RESEARCH ARTICLE

High Leptin and Low Adiponectin Levels in The Metabolic Syndrome Patients with Malignancy

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Received date: Jul 28, 2023; Revised date: Sep 14, 2023; Accepted date: Sep 19, 2023

Abstract

BACKGROUND: Metabolic syndrome (MetS), which is characterized by insulin resistance, adipocyte accumulation, and obesity, has been linked to malignancy development. Both leptin, an adipose tissue-produced cytokine-like hormone, and adiponectin, a hormone secreted by adipose tissue, play roles in the progression of MetS. However, the presence of leptin and adiponectin is also assumed to be associated with cancer proliferation. Therefore, it is necessary to investigate the profile of leptin and adiponectin levels in MetS patients with malignancy and non-malignancy.

METHODS: This was a cross-sectional study involving 80 MetS subjects with and without malignancy. Leptin and adiponectin levels of subjects were analyzed by using the enzyme-linked immunosorbent assay (ELISA) method. Mann-Whitney tests were used to compare leptin and adiponectin levels between groups.

RESULTS: Leptin levels were significantly higher in MetS patients with malignancy (32.99±22.47 ng/mL) than those without malignancy (6.17±7.46 ng/mL). Conversely, adiponectin levels were lower in the malignancy group (10.11±7.66 µg/mL) compared to the non-malignancy group (13.44±8.29 µg/mL), with both differences being statistically significant (p<0.001 for leptin, p=0.023 for adiponectin).

CONCLUSION: Leptin levels were found to be higher while adiponectin levels were found to be lower in MetS patients with malignancy compared to those without malignancy. Therefore, it is suggested that leptin and adiponectin levels might be used as malignancy markers in MetS patients.

KEYWORDS: adiponectin, leptin, metabolic syndrome, malignancy

Indones Biomed J. 2023; 15(5): 297-303

Introduction

Metabolic syndrome (MetS) is characterized by decreased tissue sensitivity to insulin action, resulting in increased insulin secretion, which can lead to cardiovascular disease, type 2 diabetes mellitus (T2DM), polycystic ovary syndrome, and non-alcoholic fatty liver.(1-3)

Leptin works by regulating adipose tissue and energy balance by binding to the leptin receptor (OB-R). Both

leptin and OB-R are elevated in patients with malignancies, and also involved in the carcinogenic pathway through tumor proliferation and progression. Leptin receptors are widely distributed in the hypothalamus, islet cells, liver, kidneys, lungs, skeletal muscle, and bone marrow. Leptin levels, secreted by adipocytes, are regulated by insulin. Its activation uses the Janus Kinase-Signal Transducer and Activator of Transcription (JAK/STAT), activating Phosphatidyl Inositol-3 Kinase (PI3K), increasing cellular growth, migration, and invasion.(4)

Adiponectin is an active hormone during starvation period, and high adiponectin levels stimulate the central nervous system and peripheral AMP-activated protein kinase (AMPK), causing increased appetite, reduced energy use, and fat accumulation. Adipocytokines are produced exclusively by adipose tissue. Adiponectin is a hormone secreted by the adipose tissue, and its circulation is associated with the risk of obesity and malignancy. Low adiponectin concentrations are associated with a high incidence and prognosis of malignancy.(5)

In previous studies, it was found that leptin and adiponectin were involved in the proliferative process in the event of malignancy. It has been argued that there is a significant molecular and clinical effect on leptin and adiponectin levels in malignancy.(5) There has been quite a lot of research related to leptin levels and adiponectin levels to assess the incidence of malignancy. However, these studies generally only assess one marker (leptin only or adiponectin only). Studies that specifically combine the assessment of leptin and adiponectin regarding the assessment of cancer incidence in MetS patients are limited. Therefore, it is necessary to investigate the profile of leptin and adiponectin levels in MetS patients with malignancy and non-malignancy.

Methods

Study Design and Subjects Recruitments

This cross-sectional study was conducted in the ward of Dr. Kariadi General Hospital, Semarang, Indonesia, from July to September 2022. This research has been approved by the Health Research Ethics Committee of Dr. Kariadi General Hospital (No.1166/EC/KEPK-RSDK/2022) and the Health Research Ethics Committee of Universitas Diponegoro (No. 3950/UN7.5.4.2.1/PP/2022).

