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The difference of high sensitivity-C reactive protein in the diabetic patients with depression and diabetic patients without depression

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ABSTRACT

A.Siswanto, E. Mudjaddid, Hamzah Shatri, Deddy N.W. Achadiono - ***The difference of high sensitivity-C reactive protein in the diabetic patients with depression and diabetic patients without depression***

Background: Both depression and diabetes mellitus have been related to a higher risk of developing coronary heart disease. Inflammation may be important in the pathogenesis of atherothrombosis. There are many markers of inflammation, one of them is high sensitivity-C reactive protein.
Objective: To determine the difference of high sensitivity-C reactive protein in the diabetic patients with depression and in the diabetic patients without depression.
Methods: This study used cross-sectional design and examined 64 diabetic patients, aged 30-60 years old. The patients were divided into two groups, i.e. with and without depression group.We measured depression using the DSM IV. The diagnosis of diabetes mellitus used PERKENI criteria 2006. We measured the serum concentration of CRP with a high sensitivity assay. Other measured factors included gender, marital status, occupation, blood glucose, HbA1c, body mass index, smoking and duration of diabetes. The association between hyperglycemia and hs-CRP were also studied.
Results: There were 32 diabetic patients with depression and 32 diabetic patients without depression. Body mass index were corelated with depression in diabetic patients ($p = 0.008$) but the other factors such as gender, age, marital status, occupation, blood glucose, HbA1c, duration of diabetes were not corellated with depression in diabetic patients ($p > 0.05$). The mean of hs-CRP consentration was higher in diabetic patients with depression (5183.44 ± 3974.66 vs $2103,17 \pm 1502.94$ mg /l, $p = 0.001$) than in diabetic patients without depression. There was no association between blood glucose control (HbA1c) and hs-CRP concentration.
Conclusion: High sensitivity-C reactive protein concentration was higher in diabetic patiens with depression compared with diabetic patients without depression.

Key words: hs-CRP – with and without depression diabetes mellitus type II

ABSTRAK

A.Siswanto, E. Mudjaddid, Hamzah Shatri, Deddy N.W. Achadiono - ***Perbedaan C-Reactive Protein sensitivitas tinggi pada pasien diabetes dengan depresi dan pasien diabetes tanpa depresi***

Latar Belakang: Depresi dan diabetes mellitus berhubungan dengan risiko yang lebih tinggi untuk terjadinya penyakit jantung koroner. Inflamasi diduga penting dalam patogenesis aterotrombosis. Terdapat banyak *marker* (penanda) untuk inflamasi, salah satunya adalah *C-reactive protein* sensitivitas tinggi (hs-CRP).

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Tujuan: Untuk menentukan perbedaan *C-reactive protein* sensitivitas tinggi pada pasien diabetes dengan depresi dan pasien diabetes tanpa depresi.
Metode: Studi ini menggunakan desain *cross-sectional* (potong lintang) dan meneliti 64 pasien diabetes, berusia 30-60 tahun. Pasien-pasien ini diklasifikasikan menjadi 2 kelompok, yaitu kelompok depresi dan tanpa depresi. Depresi dinilai dengan menggunakan DSM IV. Diagnosis diabetes mellitus didasarkan atas kriteria PERKENI 2006. Kami mengukur kadar CRP serum dengan *assay* sensitivitas tinggi. Faktor-faktor lain yang diukur adalah jenis kelamin, status perkawinan, pekerjaan, kadar glukosa darah, HbA1c, indeks massa tubuh, merokok, dan lama menderita diabetes. Hubungan antara hiperglikemia dan hs-CRP juga diteliti.
Hasil: Terdapat 32 pasien diabetes dengan depresi dan 32 pasien diabetes tanpa depresi. Indeks massa tubuh berhubungan dengan depresi pada pasien diabetes ($p = 0,008$), tetapi faktor-faktor lain seperti jenis kelamin, usia, status perkawinan, pekerjaan, glukosa darah, HbA1c, dan durasi diabetes tidak mempunyai korelasi dengan depresi pada diabetes ($p > 0,05$). Rata-rata kadar hs-CRP lebih tinggi pada pasien diabetes dengan depresi ($5183,44 \pm 3974,66$ vs $2103,17 \pm 1502,94$ mg/l, $p = 0,001$) dibanding pada pasien diabetes tanpa depresi. Tidak terdapat hubungan antara pengendalian glukosa darah (HbA1c) dan kadar hs-CRP.
Simpulan: Kadar hs-CRP lebih tinggi pada pasien diabetes dengan depresi dibanding pada pasien diabetes tanpa depresi.

