THE IGF-1 LEVEL OF ESRD PATIENTS AND ITS RISK FACTORS

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ABSTRACT

Objective: *To identify the Insulin-like Growth Factor–1 (IGF-1) level of End Stage Renal Disease (ESRD) and non ESRD populations, and correlation between IGF-1 level and ESRD incidences.* ***Material & Method:*** *This case study was carried out in Yogyakarta with 72 volunteers. The cases involved Chronic Kidney Disease (CKD) patients. The controls were non-CKD patients. CKD parameters were established with PERNEFRI diagnostic criteria. Comparison of IGF-1 levels between case and control groups was performed through ANOVA, with confidence level of 95%. Bivariate analysis to identify the correlation between IGF-1 plasma level, smoking status, illness history and body mass index (BMI) by determining odds ratio (OR) of individual risk factor of $p < 0.05$.* ***Results:*** *We enrolled 72 volunteers, 45 male and 27 female subjects. Of the 45 male patients, 15 CKD and 30 non CKD patients served as cases and controls, respectively. The difference in plasma IGF-1 level was detected in the case and control groups (42.01 ± 10.66 vs. 56.05 ± 24.91) ($p < 0.05$). The result of bivariate analysis showed passive smoking status, IGF-1 plasma level, DM history and hypertensive illness history had correlation with ESRD incidence with odds ratios of 7.88 ($p < 0.005$; CI: 1.6-37.5) for passive smokers, 4.3 ($p < 0.05$, CI: 1.36 to 13.33) for IGF-1 level, 21.5 ($p < 0.05$; CI) for DM history and 12.4 ($p < 0.05$; CI: 3.7 to 41) for hypertensive history.* ***Conclusion:*** *There was difference in IGF-1 plasma level between ESRD and non-ESRD patients. The IGF-1 plasma level, passive smoking status, diabetes history, and hypertensive history have correlation with ESRD incidence.*

Keywords: *Insulin-like Growth Factor–1 level, End Stage Renal Disease, case control, odds ratio.*

ABSTRAK

Tujuan : *Mengetahui kadar Insulin-like Growth Factor–1 (IGF-1) pada populasi Gagal Ginjal Kronik (GGK) dan bukan GGK serta mengetahui hubungan kadar IGF-1 dengan kejadian GGK.* ***Bahan & Cara:*** *Penelitian studi kasus ini dilakukan di Yogyakarta dengan72 relawan. Kasus adalah pasien GGK, kontrol adalah bukan pasien GGK. Parameter GGK ditegakkan dengan kriteria diagnosis PERNEFRI. Kemaknaan perbedaan rerata kadar IGF-1 antara kelompok kasus dengan kelompok kontrol dilakukan dengan Anova, dengan tingkat kepercayaan 95%. Dilakukan analisis bivariat untuk menentukan kaitan antara kadar IGF-1 plasma, status merokok, riwayat sakit dan indeks masa tubuh (BMI) dengan menetapkan odds ratio (OR) masing-masing faktor risiko dengan besar $p < 0.05$.* ***Hasil:*** *Dari 72 relawan, 45 pasien laki-laki dan 27 pasien perempuan. Dari 45 pasien laki-laki, 15 pasien GGK sebagai kasus dan 30 pasien tidak GGK sebagai kontrol. Ada perbedaan kadar IGF-1 plasma antara kelompok kasus dengan kelompok kontrol (42.01 ± 10.66 vs. 56.05 ± 24.91) ($p < 0.05$). Hasil analisis bivariat diketahui bahwa terdapat hubungan antara kadar, status merokok pasif, kadar IGF-1 plasma, riwayat sakit DM dan riwayat sakit hipertensi berhubungan dengan kejadian GGK dengan odds ratio masing–masing adalah 7.88 ($p < 0.005$; CI: 1.6-37.5) untuk perokok pasif, 4.3 ($p < 0.05$; CI: 1.36–13.33) untuk kadar IGF-1, 21.5 ($p < 0.05$; CI) untuk riwayat DM dan 12.4 ($p < 0.05$; CI: 3.7–41) untuk riwayat hipertensi.* ***Simpulan:*** *Terdapat perbedaan kadar IGF-1 plasma pada pasien GGK dengan bukan pasien GGK. Kadar IGF-1 plasma, status merokok pasif, riwayat DM dan riwayat hipertensi berhubungan dengan kejadian GGK.*

