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Correlation between Carbohydrate, Protein and Fat Intake with Serum C-Reactive Protein Level in Lung Cancer Patients Stage IIIB-IV

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Abstract

Introduction: The aim of the study is to determine the correlation between carbohydrates, fat and protein intake with the serum C-Reactive-Protein level in lung cancer patients stage IIIB – IV. The progression of lung cancer is influenced by immune system, genetic factors and inflammatory response, therefore CRP can be relied as one of the parameters for predicting cancer cell growth.
Methods: A cross sectional study was conducted in Dharmais Cancer Hospital Jakarta. Subjects were recruited by consecutive sampling, 49 subjects with lung cancer stage IIIB–IV who currently not receiving any treatment in Dharmais Hospital participating in this study.
Results: The mean age of subject was 55.82 $\pm$ 12.26 years old and 63.3% were male. The median value of CRP is 23.82 (0.30–207.29) mg/L. The correlation between carbohydrate, protein and fat intake with serum CRP level (r=0.015 and p=0.919; r=-0.165 and p=0.257; r=0.003 and p=0.986, respectively).
Conclusion: This study did not show significant correlation between carbohydrate, protein and fat intake with serum CRP level. In further analysis we did found that there was a negative, but non-significant correlation between protein intake and serum CRP level in cancer patient stage IV, as well as fat intake and serum CRP level.

Keywords C-Reactive-Protein, Inflammation, Lung Cancer, Carbohydrate intake, Protein Intake and Fat Intake

Introduction

Cancer is one of the non-communicable diseases with high incidence rates and the leading cause of death worldwide. Lung cancer is a type of cancer with the highest incidence and the leading cause of death from cancer in men.[1] Based on data from the Department of Pulmonology and Respiratory Medicine at the Faculty of Medicine University of Indonesia – Persahabatan General Hospital, the incidence of lung cancer has increased more than five-folds in the last 10 years, and most patients come at an advanced stage (IIIB/IV).[2] Malnutrition is a frequent manifestation in cancer patient and can negatively affect the outcome of treatments, thus a significant contributor to morbidity and mortality.[3] Studies have demonstrated that 30% to 87% of cancer patients are diagnosed with malnutrition.[4]

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Malnutrition in cancer patient is multifactorial and can be contributed to several factors: local effects of a tumor, the host response to the tumor, anticancer therapies, reduced food intake due to systemic effects of the disease, local tumor effects, psychological effects or adverse effects of treatment, and alterations in nutrient metabolism and resting energy expenditure (REE).[5] The interactions between cancer cells and normal host cells form a tumor microenvironment that causes changes in carbohydrate, protein and fat metabolism in the host body.[6] Metabolic changes that occur aim to provide the supply of energy and substrate that support the rapid growth of cancer cells.[7] Nearly a century, Otto H Warburg stated that cancer cells take glucose from their surroundings more than twice as normal cells and most of the glucose is converted into lactate, regardless of the presence of oxygen. In cancer patients, in addition to the above glycolysis changes, there is also insulin resistance.[8,9]

Changes in protein metabolism in cancer patients are characterized by decreased protein muscle synthesis, increased muscle protein catabolism and increased synthesis of acute phase proteins, such as C-reactive protein, as a response to inflammation.[10,11] Insulin resistance leads to increased gluconeogenesis pathways and decreases protein muscle synthesis. Amino acids, especially alanine are broken down for precursors of glucose formation.[9,12] Changes in lipid metabolism occur through increased lipolysis, decreased lipogenesis and adipogenesis, as well as increased fat oxidation.

The progression of lung cancer is influenced by the immune system, genetic factors and the inflammatory response.[13] Increased inflammatory response is a component in the development of cancer cells that can be demonstrated through the increase of acute phase proteins (c-reactive protein), so that CRP can be relied as one of the parameters for predicting cancer cell progression and survival rates in patients with various solid cancers.[14]

Research on the intake of carbohydrates, proteins and fats with the development of cancer cells gives inconsistent results.[15-16] Based on the above description, a study about correlation between carbohydrate, protein and fat intake with serum CRP levels as a parameter of cancer cell development in lung cancer patients at Dharmais Cancer Hospital Jakarta was conducted.

Methods

This cross-sectional study was conducted in Dharmais Cancer Hospital Jakarta from March to May 2017. The estimation of minimum sample size was calculated using the formula for a correlation study[17] with a total number of 49 subjects required in this study. Subjects were obtained using consecutive sampling method.

All men and women aged above 18 years old, diagnosed with lung cancer, stage IIIB–IV, currently not receiving any therapy were included in this study. Those who agreed to participate in this study were asked to sign the informed consent. The exclusion criteria were the patients who had chronic liver disease, chronic kidney disease, diabetes mellitus, and after injury.

