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The role of psychosocial stressors, carbohydrate and protein intake on serum serotonin and cortisol levels in patients with depression: a preliminary evaluation

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ABSTRACT

Introduction: Depression is a mental disorder associated with biological, environmental and psychological factors. Depression is estimated to be a disease that requires the second largest expense on treatment. Chronic stress will reduce serotonin activity and storage and also stimulate the adrenal cortex to release cortisol and other glucocorticoid hormones. Nutritional intake such as carbohydrates and protein also plays a role in depression with various mechanisms. The study aims to investigate the role of psychosocial stressors, carbohydrate and protein intake on serum cortisol and serotonin levels in patients with depression.

Methods: The study used an analytic observational approach with a cross sectional design. Subjects were selected by consecutive sampling and were asked to fill out the general characteristics questionnaire, Beck Depression Inventory (BDI) - II to determine depression levels, Holmes Rahe scale to measure psychosocial stressors, food frequency questionnaires to measure carbohydrate and protein intake. Subjects who met the inclusion criteria were taken blood samples to measure the cortisol and serotonin levels.

Result: Of the 79 subjects, 57 (72%) women and 22 (28%) men with an average age of 43 ± 3 years. A total of 64 (81%) subjects were with mild psychosocial stressors and 5 (6%) were severe. Psychosocial stressor were not significantly correlated with either serotonin (p=0.479), nor cortisol level (p=0.625) Carbohydrate were not significantly correlated with serotonin level (p=0.628) and cortisol level (p=0.252). Protein was not significantly correlated with serotonin level (p=0.688) and cortisol level (p=0.110).

Conclusion: There was no correlation between psychosocial stressors, carbohydrate and protein intake with serum cortisol and serotonin levels in depressed patients.

Keywords: carbohydrate, cortisol, depression, protein, psychosocial stressors, serotonin.
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INTRODUCTION

Major depression is a major cause of disability and contributes directly to the burden of disease worldwide. According to the World Health Organization (WHO) depression is a common mental disorder in the world and affects 350 million people worldwide. Depression contributes to a major cause of loss of productivity, suicide and is often comorbid with anxiety and substance abuse. Fifteen percent of patients diagnosed with depression and have received medication commit suicide. This percentage is estimated to be higher in patients who do not undergo treatment.[1] Data of Basic Health Research of Ministry of Health of the Republic of Indonesia in 2018 showed the prevalence of depression among the population of aged 15 years and above was about 14 million people or 6.1%, with a prevalence of 4.7% in Central Java.[2]

Psychosocial stressors are any circumstances or events that cause changes in a person's life so that the person is forced to adapt and cope. However, not everyone is able to adapt and cope with these stressors causing stress, anxiety and depression.[3] Although there are many effective treatments for depression, pharmacotherapy is usually costly and has potential side effects and psychotherapy requires time and commitment. Take the widely promoted monoaminergic antidepressant for example more than 30% of the patients did not respond to this treatment.[4] Therefore, there is a need to investigate alternative treatment or

prevention strategies. Recent research has focused on the role of nutrients in various mental health disorders including depression. Intake of nutrients such as carbohydrates, protein, fatty acids, omega-3, folic acid, vitamin B12, iron and zinc play a role in depression by various mechanisms.[5,6] Carbohydrates are naturally occurring polysaccharides and play an important role in structure and function of an organism. Carbohydrates have been found to affect mood and behavior. Eating a meal which is rich in carbohydrates triggers the release of insulin in the body. Insulin helps let blood sugar into cells where it can be used for energy and simultaneously it triggers the entry of tryptophan to brain. Tryptophan in the brain affects neurotransmitter levels. Consumption of diets low in carbohydrates tends to precipitate depression, since brain chemicals serotonin and tryptophan that promote the feeling of well-being are triggered by carbohydrate-rich foods. It is suggested that low glycemic index (GI) foods such as some fruits and vegetables, whole grain, pasta are more likely to provide a moderate but lasting effect on brain chemistry, mood and energy level than high GI food that then to provide immediately but temporarily relief.[7,8] Protein intake and in turn the individual amino acids can affect the brain functioning and mental health. Many of the neurotransmitters in the brain are made from amino acids. The neurotransmitter serotonin is made from tryptophan. If there is a lack of this amino acid, there will not be enough synthesis of serotonin associated with low mood. The excessive build-up of amino acids may also lead to brain damage and mental retardation.[8,9] This study aimed to investigate the role of psychosocial stressors, carbohydrate and protein intake in cortisol and serotonin levels in patients with depression. However, the type of carbohydrates and amino acids, specifically as precursors for serotonin, were not measured in this study.

METHODS

This was an observational study with cross sectional design. Subjects participated in this study were patients with depression under treatment which came to Psychiatry Clinic at Kariadi Hospital, Tugurejo Hospital, Permata Medika Hospital, Diponegoro National Hospital between January - December 2019. Subjects filled the demographic questionnaires including sex, occupation, marital status, education, and income. Holmes-Rahe scale was used to identify history of psychosocial stressors. The Holmes Rahe is a list of 43 stressful life events that can contribute to illness. Score ≥ 300 had severe risk of illness, score 150-200 had moderate risk of illness, score < 150 only had a slight risk of illness.[10] Subjects underwent a full medical evaluation which involved a medical history, physical and psychiatric examination. Beck Depression Inventory (BDI) - II was used to evaluate the severity of depression. Subjects who had diabetes mellitus, cardiovascular disease, renal disease, gastrointestinal disease, malignancy, and smoking were excluded. Body weight and height were measured to calculate the body mass index (BMI).