Kata kunci: *Kadar Insulin-like Growth Factor–1, Gagal Ginjal Kronik, case control, odds ratio.*

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INTRODUCTION

Chronic Kidney Disease (CKD) is a chronic disease, which serve as one of the major health problems in the community. CKD provides physical, economically, socially severe impacts, either for the patient, family and the nation. End Stage Renal Disease (ESRD) patients require hemodialysis or kidney transplantation; hence, along with, their quality of life declines.[1,2] The death risk of CKD/ESRD patients is 5–10 times higher.[3] ESRD patients' mortality rate in the first year of illness is 20% and increases to 60% in the fifth year.[4] When no prevention efforts in line are taken with the increasing number of diabetes mellitus and hypertensive patients, it is predicted that the number of CKD/ESRD patients in Indonesia will multiply in the next years.[5-7]

Insulin-like growth factor–1 (IGF-1) is a growth hormone with various biological activities, as mitogenic mitogen, antiapoptosis, antioxidant, and antiinflammatory factors. Results of epidemiological research in several countries has indicated that the IGF-1 level is associated with incidence of cardiovascular disease, cancer, depression, problems in growth and fitness, and health status, and length of hospital stay. Growth factors have not been extensively done in Indonesia; hence, this research serves as the early gate of scientific research on IGF-1 in Indonesia to identify whether IGF-1 also has clinical activities and benefits, as in other countries. When it is proved that IGF-1 in Indonesia is related to health status, quality of life, level of fitness and disease incidence and the treatment length in hospital, this presents scientific evidence for use of IGF-1 in managing public health problem in Indonesia.

IGF-1 may reduce the progressiveness of atherosclerosis, prevent LDL oxidation, inhibit macrophage infiltration, reduce the expression of pro-inflammatory cytokines IL-6 and TNF alpha and reduce superoxide formation in aorta. On the contrary, IGF-1 may increase the expression of eNOS and pAkt aorta and endothelial progenitor cell development.[8] The polymorphism in IGF-1 genes has been associated with the decreasing levels of IGF-1 in circulation, decreasing endogenous antioxidant capacity, decreasing immune response, atherosclerosis, and endothelial cell damages leading to the onset of cardiovascular diseases and the decreasing quality of life and CKD prognosis.[9-11] It is strongly assumed that the decreasing level of IGF-1 plasma may serve as an early marker for the damage process of the blood vessels in glomerulus, leading to CKD.[12-14] Studies describing the IGF-1 plasma level in CKD/ESRD patients in Indonesia have not been carried out. This study aimed to identify the normal level of plasma IGF-1 in healthy populations and the IGF-1 level in ESRD patients in Indonesia.

OBJECTIVE

This study aimed to identify the IGF-1 level of ESRD and non ESRD populations in Yogyakarta and the correlation between IGF-1 level and ESRD incidences.

MATERIAL & METHOD

The case-control study was conducted at PKU Muhammadiyah Yogyakarta Hospital, PKU Gamping Sleman Hospital as the Main Education Hospital of the Medical Faculty of UMY, and RSUD (District Public Hospital) of Sleman, RSUD of Bantul – Yogyakarta as hemodialysis center in Yogyakarta Special Province and its surrounding areas. The study was carried out from March to May 2012. First stage in the first year of this research aimed to collect demographic, geographic, economic-social data, and the IGF-1 level among 40 research subjects of case group and 40 research subject of control group.

