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Original Article

Adiponectin levels in myeloma patients after curcumin supplementation: A randomized clinical pilot study

Damai Santosa (MD, PhD) [1]
Damar Mashkun Rizqi (MD) [2]
Eko Adhi Pangarsa (MD, PhD) [1]
Budi Setiawan (MD, Ph.D) [1]
Suyono Suyono (MD) [1]
Mika Lumban Tobing (MD)
Suhartono Suhartono (MD) [3]
Soeharyo Hadisaputro (MD, PhD) [4]
Ignatius Riwanto (MD, Ph.D) [5]
Aru Wisaksono Sudoyo (MD, PhD) [6]
Catharina Suharti (MD, PhD) [1]

1. Division of Hematology-Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Diponegoro University/Dr. Kariadi General Hospital, Jawa Tengah, Indonesia
2. Department of Internal Medicine, RSUD Hj. Anna Lasmanah Banjarnegara, Jawa Tengah, Indonesia
3. Department of Environmental Health, Faculty of Public Health, Diponegoro University, Jawa Tengah, Indonesia
4. Division of Topical and Infectious Disease, Department of Internal Medicine, Faculty of Medicine, Diponegoro University/Dr. Kariadi General Hospital, Jawa Tengah, Indonesia
5. Department of Surgery, Faculty of Medicine, Diponegoro University, Semarang, Indonesia
6. Division of Hematology and Medical Oncology, Department of Internal Medicine, Dr. Cipto Mangunkusumo General Hospital – Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia

*** Correspondence:**
Damai Santosa, Division of Hematology-Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Diponegoro University/Dr. Kariadi General Hospital, Jawa Tengah, Indonesia

E-mail: santosaivha@fk.undip.ac.id
Tel: +24 8413476

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Abstract

Background: Multiple myeloma (MM) is characterized by reduced circulating adiponectin levels, a condition associated with various diseases such as diabetes mellitus, obesity, cardiovascular diseases, cancer, and plasma dyscrasias. Curcumin has been shown to inhibit adipogenesis and elevate serum adiponectin levels. Notably, limited studies investigating the relationship between adiponectin levels and curcumin supplementation in myeloma patients. This study is to evaluate the efficacy curcumin supplements on increasing the levels of adiponectin in myeloma patients

Methods: Patients with myeloma were randomly to melphalan, prednisone, curcumin (MPC) (n=17) and melphalan with prednisone (MP) (n=16) groups. The MPC group was treated by melphalan 4 mg/m^2 and prednisone 40 mg/m^2 for 7 days (MP), and curcumin 8 grams daily for 28 days. The MP group received MP and placebo. Subjects were followed-up every 28 days and a total of four treatment cycles. Hemoglobin, albumin, white blood cell (WBC), platelets, urea, creatinine, calcium, protein M, and adiponectin evaluated before and after treatment. Mann Whitney test or the Independent T-test were used to analysis

Results: Total subject (24 subjects) completed the treatment. Serum adiponectin levels after four treatment cycles in the MPC group were higher than in the MP group [(mean, 12227.1±5748.3) vs (11365.4±9175.5), P = 0.78]

Conclusion: Supplementing MP regimen with 8000 mg curcumin daily for 28 days increases the serum adiponectin level after four treatment cycles in myeloma patients. This research found that myeloma patients may benefit by taking curcumin supplementation.

Keywords: Multiple myeloma, Curcumin, Adiponectin.

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Of all hematologic malignancies, around 10% are plasma cell cancers like multiple myeloma (MM). Plasma cell clones multiply in the bone marrow, resulting in infections, anemia, hypercalcemia, skeletal damage, and renal insufficiency. Monoclonal gammopathy of undetermined significance (MGUS), a pre-malignant condition, is the clinically recognized precursor of MM. Mainstays of treatment for MM include alkylators, corticosteroids, and chemotherapy following autologous stem cell transplantation (ASCT) (1-3). Adipose tissue secretes a protein called adiponectin, which has several beneficial effects on the body, including insulin sensitization, anti-inflammatory, anti-atherogenic, pro-apoptotic, and anti-proliferative. A reduction of serum adiponectin levels is associated with the progression of MGUS to myeloma. Adiponectin levels decrease approximately 16-20% among individuals with smoldering myeloma and myeloma compared to healthy adults. In patients with IgG/IgA isotypes, adiponectin levels decreased by 26-28% (2-4). Adiponectin levels in MGUS patients are notably lower in individuals with the greater risk IgM isotype (a 42% drop) than in those with IgG/IgA isotypes. Therefore, a reduction in adiponectin expression may be associated with progression to myeloma (4).