Carbohydrate and protein intake were calculated from dietary intake assessment using food frequency questionnaires (FFQ).[11,12] FFQ was administered by trained physician and data conversion was carried by a nutritionist. Carbohydrate and protein daily intake of each participant was obtained from the conversion of FFQ in gram.

Serum was obtained from peripheral blood vein and Sandwich enzyme ELISA method to measure the serotonin and cortisol levels. Normal serum serotonin level ranging from 101-283 ng/ml and normal serum cortisol level ranging from 10-20 g/dL.[13]

The normality test was carried out using the Saphiro-Wilk test. Spearman correlation test was done to analyze the correlation between psychosocial stressors, carbohydrate, protein intake, serotonin, and cortisol levels. The p-value is considered significant if $p<0.05$.

Table 1. Demographic characteristics of subjects

Variable	f	%	Mean ± SD	Median (min-max)
Age			43.48 ± 12.909	45 (19 – 68)
Sex				
Male	22	27.8		
Female	57	72.2		
Family history				
Yes	4	5.1		
No	75	94.9		
Psychiatric history				
Yes	3	3.8		
No	76	96.2		
Other medical illness				
Yes	36	45.6		
No	43	54.4		
Cortisol			7.82 ± 3.71	7.40 (1.10 – 18.00)
Serotonin			95.10 ± 71.11	73.06 (12.29 -341.61)
Carbohydrate			343.89 ± 43.16	362 (220-401)
Protein			43.16 ± 14.07	42 (23-69)
Holmes Rahe				
Mild	67	84.8		
Moderate	7	8.9		
Severe	5	6.3		

RESULTS

The study was conducted from February to April 2019 and involved 79 patients with depression who met the inclusion and exclusion criteria (Table 1). The research subjects' mean age was 43.48 ± 12.91 with ranging from 19 to 68 years old. Most subjects were female (72.2%). Of the 79 subjects, 75 (94.9%) did not have family history with psychiatric disorder, 43 (54.4%) did not have comorbidity with other physical illnesses. Mean serum

Table 2. Correlation between variables and serum serotonin and cortisol levels

Variable	F	Serotonin	p	r	cortisol	p	r
Age			0.850	0.022[a]		0.780	-0.032[a]
Gender							
Male	22	71.88 (15.59-264.91)	0.457		9.10 (3.5 – 18)	0.005*	-0.311[a]
Female	57	74.89 (12.29 – 341.61)			6.90 (1.10 – 17.70)		
Family history							
Yes	4	200.10 (116.78 – 327.66)	0,010	-0.289[a]	7.00 (6.00 – 12.80)	0.894	
No	75	70.70 (12.29 – 341.61)			7.40 (1.10 – 18.00)		
Psychiatric history							
Yes	3	151.11 (36.72 – 186.76)	0.476		7.50 (4.50 – 12.90)	0.722	
No	76	71.96 (12.29 – 341.61)			7.40 (1.10 – 18.00)		
Other medical illness							
Yes	36	79.69 (12.29 – 341.61)	0.907		7.45 (1.10 – 17.70)	0.807	
No	43	70.87 (17.48-327.66)			7.10 (1.80 – 18.00)		
Carbohydrate			0.628	-0.055[a]		0.252	-0.131[a]
Protein			0.688	0.046		0.110	-0.181[a]
Holmes Rahe						0.852	0.021[a]
Mild	67	73.06 (12.29 – 341.61)			7.40 (1.10 -18.00)		
Moderate	7	45.91 (17.48 – 181.37)	0.938	0.009	7.40 (6.20 -10,10)		
Stres Tinggi	5	79.87 (39.24 – 327.66)			7.30(3.50 -12.50)		

* Significant (p<0.05); [a] Spearman's correlation test

serotonin level was 73.06 (12.29 – 341.61) ng/mL and serum cortisol level was 7.40 (1.1-18) µg/ dL, mean carbohydrate intake was 362 (220-401) grams and mean protein intake was 43 (23-69) grams.

Table 2, showed the result of the bivariate analysis between age, gender, family history, psychiatric history, other medical illness, carbohydrate, protein and Holmes Rahe scale on serum serotonin and cortisol levels. There was a significant correlation between gender and cortisol level (p=0.005) as well as family history and cortisol (p=0.010) however psychosocial stressors, carbohydrate and protein intake were not associated with serum serotonin and cortisol levels in patients with depression.