INTRODUCTION

Depression is a disease with a high prevalence rate in most countries in the world. In United States, 9.5% or 19 million adults have depression, and the prevalence of depression in women is twice higher than in men. In other studies, the one-year prevalence was different among countries, that is, 0.8% in Nigeria, 3.1% in Japan, 6.6% in Lebanon, 6.8% in Columbia, 6.9% in Netherlands, 8.5% in France, 9.1% in Ukraine, and 9.6% in United States. Depression was related to disability, a decrease in work productivity, a reduction in patient's quality of life, a decrease in patient's compliance to treatment, an increase in health service cost, blood glucose control, and an increase in risk of complications in diabetic patients.[1]

Diabetes mellitus (DM) type 2 is a main etiology of morbidity and mortality. Prevalence of diabetes related to mortality and morbidity of cardiovascular system is an important issue. Although insulin resistance and pancreatic beta cell failure were still the main causes, in these recent years new paradigms were developed, and basic evidence of inflammation in DM type 2 with cardiovascular disorders was found.[2] The increased prevalence of depression in DM type 2 patients has been known. Depression occurs in 15-20% of DM type 2 patients, three times higher than in the normal population. Meanwhile, Carnetton *et al.*[3] suggested that depression was not related to DM type 2, and in other studies, depression did not precede DM type 2.[4]

C-reactive protein (CRP) is a family of pentraxin protein. Normally, CRP is found in small quantity in human serum. In a healthy individual, the average CRP level is 0.8 mg/L. CRP is mainly produced by hepatocytes, mediated by IL-6 released in inflammation site. CRP is also found in monocytes in atherosclerotic plaques, lymphocytes, and alveolar macrophages.[5] CRP level increases as the response to inflammation, infection, and tissue destruction. An established increase in CRP level occurs in chronic inflammation, autoimmune diseases, and malignancies. A study by Danner *et al.* showed an increased CRP level in depressive patients.[6] This result was different with the study of Douglas *et al.* that suggested that there was no correlation between depression and CRP.[7] The cause of the increased CRP level in depressive patients was: depression activated immune response by stimulating IL-6 production, which in turn would stimulate hepatocytes to produce CRP.[8] Other explanation was: a change of behavior in depressive patients, such as smoking, would increase CRP level.[9]

Diabetes causes hyperglycemia, increased free fatty acid, and insulin resistance. This causes oxydative stress, activation of protein kinase C, and activation of receptor to advanced glycation end-product (RAGE). This condition results in vasoconstriction, thrombosis, and inflammation.[11] Diabetes causes inflammation, atherosclerosis, and eventually, coronary heart disease, while depression is also related to inflammation. This study was

aimed find out whether diabetic patients with depression has higher level of inflammation, as measured by hs-CRP, compared to diabetic patients without depression.

METHODS

This was a cross-sectional study, to find out the hs-CRP level in depressive diabetic patients compared to non-depressive diabetic patients.

This study was conducted in Psychosomatic Polyclinic and Endocrinology Polyclinic, RSUP dr. Soeradji Tirtonegoro in July 2007 to December 2007. Diagnosis of diabetes was established according to PERKENI consensus in 2006. Depression symptoms was measured by Beck Depression Inventory (BDI). Scores >10 was used to suspect the possibility of depression. Diagnosis of depression was established with DSM IV. Demographic characteristics were obtained by interview. Data obtained were sex, age, educational status, working status, marital status, and duration of DM. The hs-CRP level was measured by immunoluminometry with Hitachi 911 analyzer from Japan. Normal hs-CRP level was under 1000 mg/mL. Other clinical data measured were vital signs, routine blood test, urine test, routine feces test, blood glucose level, and HbA1c. Routine blood test was measured by electronic impedance with sismex kx 21 from Japan. Routine urine test was measured by carik celup with meditron junior II from Germany. Routine feces test was measured by manual microscope with Nikon Japan. Blood glucose level was measured by hexokinase methode with cobasmira analyzer from Europe. HbA1c level was measured by chromatography with D10 from Japan. All of those test was done in Prodia Laboratory.

Inclusion criteria were DM type 2 patients who were physically examined and treated routinely in Endocrinology Polyclinic of RSUP dr. Soeradji Tirtonegoro, aged 20-60 years old, willing to participate the study, and signed the informed consent forms. Patients were excluded from the study if they took antidepressants, medications causing depression, had a comorbid diseases with depression, had infections, inflammation, and malignancy.

