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ORIGINAL ARTICLE

Correlation between Zinc Intake and Zinc Serum Levels with C-reactive Protein Levels in Head and Neck Cancer Patients

Muningtya Philiyanisa Alam[1], Diana Sunardi[1], Ikhwan Rinaldi[2]

1. *Department of Nutrition, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo General Hospital, Jakarta, Indonesia*
2. *Hematology-Oncology Division, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo General Hospital, Jakarta, Indonesia*

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Abstract

Introduction The inflammatory process of head and neck cancer leads to increased proinflammatory cytokines and the synthesis of c-reactive protein (CRP), which then cause metabolic alteration and anorexia in patients. Zinc is one of nutrients that has an important role in suppressing inflammation, however it is reported that around 65% of head and neck cancer patients had zinc deficiency. The aim of this cross sectional study is to determine the correlation between zinc intake and serum zinc levels with CRP level as an effort in reducing inflammation process in head and neck cancer patients.

Methods and Results Subjects were collected by using consecutive sampling in the Oncology Clinic Dharmais Cancer Hospital. From 49 subjects, 67.3% were men, most subjects were in the age range between 46–65 years old. The most common (65.3%) was nasopharyngeal cancer and 69.4% were already in stage IV. All subjects (100%) in this study had zinc intake below the recommended dietary allowance (RDA) in Indonesia. The mean serum zinc level of the subjects was 9.83±2.62 µmol/L. Most subjects have elevated CRP levels. There was a weak negative correlation between zinc levels and CRP levels (r =-0.292, p =0.042), however there was no correlation between zinc intake and CRP levels of subjects (r =-0.25).

Conclusion There was negative correlation between serum zinc level and CRP levels in the subjects.

Keywords c-reactive protein levels, head and neck cancer, zinc intake, zinc serum levels

Introduction

Head and neck cancer is the seventh most common malignant disease in the world, where the number of new cases each year is increasing and causing many deaths.[1–3] The inflammatory process in cancer leads to increased proinflammatory cytokines such as interleukin (IL)-1, IL-6, tumor necrosis factor-alpha (TNF-α) and interferon-γ (IFN-γ).[4,5] The increase of proinflammatory cytokines will cause metabolic alteration, loss in appetite, induce satiety, resulting in anorexia and weight loss in cancer patients.[6] As response to the inflammatory process, the body will increase acute phase proteins synthesis in the liver as a defense mechanism.[6] C-reactive protein (CRP) is one of the acute phase proteins that are sensitive to acute inflammation, infections, and tissue damage.[7]

Zinc is a nutrient that plays an important role in suppressing inflammation, however it is reported that about 65% of head and neck cancer patients have zinc deficiency.[8] Zinc deficiency in head and

Corresponding author:
Muningtya Philiyanisa Alam
Departement of Nutrition, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
Email: philiyanisa@gmail.com

neck cancer patients is thought to be due to low zinc intake, low bioavailability, high molar ratio of phytate to zinc in food, and increased amount of reactive oxygen species (ROS).[9–11] Zinc deficiency in cancer patients results in decreased appetite and dietary intake, taste and smell disorder, immune system dysfunction, and increased risk of complications.[8,12] Zinc deficiency also affects the formation of cytokines, especially IL-1β, IL-2. IL-6, and TNF-α. The interaction between zinc and inflammatory cytokines is interrelated. Cytokines can increase and decrease the regulation of cellular zinc transporter expression in response to an increased need for zinc in inflammatory conditions.[13] However, zinc also has the ability to decrease the production of inflammatory cytokines through the up regulation of zinc finger protein (A20 protein) which inhibit the activation of NF-κB (nuclear factor kappa B), the major transcription factor in inflammation.[13,14]

The aim of this study is to determine the correlation between zinc intake and serum zinc levels with CRP levels in head neck cancer patients as an effort to reduce inflammation and, therefore, reduce anorexia.

