabetes mellitus. In Figure 1 it can be concluded that the IFN- γ concentration in the nonDM group was higher than the DM group. Based on Mann-Whitney test, there was a significant difference in the average concentration of IFN- γ



between the two groups ($p=0,000$).

Figure 1. The average of IFN- γ concentration in the non-DM group and the DM group

From table 1 it can be concluded that in the DM group all respondents have an increase in fasting blood glucose, while in the nonDM group there were some people who have increased in fasting blood glucose. Based on the triglyceride concentration, most DM sufferers have hypertriglycerides. Based on HDL levels, most DM and nonDM sufferers have normal HDL levels.

Table 1. The frequency distribution of DM and nonDM patients based on fasting blood glucose, triglycerides and HDL.

No	Variable	DM		nonDM	
		n	%	n	%
1	Fasting Blood Glucose				
	≥ 126 mg/dl	70	89,7	8	10,3
	< 126 mg/dl	0	0	156	100
2	Triglycerides				
	≥ 150 mg/dl	40	33,3	80	66,7
	< 150 mg/dl	30	26,3	84	73,7
3	HDL				
	Low	8	22,9	27	77,1
	Normal	62	31,2	137	68,8
	Total	70	100	164	100

Based on table 2 we can conclude that group with fasting blood glucose levels <126 mg / dl had a higher IFN- γ concentration than the group with fasting blood glucose levels ≥ 126 mg / dl. Based on Mann-Whitney test, there was a significant difference in the average IFN- γ concentration between the two groups. The grouping of blood glucose levels in this result is <126 mg / dl or ≥ 126 mg / dl without regard

to the patient diagnosed DM or not.

IFN- γ concentration in the group with triglycerides ≥ 150 mg / dl was higher than in the group with triglycerides < 150 mg / dl. Based on the Mann-Whitney test, there was a significant difference that the group with triglyceride levels < 150 mg / dl had lower IFN- γ levels compared to groups with triglyceride levels ≥ 150 mg / dl (Table 2).

The group with normal HDL levels had a lower averaged IFN- γ concentration than the group with low HDL levels, but based on the Mann-Whitney test there was no significant difference in the average of IFN- γ concentration between the two groups (Table 2). People who had fasting blood glucose ≥ 126 mg / dl and triglycerides ≥ 150 mg / dl had higher IFN- γ concentration than people who had fasting blood glucose ≥ 126 mg / dl and triglycerides < 150 mg / dl. Based on Mann-Whitney test, there was a significant

difference in the average IFN- γ concentration between the two groups (Table 2).

Table 2. Differences in the average of IFN- γ concentration in various groups based on fasting blood glucose, triglycerides, and HDL (n = 234).

No	Variable	IFN		
		Mean (min-max)	SD	P value
1	Fasting Blood Glucose			
	≥ 126 mg/dl	0,0423 (0,026-0,118)	0,01489	0,000
< 126 mg/dl	0,0496 (0,026-0,109)	0,01326		
2	Triglycerides			
	≥ 150 mg/dl	0,0499 (0,026-0,118)	0,01411	0,001
< 150 mg/dl	0,0444 (0,026-0,109)	0,01384		
3	HDL			
	Low	0,0501 (0,026-0,118)	0,01474	0,057
Normal	0,0467 (0,026-0,109)	0,01410		
4	Fasting Blood Glucose ≥ 126 mg/dl			
	Triglycerides ≥ 150 mg/dl	0,0442 (0,026-0,118)	0,01538	0,000
	Triglycerides < 150 mg/dl	0,0395 (0,028-0,091)	0,01389	

DISCUSSION

Interferon-gamma is a cytokine produced by CD4 + and CD8 + T lymphocytes and natural killer cells.¹⁹ Plays a role in various infections, the production of IFN- γ is important to increase the activity of macrophages to fight infection through the mechanism of phagosome maturation blockade and nitrite oxide production (NO).¹² The study revealed that the immune system of DM patients can express different cytokine patterns, including the expression of proinflammatory cytokines IFN- γ .²⁰ Our discovery previously concluded that in patients with DM accompanied by TB there was a decrease in IFN- γ production.¹⁵ This study also found similar results, a decrease in the production of IFN- γ in patient diagnosed with DM. A similar result was expressed by Price which stated that patients diagnosed DM because of increased glycation resulted in a decrease in IFN- γ production.²¹