Subject characteristic data were described in proportion, average, and standard deviation. Kolmogorov-Smirnov analysis was conducted to find out the normal distribution of data. Independent t-test was used to analyze the normally distributed data. If the data were not normally distributed, the data were analyzed with Mann-Whitney U test. Accepted significance level was $p<0.05$. To compare the two groups with categorical variables, Chi-square or Fisher's exact test were used.

RESULTS

The subjects of the study satisfying the criteria and willing to participate this study were 64, consisted of 27 women (43.54%) and 37 men (57.81%). There were 32 subjects in depressive group and 32 subjects in non-depressive group.

In this study, depression was not significantly related to age (p=0.239), sex (p=0.211), educational status (p=0.427), marital status (p=1.00), working status (p=0.179), blood glucose control (p=0.547), and DM duration (p=0.826), but it was significantly related to body mass index (p=0.008) (TABLE 1 and 2).

TABLE 1 Clinical characteristics of the subjects

Variable	Non-Depressive	Depressive	p value
BMI (kg/m^2)	23.98± 2.949	26.48± 4.301	0.008
FBG (mg%)	214.28± 80.679	181.56± 53.093	0.060
2hPP BG (mg%)	397.03± 96.201	266.38± 79.660	0.170
HbA1c (%)	9.87± 2.771	9.44 ± 2.704	0.547
DMD (years)	2.56 ± 1.645	2.69± 2.753	0.826

Note: BMI = body mass index, FBG = fasting blood glucose, 2hpp BG = 2 hours post-prandial blood glucose, HbA1c = hemoglobin A1c, DMD = DM duration.

TABLE 2 Demographic characteristics of the subjects

Variable	Non-Depressive	Depressive	*p value*
Age (years)	48.47 ± 6.768	50.56 ± 7.313	0.239
Sex			
Men	18 (56.3%)	19 (59.4%)	0.211*
Women	14 (43.8%)	13 (40.6%)	
Education			
Elementary school	10 (31.3%)	9 (28%)	
Junior high school	3 (9.4%)	2 (6.3%)	
Senior high school	8 (25.0%)	14 (43.8%)	0.427
Higher education	11 (34.4%)	7 (21.9%)	
Marital status			
Married	31 (96.9%)	31 (96.9%)	1.00*
Widow/widower	1 (3.1%)	1 (3.1%)	
Work			
Governmental officer	14 (43.8%)	10 (31.3%)	0.179*
Not working	5 (15.6%)	2 (6.3%)	
Private company/self-employed	13 (40.6%)	20 (62.5%)	

** Statistical analysis with Chi Square test.*

The average in hs-CRP level of the subjects in non-depressive group was 2103.177±1502.94 mg/L, while in depressive group was 5183.44±3974.667 mg/L.

Kolmogorov-Smirnov test was used to find out the normal distribution of hs-CRP data. Result of the test showed a significant level of 0.009, which meant that the distribution of hs-CRP data was not normal.

Spearman's correlation analysis was conducted to find out the correlation of hs-CRP level in depressive diabetic patients and non-depressive diabetic patients. In this study, there was a correlation between hs-CRP level and depression (p=0.001).

If subjects included were only the obese and non-smoking patients, there were 11 subjects in non-depressive diabetic group and 20 in depressive diabetic group. There was a significant difference in hs-CRP level average (2785.09 mg/L) between both groups (p=0.0001).

DISCUSSION

This was a cross-sectional study, where the independent variables were measured once, thus, no causal relationship could be established. Depression may cause an increase in hs-CRP level; or an inflammatory process caused depression or both, depression and the increase in hs-CRP, were caused by other undetected disease process. To find out the causal relationship, a prospective cohort study is needed. Although the sample size of this study has satisfied the minimal sample size in statistic, a bigger sample size is desirable, and a comparison to other types of diabetes or non-diabetic patients are needed. Factors affecting depression and hs-CRP are considerable, and due to the limitation of this study, not all factors were studied.

One of the psychosocial factors affecting the prevalence of depression in DM patients was sex. Several studies showed that women had twice the possibility to have depression compared to men, probably because of hormonal effect.[6] In this study the male proportion was bigger than female, but statistically there was no significant correlation between sex and depression.

Age was also one of the factors affecting depression events in DM type 2.[14] Depression was found in 35-64 age group. It might be that when diabetes was diagnosed the patients had a false view of their disease, causing mood changes.[15] In this study, patients under 60 years old were included to avoid other factors affecting the increase of hs-CRP level. Depressive diabetic patients were older than non-depressive diabetic patients, but the difference was not significant.