Data were collected through interviews, anthropometric measurements and blood sampling. Interviews were conducted to determine the characteristics of subjects. Macronutrients intake was obtained by using a semi-quantitative Food Frequency Questionnaire (FFQ). The FFQ was used to estimate the macronutrient usual intake in the past one month. Anthropometric measurements was performed by doing height measurement using *Microtoise Stature Meter* and weight measurement using *SECA® electrodigital* scale. The serum levels of CRP were examined using COBAS C311 using immunoturbidimetric assay.

Data was processed using the program Statistical Package for Social Sciences (SPSS) for Windows version 20. The normality of data distributions was analyzed using Shapiro-Wilk test. If $p < 0.05$ data were normal distributed and were presented as mean ± standar deviation, otherwise data were presented as median (minimum-maximum). The correlation of carbohydrate, protein and fat intake with CRP serum were analyzed by Spearman rank collection test.

Results:

Subjects characteristics

The characteristics of the subjects were summarized in Table 1. The mean age of subjects was 55.82 ± 12.26 years old, most of them were men. A total of 67.4% subjects have middle low education level and 79.6% have incomes above the minimum wage. Cancer histopatology were 95.9% non-small cell lung cancer (NSCLC). About 79.6% subjects were in stage IV and 57.1% subjects had smoking history. Nutritional status assessment used body mass index (BMI) parameters based on Asia Pasific classification. There were 36.7% normoweight subjects and 20.4% underweight subjects.

The median energy intake of the subjects were 1740.5 (207.5–2527.9) kcal/day, with 53.1% subjects showed that energy intake still below ESPEN recommendations (30 kcal/kgBW per day). The average carbohydate intake were 59.59 ± 8.11%, with 75.5% subject at range of 45–65% carbohydrate from total energy. Mean protein intake were 63.65 ± 25g per day or 15,53 ± 3,83% of total energy intake. Mean fat intake were 46.57 ± 22.62 g per day or 24.73 ± 6.7% of total energy intake.

Median serum CRP levels were 23.82 mg/L (0.30–207.29 mg/L), with 61.2% of subjects having serum CRP levels > 10mg/L (Table 2)

Table 1 Characteristics of subjects (n=49)

Variabel	Value
Age, (year)	55.82 ± 12.26*
Sex, n (%)	
Men	31 (63.3%)
Women	18 (36.7%)
Education, n (%)	
Low	12 (24.5%)
Middle	21 (42.9%)
High	16 (32.7%)
Income, n (%)	
Below minimum wage	10 (32.7%)
Above minimum wage	39 (79.6%)
Smoking history, n(%)	
Never smoked	21 (42.9%)
Smoking	28 (57.1%)
Body mass index, n (%)	
Underweight	10 (20.4%)
Normoweight	18 (36.7%)
Overweight	10 (20.4%)
Obese 1	7 (14.3%)
Obese 2	4 (8.2%)
Histopatology, n(%)	
NSCLC	47 (95.9%)
SCLC	2 (4.1%)
Stage, n (%)	
III B	10 (20.4%)
IV	39 (79.6%)

*Mean ± standard deviation ** Median (minimum value - maximum)

Table 2 Serum CRP level

Variabel	Value
Serum CRP level, mg/L	23,82 (0,30 - 207,29)**
≤10 mg/L, n(%)	19 (38,8%)
>10 mg/L, n(%)	30 (61,2%)
Stage IIIB	14,46 (0,30-141,17)**
Stage IV	23,82 (1,23 – 207,29)**

** Median (Minimum – Maksimum)

In this study, we did not find significant correlation between carbohydrate, protein and fat intake with serum CRP levels. (Table 3)

symptoms or showing unspecific symptoms, so lung cancer was diagnosed when the disease has been in an advanced stage.[21]

Table 3 Correlation between carbohydrate, protein and fat intake with serum CRP levels (n=49)

Variable	Variable Serum CRP	
	r value	p value
Carbohydrate intake to total energy (%)	0.015[†]	0.919
Protein intake to total energy (%)	-0.165[†]	0.257
Fat intake to total energy (%)	0.003[†]	0.986

[†] Spearman rank correlation test

Discussions

In this study, the number of male subjects were more than women with a ratio of 1.8:1, with average age of the subjects of this study was 55.83 ± 12.62 years. Study by Sutandyo[18] conducted at the Dharmais Cancer Hospital found similar results to the male: female ratio = 3.1:1 and the mean age of the patients were 58 years. A total of 57.1% of subjects in this study had a history of smoking. This is different from the theory that 90% of lung cancer incidence is associated with smoking.[19] This difference may be due to a decrease in the prevalence of smoking and the presence of other risk factors that can cause lung cancer, such as air pollution, prolonged exposure to carcinogenic substances.[19] Based on data of cancer stage distribution, most of research subjects are in stage IV. Similar results were also obtained in the Sanchez-Lara study.[20] This was consistent with the prevalence of advanced lung cancer higher than the early stages. This condition occured because in the early stages, lung cancer often does not show