Methods

Subjects and Study Design

This cross sectional study conducted in Oncology Clinic of Dharmais Cancer Hospital, Jakarta. Sample size was determined based on the correlation analysis ($\alpha = 0.05$; $\beta = 0.20$; $r = 0.4$), with estimated 10% of drop out, the sum of samples was 52 subjects. However, the subjects who completed the research were 49 subjects. Inclusion criteria were: patients at the Oncology Clinic of Dharmais Cancer Hospital who were diagnosed with head and neck cancer, stage I-IV, age above 18 years, had not received surgical therapy, radiation, or chemotherapy, willing to participate by signing the informed consent. Exclusion criteria were: had acute or chronic infections, had diarrhea, impaired liver and kidney function.

Data Collection

Data collection was conducted in September 2016 until December 2016 after obtaining approval from the Health Research Ethics Committee of Dharmais Cancer Hospital Number 054 / KEPK / IX / 2016. Subject characteristics including age and sex were collected by interview. Assessment of zinc intake was done by using semi-quantitative FFQ, which was then processed using Nutrisurvey 2007. Anthropometric measurements were performed to obtain data of height and weight. Heights were measured using Microtoise Stature Meter 200 cm (with 0.1 cm accuracy). Weight measurement was done by using Seca electro digital scale 876, Germany. Both anthropometric measurements were performed twice and the average results will be used. Nutritional status assessment were based on body mass index. Type and stage of cancer were obtained from medical records. Three mL of blood samples were taken from the cubital vein, which were then centrifuged at 3000 rpm to obtain the serum. Atomic absorption spectrophotometry method was used for the serum zinc examination using 1 ml of serum which has been transferred to the acid-washed serum cup. Whereas examination of CRP levels used immunoturbidimetry method of COBAS 501.

Statistical Analysis

Data were analyzed by using SPSS version 20.0. Normality test was done by using Kolmogorov Smirnov. Spearman correlation test was used to determine correlation between zinc intake with CRP levels and serum zinc levels with CRP levels.

Results

A total of 49 subjects participated in this study. Most subjects (67.3%) were male, the mean age was 48.33±12.73 years old and most of them (53.1%) were in the age range 46-65 years. Characteristic subjects based on age, gender, type of cancer, stage of cancer, status and nutritional intake, serum zinc levels, and CRP levels are shown in Table 1. Types of cancer consist of nasopharyngeal cancer, larynx, tonsil, sinonasal, and tongue. Nasopharyngeal cancer was the most common (32 people (65.3%)). Most subjects (69.4%) were in stage IV. Mean of body mass index was 22.20±4.2 kg/m^2: 42.9% subjects were overweight, 32.7% were normoweight, and 24.5% were underweight.

Table 1. Characteristics of the subjects

Characteristics	Frequency 47 (%)	Mean±SD or Median (min–max)
Age(year)		48.33±12.73
18 – 25	1 (2)	
26 – 45	19 (38.8)	
46 – 65	26 (53.1)	
>65	3 (6.1)	
Gender		
Male	33 (67.3)	
Female	16 (32.7)	
Type of cancer		
Nasopharynx	32 (65.3)	
Larynx	5 (10.2)	
Sinonasal	4 (8.2)	
Tonsils	4 (8.2)	
Tongue	3 (6.1)	
Stage of cancer		
I	1 (2.0)	
II	7 (14.3)	
III	7 (14.3)	
IV	34 (69.4)	
Body mass index (kg/m^2)		22.20±4.52
Underweight	12 (24.5)	
Normoweight	16 (32.7)	
Overweight	21 (42.9)	
Energy intake		1434.07±558.02
Adequate (≥30 kcal/kg BW/day)	15 (30.6)	
Inadequate (<30 kcal/kg BWday)	34 (69.4)	
Protein intake		46.66±22.96
Adequate (≥1 g/kgBW/day)	16 (32.7)	
Inadequate (<1 g/kgBW/day)	33 (67.3)	
Zinc intake		
Adequate (≥13 mg/day)		3.70 (1.20-11.70)
Inadequate (<13 mg/day)	0 (0)	
	47 (100)	

The mean zinc serum levels were 9.3±2.62 µmol/L and more than half the subjects (59.2%) has low serum zinc level. The median CRP serum of the subjects was at 6.03 (0.33 to 339.29) mg/L and most (51.0%) subjects had levels greater than 5 mg/L (data are shown in Table 2).