DISCUSSION

There was no significant correlation between psychosocial stressors and serum cortisol level. Psychosocial stressors are associated with the severity of symptoms and disease course of major depression. The related mechanism is a change in the function of hypothalamus pituitary adrenal axis where the function is used so that individuals can adapt to physical and psychosocial changes. This may be due to the differences in hypothalamic-pituitary-adrenal (HPA) axis activity between individuals caused by several factors, including gender, age, severity of depression, hospitalization status, stress in early life, or post-traumatic stress disorder (PTSD) comorbidity and characteristics of stressors.[14] Most of the subjects experienced depression for more than three months so that cortisol levels were not as high as during the acute phase.

In individuals with an adequate supply of carbohydrates, insulin, glucagon, and epinephrine play a major role in controlling glucose concentration.

However, carbohydrate intake can likely cause changes in human growth hormone and cortisol. High consumption of carbohydrates causes a decrease in blood cortisol levels.[15] In this study, there was no significant correlation between carbohydrate intake and serum cortisol level. The factors that affect cortisol levels are the amount of carbohydrates and the type of carbohydrates and insulin. In this study, the type of carbohydrates consumed was not classified and the insulin was not examined.

Protein is one of the dietary components that are mostly related to the response of cortisol and adrenocorticotropic hormone (ACTH). The mechanism of food consumption-induced cortisol stimulation is not known, it may be due to stimulation of pituitary ACTH secretion by amino acid products or protein digestion, release of gut messengers that secondarily release ACTH or release locally generated ACTH from the intestine.[16] This study found that protein intake was not correlated with serum cortisol levels.

The role of psychosocial stressors as the etiology and development of depression has been widely demonstrated. The central nervous system response to psychosocial stressors is dominated by activation of the locus coeruleus or sympathetic nervous system causing the release of noradrenaline or adrenaline as well as the limbic or HPA axis. The serotonin transporter regulates this system at the molecular level, which is responsible for maintaining effective serotonin concentrations in the synaptic cleft. Therefore, serotonin transporters have become an important element in psychopharmacology as the target of most antidepressants. Disruption of the hippocampus caused by prolonged exposure to stressors causes modulation of several neural pathways including serotonergic input from the raphe nucleus, particularly the median raphe nucleus, which innervates various forebrain structures.[17] However, this study found stressor psychosocial was not associated with serotonin levels in patients with depression. This may be because the Holmes Rahe scores of most subjects were not really high and because every person has a different susceptibility to stress. Across multiple mental health-related measures, a polymorphism (5-HTTLPR) within the serotonin transporter gene's promoter has been associated with differential psychological sensitivity to stressful experience. The short/short genotype of the 5-HTTLPR is associated with greater cortisol reactivity to social threat. When short/short individuals experience stressful life events, they might be at greater risk for the adverse psychological and physical health consequences associated with heightened cortisol exposure.[18]

Increased levels of tryptophan lead to increased serotonin released into the synapse.[19] Carbohydrate intake increases tryptophan uptake which is modified by amino acid patterns. Insulin has little effect on plasma tryptophan levels, but it can lower plasma levels of neutral amino acids that compete with tryptophan to cross the blood-brain barrier.[9] Research conducted by Markus et al. demonstrated a significant correlation between a high carbohydrate and low protein intake and the ratio of tryptophan or amount of neutral amino acids.[20] However, this study showed that carbohydrate intake was not associated with serotonin levels in patients with depression.

The reward circuit involves specific neuropeptides, one of which is the serotoninergic pathway. Thus, it has been investigated that dietary protein can influence amino acid precursors' availability in the brain. The synthesis of serotonin in brain neurons may vary according to the availability of the precursor tryptophan. Tryptophan is one of the required amino acids obtained from dietary protein and the increased availability of tryptophan can lead to greater serotonin concentrations in the rat brain. Serotonin is the brain can be sensitive to the presence of specific proteins. Brain serotonin levels play a role in regulating stress, mood and eating behavior where this process can be influenced by protein intake.[21,22] However, this study found no significant correlation between protein intake and serotonin levels in patients with depression. This is because it was not known with certainty the type of protein consumed, where the tryptophan, the type of amino acid which is the precursor is not studied in-depth about serotonin. Other variables that may affect the results of the study were not investigated such as length of treatment, insulin levels, and early life stressors. Subjects on long-term antidepressant therapy may have low serotonin levels than those who do not receive therapy or short-term therapy.

CONCLUSION

From the study we conclude that psychosocial stressors, carbohydrate and protein intake were not associated with serum serotonin levels in patients with depression. Psychosocial stressors, carbohydrate and protein intake were also not associated with serum cortisol levels in patients with depression. Further research needs to be carried out by investigating other variables that can affect cortisol and serotonin levels such as length of therapy, insulin level, and early life stressors.

ETHICAL APPROVAL

This study has been approved by Ethical Committee Faculty of Medicine Universitas Diponegoro/Kariadi Hospital, Semarang, Indonesia, with Ethical Clearance reference number 014/EC/KEPK-RSDK-2018.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTION

Conceptualization, Natalia Dewi Wardani and Alifiati Fitrikasari; Methodology and Analysis Fanti Saktini; Resources Alifiati Fitrikasari and Hang Gunawan Asikin; Writing, Review and Editing Alifiati Fitrikasari and Tanjung Ayu Sumekar; Supervision and Funding Acquisition Alifiati Fitrikasari and Mohamad Sulchan.

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