Population included community members of Yogyakarta aged 15-75 years. The criteria of CKD diagnosis was creatinine clearance < 5 ml/minute or the creatinine level of blood serum higher than or equal to 10 mg/dl, which was identified from medical records. Inclusion criteria were Indonesian (Javanese, Sundanese, Malay), aged between 15-75 years old, willing to participate in this research by completing and signing informed consent sheet, and cooperative. Case group consisted of patients diagnosed with CKD/ESRD underwent hemodialysis at the PKU Muhammadiyah Yogyakarta Hospital, PKU Gamping Sleman Hospital, RSUD Sleman, RSUD Bantul Yogyakarta, Indonesian, living in Yogyakarta and willing to be research subjects in this research as with completed informed consent forms. The control group comprised of those with no CKD/ESRD diagnosis based on age, gender and hospital of origin in each case, and willing to be research subjects, not hospitalized due to DM, heart

and lung diseases, shown from medical records. The selected subjects based on the inclusion criteria were excluded when they (a) suffered from congenital kidney disease, (b) underwent kidney transplants, or (c) suffered from mental illness. Based on the calculation, the minimum total sample was 40. The estimated OR was = 2.5 proportion of the group α of 0.2 with the significance β of 0.05 and a power of 80%.

Independent variables involved socio-economic status, hypertensive disease history, diabetes mellitus history, smoking activity, hemoglobin level, plasma IGF-1 level. The dependent variable was the CKD/ESRD.

The primary data were collected through interviews using a questionnaires stating the respondent identity, socio-economic status, history of hypertension, history of diabetes mellitus, smoking activity, treatment history of anti DM, treatment history of anti-hypertensives and other data related to the variables of this research. The primary data collection was carried out through laboratory examination of plasma IGF-1 level, hemoglobin level and sugar level, and serum creatinine level. The laboratory procedures were conducted as the following: blood sampling, 5 ml of blood was taken by hospital personel from the respondents. Total blood samples taken were 40 for pre-treatment, and 40 for post-treatment. Blood sampling was carried out at the cubital fossa using 5 ml injection syringe and by maintaining safety and sterility principle. Blood samples were introduced in tubes labeled with code number of the tube, the name, sex and age of the respondent; then, they were kept in a flask containing cold pack, to be transported to the laboratory for IGF-1 marker examination. Elisa-based test was carried out on IGF-1. The bloods in vacutainer tubes that contained anticoagulant, were ready for plasma IGF-1 level test by using Elisa kit. The procedures for IGF-1 level test was performed as those conducted by the previous researchers. Routine blood and chemical blood tests were carried out by using hemocitometer.

ANOVA testing (mean) was conducted to identify the mean differences of IGF-1 level, serum creatinine level, serum blood sugar level and hemoglobin level between CKD/ESRD patients and the control group. The mean significances of IGF-1 level in case and control groups were analyzed by using one-way ANOVA test. The relationship between IGF-1 level, hypertensive illness history, DM illness history, education status and other risk factors with the CKD/ESRD incidences was identified through the use of bivariate tests (chi-square) by 2 x 2 table; therefore, odds ratio (OR) of individual factor risk was identified.

RESULTS

The general description of the case and control respondents is showed in Table 1. Of 72 volunteers, 45 and 27 were male and female respondent, respectively. Of the 45 male respondents, 15 and 30 were ESRD and non ESRD patients as cases and controls, respectively.

Table 1. Description of respondent.

Variable	Respondents		Total
	Case	Control	
Sex			
Male	15	30	45
Female	8	19	27
Total	23	49	72
Age			
< 40	5	7	12
41-60	12	33	45
> 60	6	9	15
Total	23	49	72
Marital status			
Married	21	46	67
Not married	2	1	3
Widow - widower	0	2	2
Total	23	49	72
Education level			
Not an education	1	8	9
Primary school	5	16	21
Middle school	3	9	12
High school	8	8	16
Associate degree	3	2	5
Bachelor's degree	3	6	9
Total	23	49	72
City			
Yogyakarta	2	4	6
Sleman	5	14	19
Bantul	13	27	39
Kulon progo	2	2	4
Wonosari	1	2	3
Total	23	49	72

Most respondents belonged to productive age; 12 respondents aged less than 40 years old; 45 respondents aged between 41-60 years, and 15 respondents aged over 60 years. Based on marital status, most respondents were married, i.e. 67 of 72 respondents. 42 respondents graduated from junior high school; only 30 respondents graduated from senior high school and college. 39 respondents were from Bantul; 19 were from Sleman; 6 were from Yogyakarta Municipality, 4 were from Kulon Progo and 3 were from Wonosari.