The sample size calculation was carried out using 90% power so that a research sample of 80 research subjects was required. The research sample was obtained using the consecutive sampling method until the minimum sample size was met. The inclusion criteria used in this study were MetS patients (either with or without malignancy) aged ≥18 years that met the criteria for MetS based on National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III).(6) Pregnant patients were excluded from the study.

Measurement of Leptin and Adiponectin Levels

Leptin and adiponectin levels of subjects were measured with enzyme-linked immunosorbent assay (ELISA) methods. A 10-mL blood sample was drawn into coded Ethylenediaminetetraacetic acid (EDTA) tubes then centrifuged for 10 minutes within 10 hours of collection. Plasma, buffy coat and red blood cells were separated and stored. Then an examination of leptin and adiponectin levels were examined using leptin ELISA (ProIntech, Rosemont, IL, USA) and adiponectin ELISA (Invitrogen, Carlsbad, CA, USA).

Medical Record Collection

Data regarding subjects' body height, body weight, body mass index (BMI), abdominal circumference, age, gender, haemoglobin (Hb), hemoglobin A1c (HbA1c), blood sugar, fasting blood glucose, 2 h postprandial blood glucose, total cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), history of hypertension, and the component of Mets were obtained from subjects' most updated medical record. The mentioned blood profile data were taken maximum within the last 3 months before the assessment of leptin and adiponectin levels.

Statistical Analysis

Chi-square test was used to find the association of the categorical bivariate data, while Mann-Whitney test was performed to determine differences in leptin and adiponectin levels. The relationship between leptin and adiponectin levels was determined using Spearman correlation test. The statistical significance level was set at $p<0.05$. To analyze the presence of confounding factors, a multivariate test was performed with a confidence interval of 95%. The data was analyzed using SPSS ver. 24 (IBM Corporation, Armonk, NY, USA).

Results

A total of 80 participants met the inclusion and exclusion criteria, consisting of 40 MetS subjects with malignancies

and 40 non-malignancies subjects. There were more woman subjects with MetS in both malignancy group (60%) and non-maligancy group (87.5%). Median of age for the malignancy group was 52.5 years old, while for the non-malignancy group was 64 years old (Table 1).

High Leptin Levels in Mets Subjects with Malignancy

There were 16 subjects with low leptin levels, 5 subjects with normal leptin levels, and 19 subjects with high leptin levels. There was a significant difference in leptin levels (p<0.001) between the two study groups, and it was found that the leptin levels were higher in the malignancy group (Table 1). Leptin levels in the malignancy group were obtained with a median value of 26.7 ng/mL, the lowest 3.2 ng/mL, and the highest 87.1 ng/mL. In the non-malignancy group, the median value was 2.05 ng/mL, with the smallest 0.1 ng/mL and the most significant value 27.2 ng/mL.

Eventhough in MetS subject with malignancy, the low and normal level of leptin were both undetectable, but interestingly, in the group of subjects with malignancy, the high leptin levels were significantly higher (32.99±22.47 ng/mL) compared to the non-malignancy group (12.23±6.83 ng/mL) (Table 2).

Low Adiponectin Levels in Mets Subjects with Malignancy

There was a significant difference in adiponectin levels (p=0.023) between the two groups, where adiponectin levels

Table 1. MetS subjects characteristics.