Median total energy intake of the subjects in this study were 1740.5 (207.5–2527.9) kcal per day or 29.68 ± 10.67 kcal/kgBW per day. A total of 53.1% of subjects showed total energy intake under the recommendation of ESPEN. In this study, 42.9% of subjects were found to have protein intake below 1g/kg BW per day with average protein intake of 63.65 ± 25 g per day or 1.14 g/kg BW per day, obtained by dividing total protein intake per day per subject with actual body weight. Around 57.1% of subjects in this study had low fat intake (<25%) with an average fat intake of 24.73 ± 6.7% of total energy intake per day. A few reasons that can cause low energy intake in cancer patients including the decrease in appetite due to the role of pro-inflammatory cytokines in inhibiting the orexigenic pathway neuropeptide Y and stimulate anorexigenic α-MSH pathway, nausea, satiety and chemosensory disorders such as persistent bad taste in the mouth, taste distortion, and heightened sensitivity to odors that often occurs in patients with advanced cancer.[10,22]

Serum CRP levels can be relied upon as one of the parameters for predicting cancer cell progression in patients with various solid cancers.[14] This study found no correlation between carbohydrate intake to total energy ($p = 0.919$) with serum CRP levels. In contrast to studies conducted by Ho et al[23] using tumor size in mice to assess cancer cell progression, there was a significant positive correlation between low carbohydrate intake (15% of total daily intake) and tumor size ($p < 0.05$). In this study, in addition to using tumor size, insulin levels and lactate levels are also used as a parameter of cancer development. There was positive correlation between low carbohydrate diet with insulin level and lactate level ($p < 0.05$). The difference in outcomes between these two studies may be due to low carbohydrate intake, parameters used to assess tumor progression, type and stage of cancer. Percentage of carbohydrate intake used was 15%, whereas in this study the average carbohydrate intake of the subject was $59.59 \pm 8.11\%$.

This study has not proved the correlation between protein intake to total energy ($p=0.257$) with serum CRP levels. Similarly, a study conducted by Lima et al[24] found no association between protein intake and serum CRP levels ($p>0.05$) in 30 gastrointestinal cancer patients. The study by Stobaus et al[25] in 285 cancer patients with chemotherapy found that a low protein intake group (<1 g/kg BW) showed a significant difference in mortality ($p = 0.024$) compared with patients from the high protein intake group (≥ 1 g / kg BW) and low protein intake is associated with fatigue and nausea/vomiting. The results of study conducted by Stobaus et al indicate that protein intake is good for supporting cancer patients.

This study has not proved the correlation between fat intake to total energy with CRP levels ($p=0.986$). In contrast to a study conducted by Fontana et al[15] found a significant association between fat intake and CRP levels ($p<0.027$). In the study of Fontana et al, a significant relationship between fat intake with levels of IGF-1 ($p<0.003$) and leptin levels ($p<0.027$) was also discovered. IGF-1 is mainly regulated by dietary intake to stimulate cell proliferation and inhibit cell death, so IGF-1 can support tumor development.

CRP levels are influenced by many factors.[26-27] Some have been controlled such as acute infection, chronic illness, acute trauma and pregnancy. But there are still those that have not been controlled like allergic complication of infection and inflammatory diseases. Between macronutrients with inflammatory levels in this study using serum CRP level as a marker, chronic inflammatory biomarkers may be more meaningful when associated with intake, since intake is a long-term exposure factor.

In a further stage-based analysis, we did found in stage IV cancer patient there was a negative correlation but not significant between protein intake to total energy and serum CRP levels ($r=-0.293$ and $p=0.070$) as well as fat intake to total energy and serum CRP levels ($r=-0.060$ and $p=0.717$). From these findings, we further research using a larger number of subjects.

In conclusion, the results of this study can not prove that there is a correlation between carbohydrate, protein and fat intake with serum CRP level in lung cancer stage IIIB–IV. Further study regarding the association of macronutrient intake with serum CRP level using equally distributed subjects according to cancer stage is necessary. Early detection on malnutrion and early nutrition therapy, education and counseling are given to patients and their family to prevent malnutrition, which potentially increased morbidity and mortality in advanced cancer patient.

Conflict of Interest

Authors declared no conflict of interest regarding this study.

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Acknowledgement

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