Table 2. Zinc serum and CRP levels of the subjects

Variable	Frequency n (%)	Mean±SD or Median (min–max)
Zinc serum (µmol/L)		9.83±2.62
Adequate	20 (40.8)	
Deficiency	29 (59.2)	
CRP serum (mg/L)		6.03 (0.33–339.29)
Adequate	24 (49.0)	
High	25 (51.0)	

This study found a negative weak correlation between serum zinc levels and CRP levels (r = -0.292, p =0.042), but no correlation between zinc intake and CRP levels (r= -0.25, p =0.86). Data are summarized in Table 3.

Table 3. Correlation between zinc intake with CRP levels and zinc serum levels with CRP levels

Variable	CRP serum (mg/L)	
	r	p
Zinc intake (mg/day)	-0.25	0.86
Zinc serum (µmol/L)	-0.292	0.042

Discussion

Dietary zinc intake of all subjects in this study did not meet the Indonesian RDA (13 mg/day for male and 10 mg/day for female).[12] The lowest and highest intake of zinc in male subjects were 1.5 mg/day and 11.7 mg/day, while in female subjects the lowest zinc intake was 1.2 mg/day and the highest was 6.3 mg/day. Similar results were obtained by Westin et al[13] who found the zinc intake in cancer subjects for two days food record was 9±2 mg/day. A cross sectional study by Irene et al[3] in the 2011 found that most of the subjects (80.6%) were included in the inadequate zinc intake group. The lack of zinc intake in this study is thought to be due to various factors including the presence of intake disorders due to tumor sites in the aerodigestive tract and pain that causes the anorexia. Most of the subjects in this study deliberately reduced the portion of food and avoid eating red meat, offal, eggs, milk, and animal-derived food, albeit high protein food are the main source of zinc in the diet. Therefore, the increase of zinc intake depends on increasing protein intake.

The mean serum zinc level in this study was 9.83±2.62 µmol/L and 52% of subjects were in the low serum zinc group. This is similar to study by Irene et al[3] which found serum zinc level median of 7.42 (4.16-14.67) µmol/L and 88.89% of the subjects had low serum zinc level. Sattar et al[14] also revealed that zinc concentrations in lung cancer patients were lower than controls. Based on the theory, low zinc levels in cancer patients can be caused by low intake, inflammatory state, the influence of proinflammatory cytokines, and increased number of ROS.[3–5,8,11] In this study most of the stage IV subjects (61.8%) had low serum zinc levels. This low serum zinc level is thought to be associated with low total zinc intake of subjects and the redistribution to the intracellular compartment as a defense mechanism.

The median of serum CRP level in this study was 6.03 mg/L with a wide range of 0.3 to 339.29 mg/L. A total of 51.0% of subjects had elevated CRP levels above 5 mg/L. Increased levels of CRP may be associated with an increased risk of cancer, proportional to the severity of disease, and increased tumor size.[15,16] Increased levels of CRP is also associated with poor prognosis of cancer.[10]

In this study, there was a statistically significant negative weak correlation between serum zinc level and serum CRP levels in head and neck cancer patients (r =-0.292, p =0.042). No literature mention the correlation between serum zinc levels and serum CRP levels in head and neck cancers yet, however there were reports of zinc levels with CRP levels correlation in lung cancer patients. Study by Sattar et al[14] in lung cancer subjects had significant negative correlation between zinc and CRP concentration (r =-0.66, p <0.05). This is consistent with the theory that zinc has anti-inflammatory properties which can inhibit the formation of

proinflammatory cytokines and then decrease the CRP. Studies of cell cultures in less and enough zinc conditions found that zinc induces upregulation of A20 protein which is one of the inhibitors of NF-κB activation as a major transcription factor of inflammation.[17] However, zinc deficiency condition may also induce the apoptosis and endothelial cell dysfunction due to increased concentrations of proinflammatory cytokines and oxidative stress.[8]

In conclusion, we found negative correlation between serum zinc level and c-reactive protein level in head and neck subject, so it can be used as the basic data for further research development of the possibility of providing supplementation for head and neck cancer patients.

Conflict of Interest

Some of this study funds was supported by the Tulang Bawang district government.

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