Variable	Malignancy (n=40)		Non-Malignancy (n=40)		*p*- value
	n (%)	Median (Min-Max)	n (%)	Median (Min-Max)	
Gender					
Man	16 (40%)	-	5 (12.5%)	-	0.010§*
Woman	24 (60%)		35 (87.5%)		
Age (years)	-	52.5 (36-70)	-	64 (52-80)	<0.001†*
Hemoglobin (g/dL)	-	11.35 (7.1-15.1)	-	13.4 (11.1-15.8)	<0.001‡*
HbA1c (%)	-	7.9 (4.4-18.1)	-	10.8 (7.1-13.6)	<0.001†*
Random blood glucose (mg/dL)	-	216.5 (113-491)	-	268 (103-433)	0.097†
Fasting blood glucose (mg/dL)	-	204 (101-417)	-	196.5 (103-343)	0.847†
2 h postprandial blood glucose (mg/dL)	-	226.5 (111-536)	-	291 (240-356)	0.001†*
Total cholesterol (mg/dL)	-	214 (89-350)	-	225.5 (191-258)	0.642‡
Triglyceride (mg/dL)	-	187 (68-410)	-	177 (140-219)	0.324†
HDL (mg/dL)	-	33 (10-106)	-	32.5 (21-47)	0.491†
LDL (mg/dL)	-	110 (52-190)	-	162.5 (121-195)	<0.05‡*
Body weight (kg)	-	57.5 (35-155)	-	77.5 (40-99)	0.001†*
Body height (cm)	-	155 (145-178)	-	158 (142-169)	0.517‡
BMI (kg/m^2)	-	22.96 (14.98-64.51)	-	31.23 (14.88-47.11)	<0.001†*
Abdominal circumference (cm)	-	90 (78-115)	-	84.5 (70-99)	<0.001‡*
Diabetes duration (years)	-	3 (1-20)	-	3.5 (1-7)	0.264†
Hypertension					
Yes	36 (90%)	-	18 (45%)	-	<0.001§*
No	4 (10%)		22 (55%)		
MetS					
3 components	12 (30%)	-	24 (60%)	-	0.001§*
≥4 components	28 (70%)		16 (40%		
Leptin					
Low (<1 ng/mL)	0	26.7 (3.2-87.1)	16 (40%)	2.05 (0.1-27.2)	<0.001†*
Normal (1-3 ng/mL)	0		5 (12.5%)		
High (>3 ng/mL)	40 (100%)		19 (47.5%)		
Adiponectin					
Low (<0.5 ug/mL)	0	7.9 (1-46)	0	12.8 (3.0-45.4)	0.023†*
Normal (0.5-30 ug/mL)	39 (97.5%)		38 (95%)		
High (>30 ug/mL)	1 (2.5%)		2 (5%)		

†Mann Whitney U; ‡Independent T test; §Chi-Square; *considered significant with p<0.05.

Table 2. Leptin level in MetS subjects.

Variable	mean±SD		
	Low Level (<1 ng/mL)	Normal Level (1-3 ng/mL)	High Level (>3 ng/mL)
Malignancy	-	-	32.99±22.47
Non-malignancy	0.4±0.28	1.62±0.48	12.23±6.83

were lower in the malignancy group (Table 1). Adiponectin levels in the malignancy group obtained a median value of 7.9 µg/mL with the smallest value was 1 µg/mL and the largest value is 46 µg/mL. In non-malignancy group obtained a median value of 12.8 µg/mL with the smallest value of 3 µg/mL and the largest value of 45.4 µg/mL.

Both in MetS subjects with and without malicnancy, the low adiponectin level were not detectable. However, the normal adiponectin level, subjects with malignancy have an average level of 9.19±5.05 µg/mL, which was lower while compared to the subjects without malignancy have an average level of 12.14±5.89 µg/mL (Table 3).

Age, Hemoglobin, LDL Level, and Hypertension History were Associated with Malignancy Incidence

Spearman correlation test was carried out to determine correlation between leptin levels and adiponectin levels. This study showed no correlation (p=0.682, r=-0.047) between leptin and adiponectin levels. Confounding variables for malignancy, such as age, Hb, LDL, BMI, abdominal circumference, and history of hypertension, were analyzed by multivariate tests to determine which variable had the most influence on the incidence of malignancy. It was found that there were relationships between the incidence of malignancy and age (p=0.015), hemoglobin level (p=0.025), LDL level (p=0.020), and history of hypertension (p=0.028) (Table 4).