The concentration of IFN- γ obtained by various other cytokines on the production of IFN- γ . Tan found that there was two to three-fold decrease in the levels of IFN- γ . The decreasing IFN- γ concentration in DM patients increased the chance of bacterial infection. Furthermore, the decrease in IFN- γ production is the effect of decreasing interleukin-12 (IL-12).⁹ Lagman found that there was a decrease in IFN- γ concentration two-fold lower in DM compared to healthy, linking the decrease in IFN- γ with a decrease in (NO), which resulted in susceptibility to *M. tb*.²² The decrease in NO production will affect the bacteria killing mechanism. Furthermore, the decrease is also accompanied by a decrease in GSH which results in oxidative stress. This is reinforced by the increased susceptibility to the incidence of diabetic foot in patients with long-standing DM and uncontrolled blood sugar level.²³

However, if there is an increase in IFN- γ in DM patients, this indicates pathogenesis of hypertension in these DM patients.²⁰ This occurs by involving the renin-angiotensin-angiotensinogen system (RAS). The binding between angiotensin II on immune cells will increase the production of IFN- γ and the effect of adhesion that results in inflammation.²⁴ This continuous inflammatory process will result in hypertension.

A similar condition was also found in patients with increased fasting blood glucose levels even though they were not diagnosed with DM by health workers (Table 1). This data showed a fasting blood glucose level <126 mg / dl or ≥ 126 mg / dl without regard patients diagnosed diabetes or not. Many DM patients failed to control blood glucose levels. This is evidenced by Ramadhan in his research which concluded that 84% of DM patients were unable to control their blood glucose levels.³ Chronic hyperglycemic conditions either due to inadequate treatment or ignorance of suffering from DM can result in impaired immune function.

DM patients are also often accompanied by poor triglyceride control. Research conducted by Arifin proved that there was a relationship between increased blood glucose levels and triglyceride levels increased.⁴ This study found that the group with triglyceride levels ≥ 150 mg / dl had a higher IFN- γ concentration than the group with triglycerides <150 mg / dl (table 2). Mirhafez showed similar results, an increase in IFN- γ concentration in people with hypertriglycerides.²⁵ Research conducted by Pacifico concluded that there is an increase in IFN- γ production in obese people. Okopien explained in his study that in dyslipidemic patients occurred an increase in IFN- γ which resulted in chronic inflammation.²⁶ Peningkatan ini mungkin terjadi karena peningkatan CD4⁺ dan CD8⁺.²⁷ An increase in IFN- γ concentrations also occurred in people who had fasting blood glucose ≥ 126 mg / dl and triglycerides ≥ 150 mg / dl compared to people who had fasting blood glucose ≥ 126 mg / dl and triglycerides <150 mg / dl. Mirhafez also showed an increase in IFN- γ concentration in the group with metabolic syndrome compared to the normal. Among the various cytokines examined (IL-2, IL-4, IL-6, IL-8, IL-10, VEGF, TNF- α), IFN- γ is the most associated with the incidence of metabolic syndrome.²⁸ Furthermore, IFN- γ alters cell metabolism through inhibition of SIRT1. As a result of this inhibition causes metabolic disorders in skeletal muscle cells.²⁹ IFN- γ decreases insulin sensitivity. This also decreases

glucose uptake in adipose cells.³⁰ Rocha proved that a decrease in IFN- γ will decrease triglycerides and glucose levels.²⁷

Condition dyslipidemia is also characterized by decreased HDL levels. Low levels of HDL in the blood are used as a predictor of prognosis for patients with cardiovascular disease.³¹ The results of Purwanti's study showed that 74.3% of respondents who had higher fasting blood sugar levels had low HDL levels.³² In this study, it can be seen in table 1 that IFN- γ levels increased in the group with low HDL. This result is similar to the study conducted by Bengalem.³³ Other studies revealed a negative correlation between IFN- γ and HDL levels. IFN- γ levels in obesity with atherosclerotic can predict the potential and parameters for detection of coronary artery disease.³⁴

In conclusion, there was a decrease in IFN- γ in people with increased fasting blood glucose, while in hypertriglycerides there was an increase in IFN- γ . However, in people with hyperglycemia and hypertriglyceridemia, there was an increase in IFN- γ concentration, compared to people with hyperglycemia and normal triglycerides.

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