Table 2. Description of spread of illness history, active smoking status, passive smoking status and sport habit with the ESRD incidence.

Variable	Respondents		Total
	Case	Control	
Current smoking			
Yes	2	13	15
No	21	36	57
Total	23	49	72
Passive smoking			
Yes	21	28	49
No	2	21	23
Total	23	49	72
Diabetes			
Yes	11	2	13
No	12	47	59
Total	23	49	72
Hypertension			
Yes	18	11	29
No	5	38	43
Total	23	49	72
Dyslipidemia			
Yes	5	6	11
No	18	43	61
Total	23	49	72
Urinary tract infections history (UTI)			
Yes	1	6	7
No	22	43	65
Total	23	49	72

Table 2 shows data on the respondents' active and passive smoking status and respondents' history of illness. Of 72 respondents, only 15 were active smokers until date of interview; remaining 57 respondents were not smokers. Of the 15 active smoker respondents, only 2 suffered from ESRD as cases. Even most respondents were not active smokers, they were passive smokers, 49 of 72 respondents. Of the 49 passive smokers, 21 of them were ESRD patients. Respondents that were passive smokers were those living together in the similar house with one or more active smokers who performed smoking activity in the house. Based on the history of respondents' illness history, 13 respondents were with DM history; 29 hypertensive were with hypertensive disease history; 11 were with dyslipidemia history and 7 respondents were with UTI history. Of the 13 respondents with diabetes history, 11 of them were ESRD patients. Of the 29 respondents with hypertensive disease, 18 of them were ESRD patients.

The average age of the respondents in the case and the control groups were relatively similar or statistically not significantly different ($p > 0.05$). The average body height (BH) of respondents in case and control groups were significantly different ($p < 0.05$); however, the medians of body weight (BW) of the respondents in case and control groups significantly were not different ($p > 0.05$); this also true with the average size of body mass index (BMI) of the respondents in case and control groups that significantly were not different ($p > 0.05$).The results of measurements on the serum IGF-1 level in ESRD patients as the case group were different with those

Table 3. Description of measured parameters of age, height (TB), weight (BW), BMI and serum IGF-1 level.

Variable	Results		p
	Case (N = 23)	Control (N = 49)	
Age (years)	51.44 ± 10.74 (28.00-65.00)	50.76 ± 10.67 (25.00-65.00)	> 0.05
Height (cm)	163 ± 7.77 (150.00-182.00)	159 ± 7 14 (145.00-172.00)	< 0.05
Weight (kg)	57.95 ± 10.65 (35.00-75.00)	58.10 ± 12.39 (35.00-82.00)	> 0.05
BMI (kg/m^2)	21.65 ± 3.54 (15.56-27.22)	22.70 ± 4.26 (14.20-32.05)	> 0.05
IGF-1 serum levels (ng/ml)	42.01 ± 10.66 (24.23-69.75)	56.05 ± 24.91 (33.51-172.72)	< 0.05

Table 4. Results of bivariate analysis of IGF-1 level, passive smoking status, DM history and hypertensive illness as the risk factors of ESRD incidence.

Risk Factor	Results		p
	OR	CI	
Current smoking	0.26	0.054 - 1.28	> 0.05
Pasive smoking	7.88	1.6 - 37.5	< 0.005
Low IGF -1 serum level (< 50 ng/ml)	4.3	1.36 - 13.33	< 0.005
Diabetes	21.5	4.2 - 110.5	< 0.005
Hypertension	12.4	3.7 - 41	< 0.005
Asma Bronchiale	1.4	0.2 - 9.4	> 0.05

of non ESRD patients as a control group. The average serum IGF-1 level of ESRD patients was lower than those of non ESRD patients (42.01 ± 10.66 vs. 56.05 ± 24.91) ($p < 0.05$).