Discussion

There are more men in the malignancy group than in the non-malignancy group, where the malignancy group had a younger mean age than the non-malignancy group. Gender differences in the incidence of malignancy are associated with regulation at the genetic/molecular level and sex hormones, such as estrogen. The lifetime probability of developing malignancy was 44.85% for males and 38.08% for females. Tox21 indicates a relationship between male-specific carcinogens such as testosterone and oxidative stress.(7,8) The younger age of the malignancy patients found in this study is thought to be due to a decrease in the life expectancy of malignancy patients compared to non-malignancy patients, where most of the malignancy patients are elderly and generally unable to survive in their current condition.(9)

Lower levels of hemoglobin, HbA1C, random blood glucose, and 2 h postprandial blood glucose, and higher levels of fasting blood glucose were found in malignant patients than in non-malignant patients. Lower hemoglobin levels are expected in patients with malignancies. Occult bleeding and iron deficiency are often prominent in gastrointestinal, urogenital, and gynecological tumors.(10) Tumor cells alter their metabolism by increasing glucose uptake and fermentation of glucose to lactate. Aerobic glycolysis become main pathway of glucose metabolism in malignant cells. Malignant cells will increase glucose uptake and lactate production dramatically.(11) Lower total cholesterol, LDL, triglyceride levels, and higher HDL levels were found in malignant patients than non-malignant patients. Consumption of large amounts of fat can increase circulating estrogen levels, thereby increasing the likelihood of cell damage and proliferation, which are responsible for the development of malignancy. Increased LDL levels are significantly associated with the incidence of metastasis.(12)

Table 3. Adiponectin level in MetS subjects.

Variable	mean±SD		
	Low Level (<0.5 µg/mL)	Normal Level (0.5-30 µg/mL)	High Level (>30 µg/mL)
Malignancy	-	9.19±5.05	46±0
Non-malignancy	-	12.14±5.89	38.2±10.18

Table 4. Confounding factors affecting the incidence of malignancy in MetS subjects.

Variable	B	*p* -value	OR	95% CI
Age	-0.229	0.015*	0.796	0.662–0.956
Hemoglobin level	-1.225	0.025*	0.294	0.101–0.859
LDL	-0.048	0.020*	0.953	0.916–0.992
BMI	-0.14	0.05	0.87	0.756–1.000
Abdominal circumference	0.133	0.095	1.142	0.977–1.336
History of hypertension	-4.213	0.028*	0.015	0.000–0.640

Regression analysis; *considered significant with $p<0.05$.

Malignant patients had lower body weight, lower body mass index, and wider abdominal circumference than non-malignant patients. BMI <22.5 was associated with an increased risk of all causes of death in 24 types of malignancy.(13) In this study, among patients with malignancy, the number of hypertensive patients was more significant, and the duration of DM was shorter than non-malignant patients. Hypertension has been reported to be the most common comorbidity found in patients with malignancy (37%). Much higher rates were observed after the initiation of specific chemotherapeutic agents. The number of MetS components in this study was higher in patients with malignancy than those without. This aligns with previous cohort studies and meta-analyses, where Mets increases the risk of malignancy. Malignancy-related mortality in this study was high in patients with Mets.(14) Patients with MetS were found had a 56% greater risk of death from malignancy based on 14-year cohort study. The risk of death was 83% higher in individuals with three or more components of Mets than in those without.(15)

There are significantly higher leptin levels in patients with malignancy than those without. In general, malignant patients had lower adiponectin levels than non-malignant patients.(16,17) Leptin receptor dysregulation plays a role in the development of various malignancies.(4) In this study, it was found that leptin production decreased with increasing age. Leptin levels progressively decrease with increasing age in women, but in men even though there was decreasing of leptin levels in subjects over 50 years of age, but there are no significant differences.(18) There was increased fat mass and central-peripheral leptin resistance in aging that lead to weight loss. Age-related decreases in leptin mainly affect the hypermetabolic component of the central catabolic action of leptin, whereas the anorexigenic component appears more strongly in the later phases of aging.(19) Higher plasma leptin levels are positively related to hypertension. Animal studies have shown that high leptin levels can activate the sympathetic nervous system and cause chronic elevated blood pressure and kidney dysfunction. High leptin levels can also affect the renin-angiotensin system. Since leptin is a hormone derived from adipose tissue, its relationship with blood pressure may be partly due to obesity and weight gain, one of the well-known risk factors for hypertension.(20)