Egede *et al.* conducted a study in 1810 DM patients. Other independent factors affecting depression were lower educational level, work, lower income, marital status, and obesity.[14] This is similar to Fisher *et al.* study, which suggested that income, work, and family were stressors related to depression.[16] In this study age, sex, educational status, marital status, and work status were not related to depression. But similar to the result of Egede *et al*. study, body mass index was significantly correlated to depression (p=0.008). On the contrary, Fisher *et al.* found that depression was not related to body mass index.[16] Blood glucose control was determined by many factors, that is diet, exercise, and drugs. The compliance of depressive patients in carrying out the programs was decreased. Larijani *et al.* found that depressive diabetic patients had a worse blood glucose control than in non-depressed diabetic patients.[17] This is similar to a study by Putranto that suggested that depressive diabetic patients had higher blood glucose control average than non-depressive diabetic patients ($p<0.05$).[18] In this study, blood glucose level control was not significantly different between depressed and non-depressed patients.

The result of our study in Psychosomatic Division and Endocrinology Division of RS dr. Soeradji Tirtonegoro Klaten showed that there was a significant difference in hs-CRP level between depressive and non-depressive DM patients (p=0.001). After corrected to their body mass index, the difference of hs-CRP in depressive and non-depressive DM patients was still significantly different (p=0.004).

This is similar to a study by Ford *et al.* who found that depression was related to the increase in hs-CRP level, but only in men. This relationship was still significant after other confounding factors were corrected. However, there was no relationship between hs-CRP level and depression in women.[12]

Kop *et al.* conducted a study on over 65 years old patients, and found that hs-CRP was increased in all patients with depression symptoms, both in men and women.[13]

Salkeld *et al.* found a significant difference between men and women in terms of depression and hs-CRP level. Although the prevalence of depression and hs-CRP level increase was higher in women compared to that in men, there was no relationship between depression and the increase in hs-CRP level in women. The change in depression and the increase in hs-CRP level showed no relationship in women. It was assumed that hs-CRP level was affected by hormonal factor. By excluding pregnant women or women who used oral contraceptives, the result was not changed. It was interesting that the hs-CRP level was changed according to menstrual cycle.[19] Another study showed that hs-CRP level was increased 44% in the middle of the cycle and 30% in luteal phase.[20]

A study by Douglas *et al.* showed that depression had no correlation to hs-CRP, and a correlation between depression and CRP may be explained through their relationship to BMI.[7]

Other studies analyzing the correlation between hs-CRP and depression showed evidence supporting the conclusion that depression was related to hs-CRP, but these evidence were affected by other variables, especially body fat.[13,21].

Sluwzewska *et al.* conducted a cross-sectional study (n=64) and showed that hs-CRP level was significantly higher in depressive patients than in non-depressive patients, but the result was not corrected to other confounding factors.[11]

In 2002, Kop *et al.* conducted a screening on 4268 older subjects (72±5 years old, 61% women) for depression and their hs-CRP were also measured. The result showed a significant difference between depressive and non-depressive patients (3.51±0.21 vs 3.31±0.10 mg/L; p=0.0008), and this relationship was insignificant after corrected to other variables, including body weight.[13]

Temeier *et al.* conducted a cross-sectional study in Rotterdam, involving 263 elderlies with depression symptoms. There was a positive correlation between depression and hs-CRP. This correlation was insignificant after correction to other confounding factors (smoking, stroke, functional disability, and cognitive).[22]

Based on the studies reporting a positive correlation between hs-CRP level and depression[11,13,22] that became insignificant after corrected the confounding factors, there was another cross-sectional study (n=100, 60% women with average age of 30 years

old) by Miller *et al.* which found an established correlation between hs-CRP and depression, especially in obese patients. But they also reported that, when this correlation was corrected to BMI as continuing variable, depression was not related to hs-CRP level. Similar result was obtained when BMI dichotomous measurement used.[23]

In 2003, Peninx *et al.* conducted a cross-sectional study (n=3024; 70-79 years old) to examine the relationship between depression and inflammation. After dichotomizing depression scores and stratifying hs-CRP level in quartiles, they found a correlation between depression and hs-CRP level. After confounding factors were considered, including body fat, the correlation was established, but only for the highest quartile of CRP level, but not for the three first quartiles.[21]

CONCLUSION

In this study, we found out that hs-CRP level in depressive diabetic patients were higher than that in non-depressive diabetic patients.

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