Based on the results of the bivariate analysis, it was found that passive smoking status, DM history and hypertensive illness history and lower levels of IGF-1 associated with the ESRD incidences. DM history and hypertensive disease history were two factors having strongest relationship with ESRD, odds ratio (OR) of 21.5 (CI: 4.2-110.5, 95%), and 12.4 (CI: 3.7-41, 95%). Passive smoking status and lower level of IGF-1 also indicated a strong relationship with ESRD, with OR of 7.9 (CI: 1.6-37.5, 95%) and 4.3 (CI: 1.36-13.33, 95%). Current smoking status and history of asthma was not shown related to ESRD; $p > 0.05$.

DISCUSSION

CKD has turned out to be an epidemic; and new cases are been increasing from year to year, while older cases have been still under treatment with the increasing level of morbidity and mortality. As found in other developing countries, incidence and prevalence of ESRD in Indonesia is unclear. It is estimated that ESRD incidence and prevalence in Indonesia is level of 100-150 and 200-250 people per 10 million population annually, respectively.[15] Indonesia with a population of 220 million has the addition of new ESRD cases between 2000-4000 patients per year. To date, the incidence and prevalence levels of CKD/ESRD in Yogyakarta has also not been identified yet.

Many factors may affect CKD incidence. Bases on some studies, it is suspected that factors relating the CKD incidences and its progressivity, among others, involve age, gender, ethnicity, lower birth weight, body weight, socio-economic status, smoking, blood pressure, blood cholesterol, alcohol and other prohibited drugs, analgesic drugs and NSAID, and diabetes.[16-18] While the major marker of kidney failure is CRP, pro-BNP, hemoglobin, GFR and albuminuria.[19]

Morbidity and mortality, and decreasing quality of life of ESRD patients is increasingly greater with weighting factors, in terms of comorbidity (cardiovascular, DM and infectious hepatitis), family factors and socio-economic status, quality of service, and lifestyle (smoking). Smoking habit does not only serve as a risk factor for ESRD, but it is also a weighting factor and worsening factor for prognosis and the decreasing quality of life of patients.[9-11] Smoking may cause destructively oxidative stress. Oxidative stress is the imbalance state between prooxidant and antioxidant. Actually, the oxidative stress state may be induced by a variety of factors; among others, are less antioxidants or the excess production of free radicals. In fact, free radicals are physiologically produced by cells as the logical consequence of biochemical reactions in aerobic life. However, when free radicals are excessive, and cellular antioxidant is consistent or even less in number, then the excess of free radicals may be neutralized and will not result in cell damages. The conditions of oxidative stress that may result in cell damage, may cause accelerated aging process, and also may lead to coronary heart disease (CHD), diabetes mellitus (DM) and cancer. The endogenous antioxidant activity of ESRD patients has decreased, leading to the susceptibility against the oxidative stress. It is assumed that chronic oxidative stress may cause polymorphism in IGF-1 gene that will impact various growth and development mechanisms, and degenerative processes.

Insulin-like growth factor-1 (IGF-1) is a growth factor with endocrine and paracrine activity serving as the main mediator of growth hormone (growth hormone/GH) on the development and growth process. IGF-1 is expressed by vascular cells and monocytes or macrophages. IGF-1 is a mitogen for endothelial cells and vascular smooth muscle cells. IGF-1 may increase the activity of cJun and NFkB-induced endothelial cells. In addition, IGF-1 has the effect of maintaining the life of blood vessels and prevents the oxidation of LDL-induced apoptosis in vascular smooth muscle cells. The oxidized LDL may reduce IGF-1 and IGF-1 receptor expression in vascular smooth muscle cells. The expression of IGF-1 is reduced in plague areas with positive staining for oxidized LDL. These condition indicates that the decreasing IGF-1 activity may contribute to the process atherosclerosis.[8] IGF-1 may lessen the progression of atherosclerotic plaque formation, inhibit macrophage infiltration into the lesion, decrease the expression of proinflammatory cytokines IL-6 and TNF alpha and reduce superoxide formation in the aorta. On the contrary, IGF-1 may increase the expression of eNOS and pAkt aorta and endothelial progenitor cells.[8]