In this study, adiponectin levels were significantly lower in patients with malignancy than those without malignancy. While, in previous studies have found that patients with malignancy have lower adiponectin levels than those without. Circulating adiponectin levels are decreased in patients with obesity-associated malignancies. Various types of malignant cells express adiponectin receptors, and adiponectin *in vitro* limits cell proliferation and induces apoptosis. Adiponectin levels and tissue adiponectin receptor expression are related to the clinicopathological characteristics of colorectal malignancies, especially the stage. Serum adiponectin may also be used as an additional diagnostic tool for malignancy recurrence and a predictor of adverse clinical outcomes about leptin (leptin to adiponectin ratio).(21,22) Serum adiponectin levels were significantly lower in patients with advanced disease, suggesting that adiponectin could be a potential marker for lung malignancy development.(23) Examination of lung tissue showed that both adiponectin receptors are expressed only in malignant lung tissue, whereas AdipoR2 is mainly expressed in non-small cell lung carcinoma (NSCLC) tissue and advanced disease tissue. In addition, low adiponectin levels correlate with other malignancies, including breast, endometrium, stomach, esophagus, pancreas, liver, kidney, and hematological malignancies. Adiponectin negatively affects the growth of most obesity-related malignancies. The mechanism depends on the cell type of malignancy, as seen in the cases of endometrial malignancy.(24)

There were relationship between age, hemoglobin level, LDL level, and history of hypertension with the incidence of malignancy in research subjects. Malignancy can be considered an age-related disease because the incidence of most malignancies increases with age. Age indicates the duration of exposure and the accumulated risk of malignancy. The multifactorial transformation process from normal cells to malignancy includes accumulating DNA damage and mutations over time, coupled with the disruption of DNA repair and abnormal cell growth regulation systems.(25) Anemia refers to low hemoglobin (Hb) levels and is a risk factor related to patients with malignancy survival. Anaemia associated with malignancy (cancer-associated anemia) is one of the most common paraneoplastic syndromes occurring during the development or treatment of malignancy. It is commonly found in 30-90% of patients with malignancy.(26) High plasma cholesterol levels are known positively correlated with the risk of death in certain types of malignancies. Abnormal lipid metabolism can result in oxidative stress-inducing lipotoxicity, which can significantly increase reactive oxygen species (ROS) levels. Gradually increasing oxidative stress can lead to intracellular oxidation of LDL to oxidized low-density lipoprotein (ox-LDL). Oxidative stress increases DNA damage which further results in malignant transformation.(27) Hypertension has been associated with an increased incidence of certain types of malignancy and higher malignancy-related mortality. Hypertensive men have a higher risk of developing prostate malignancy, and hypertensive women have a higher risk of endometrial and breast malignancy. Hypertension also increased the risk of renal malignancy two-fold in Caucasian patients and up to three-fold in African-American patients.(28)

Younger age, lower hemoglobin levels, lower LDL levels and the presence of a history of hypertension are associated with a higher risk of cancer incidence. However, the results of this study showed that there were differences with other studies in general regarding the age factor, which stated that older people had a higher tendency to experience cancer due to the accumulation of proto-oncogene factors. Therefore, it is necessary to re-evaluate the effect of age on the risk of cancer.

Future research which include the control of age, hemoglobin levels, LDL levels and history of hypertension in future study should be suggested, since it may affect incidence of malignancy in research subjects. Further research can be conducted with prospective research methods, as well as with subjects with different type of malignancy

Conclusion

Leptin levels are higher in patients with MetS and malignancy compared to those without malignancy. Conversely, adiponectin levels are lower in MetS subject with malignancy compared to those without malignancy. Assessment of leptin levels and adiponectin levels can be used to evaluate the development of malignancy in patients because there is evidence of a relationship between leptin and adiponectin levels and the incidence of cancer.

Acknowledgments

We want to express our sincere gratitude to all the individuals and organizations that have contributed to the publication of this research paper.

Authors Contribution

RA, DS, EAP, BS, CS, and TGDP contributed in the study conception and design. RA, DS, TGDP, and D collected and analyzed the data. DS, MLT, and MAUS provided critical revisions to the manuscript and editing. All authors have agreed with the final revision of the manuscript.

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