IGF-1 activity is affected by IGF-binding protein 6 types (IGF = binding protein IGFBP). Among the six IGFBPs, IGFBP-3 is the most one affecting the activity, bioavailability and IGF-1 degradation. More than 90% of IGF-1 in plasma is bound by IGFBP-3, and only around 1% of IGF-1 is free.[13] In a healthy community, the free IGF-1 level within the blood is associated with fitness level and health status. Increasing levels of IGFBP-1 and IGFBP-3 will reduce the free IGF-1 level within the blood. Epidemiologically, it has indicated that lowering IGF-1 level is associated with the cardiovascular disease incidence, stroke incidence, length of hospital stay and diabetes mellitus morbidity level.[12]

Signaling pathway activation may induce different biological effects of IGF-1, including cell growth, differentiation, migration and survival.[20] Maturation and maintenance of T lymphocytes survival in the body are also affected by IGF-1. IGF-1 may reduce the progression of atherosclerotic plaque formation, inhibiting the infiltration of macrophages into the lesion, decrease the expression of proinflammatory cytokines IL-6 and TNF alpha and lessen superoxide formation in the aorta. On the other hand, IGF-1 may increase the expression of eNOS and pAkt aorta and endothelial progenitor cells.[8]

Differing from previous results, most recent research in animal models demonstrate that the decreasing level of IGF-1 has been associated with glomerulosclerosis. This is consistent with the clinical evidences that change in IGF-1 level is associated with micro albuminuria incidences and increasing cardiovascular disease risk among CKD or ESRD patients with hemodialysis.[12] Free IGF-1 level in plasma is associated with the incidence and morbidity of ESRD patients.

In general, the results of the present research indicated that ESRD incidence in Bantul was higher than any other city in Yogyakarta. Of 23 cases ESRD, more than 50% (13 cases) were from Bantul, followed by Sleman (6 cases), Yogyakarta Municipality (2 cases), Kulon Progo (2 cases) and Wonosari (1 case). ESRD cases were more commonly found among those of productive ages, i.e. 40-60 years (12 cases) and in men compared to women (15 vs 8). These results are consistent with of previous results[21] Other interesting new findings from the present research concerns with that active smoking status is not associated with ESRD incidence. Previous results from a study in PKU Muhammadiyah Hospital indicated that active smoking status was associated with CKD incidence. Factors contributing to difference in these results and those previous research concerns with the difference in the active smoker prevalence. Previous research found prevalence of active smokers was higher in CKD patients, i.e. reaching 30%, while the present research has showed the level of less than 10% (2 of 23 cases CKD). Although the status of active smokers among ESRD patients decreased, but it was not found among the passive smokers. Results of present research has indicated the importance of regulation/restriction in smoking activity.

In general, the IGF-1 level measured in this research was lower than those of found in other researches. De Sauja Vale et al. (2009) reported the results of geriatric IGF-1 level in Brazil that was 80.6 ± 28 ng/ml. It was higher than the results of this research. The results of IGF-1 level among DM patients in Malaysia also showed higher IGF-1 level compared to the results of this research.[22] One of the results in IGF-1 level which was quite similar with the results of this research, was reported by Zuppi et al,[23] who conducted a research on healthy populations in Africa. Some results of this research and previous research have suggested there are several factors affecting IGF-1 level; among others; they are health condition, age, activity and body mass index.

CONCLUSION

There was difference in IGF-1 plasma level between ESRD and non-ESRD patients. The IGF-1 plasma level, passive smoking status, diabetes history, and hypertensive history have correlation with ESRD incidence.

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