The protein kinase A/adenosine monophosphate-activated protein kinase (AMPK) signaling pathway mediates the anti-proliferative effect of adiponectin on MM cells. Adiponectin also plays a role in inhibiting osteoclast differentiation and maturation via the mechanistic target of rapamycin kinase (mTOR) pathway, which controls osteoclast production and influences their ability to resorb bone (5, 6). The precise physiological function of adiponectin and its receptors remains elusive, yet a deficiency in adiponectin is believed to contribute to conditions such as diabetes, obesity, and cardiovascular disease (6). Curcumin supplementation is known to increase adiponectin and leptin levels in individuals with metabolic syndrome (7). Patients with non-alcoholic fatty liver disease have demonstrated increased levels of leptin and adiponectin following treatment with phytosomal curcumin. Curcumin supplementation also prevents *in vivo* tumor growth and adiponectin expression (7). It has been demonstrated that A549 cells' capacity to migrate and infiltrate tissue is inhibited by the expression of adiponectin. This inhibiting effect was mediated through the NF-κB/MMP pathways (8). Studies examining the potential benefit of curcumin supplementation on serum adiponectin levels in myeloma patients receiving melphalan-prednisone (MP) therapy are currently lacking. This study aimed to prove the efficacy of curcumin supplementation in increasing adiponectin levels in myeloma patients.

Methods

Patients and data collection: We used primary data from native myeloma patients. The International Myeloma Working Group (IMWG) 2014 criteria were used to establish the diagnosis of myeloma. (9). The Durrie Salmon (DS) system and International Staging System (ISS) were used for myeloma staging. (10, 11). The American Diabetes Association's (ADA) criteria were used to diagnose diabetes mellitus (12). Anemia was diagnosed by the World Health Organization (WHO) criteria for anemia in adults (13). The inclusion criteria were: naive myeloma patients, over 18 years of age, who were ineligible for transplantation. Severe infection, pregnancy, sepsis, elevation of aspartate aminotransferase (AST) by more than three times the upper limit normal (ULN), patients with severe liver disease (acute hepatitis, chronic hepatitis, cirrhosis), individuals involved with other studies, and poor ECOG performance status were considered as the exclusion criteria.

Sample size and randomization: The sample size was calculated based on the proportion difference of the two groups with minimal sample each group was 10 subjects. The selected significance levels for these computations were 0.05 for type I error (α) and 0.2 for type II error (β). The statistical power was set at 80%. Randomization was done by simple random sampling, and single-blind for patient. Every patient who met the criteria received one envelope with a specific code number inside to determine their treatment category. Patients were given a booklet with information on how to take the drug/placebo. Patients were not permitted to consume traditional medicines that could interfere with the research process. The amount of drug/placebo taken was calculated when patients came to the hospital.

Two groups were randomly selected from among the subjects: Melphalan, prednisone, curcumin (MPC) group which received an MP regimen (melphalan 4mg/m^2, prednisone 40mg/m^2, for 7 days) with the supplementation of 8 grams curcumin daily orally for 28 days; and MP group (control group) which received an MP regimen with placebo. Treatment procedures were repeated every 28 days, for a total of four treatment cycles (112 days). Four caplets of curcumin were administered orally, twice a day. Curcumin 1000 mg (BCM 95, Biocurcem ®) is made up of essential oils derived from turmeric that were acquired from PT. SOHO Global Health and 95% curcuminoid complex. Melphalan (Alkeran®, 2 mg) was obtained from Glaxo Smith Kline (14). Prednisone (Generic, 5 mg) was got from PT. Kimia Farma. The placebo contained amylum, and was similar to the curcumin caplets in size, color, and shape that was obtained from Faculty of Pharmacy Universitas Gajah Mada, Indonesia. Staging, hemoglobin, albumin, white blood cell count (WBC), platelet, urea, creatinine, calcium, protein M, and adiponectin levels were evaluated at baseline. After 4 months (112 days) of treatment, the patients were re-evaluated for hemoglobin, WBC, platelet, urea, creatinine, calcium, and protein M, and adiponectin levels.

Blood sampling: Venous blood samples were collected in 5 ml sterile vacutainer tubes containing 0.5 ml of liquid anticoagulant. To extract plasma, the citrated blood was centrifuged at 1000g (3000 rpm) for 15 minutes. Aliquots of plasma were kept at -20 °C. The blood samples were coded before laboratory analysis. The Quantikine Human HMW Adiponectin/Acrp30 ELISA Kit was used to measure the levels of adiponectin in serum. Using a flow cytometer (Cell-Dyn Saphire; Abbot Park, Illinois, USA), the full blood count (FBC) was determined. The homogeneous enzymatic colorimetric test (Dade Behring Siemens, Marburg, Germany) was used to measure serum calcium. Immunofixation electrophoresis was done on agarose, low electroendosmosis (EEO) containing sulphate ≤ 0.20%, gel

strength ≥1200 at 1.0% (g/cm^2) (Merck/Sigma-Aldrich, Jakarta, product no. 4679)**.**

Data analysis: For statistical analysis, an IBM SPPS Version 22 was utilized. The mean ± standard deviation (SD), the median, and the interquartile range (IQR) are used to express all of the findings. The significance of group differences was examined using the independent t-test, while the unpaired t-test was used to analyze the differences intergroup. The Mann Whitney U test, a non-parametric test, was employed when the data did not have a normal distribution. Chi-square was used for the nominal data. A statistically significant difference was defined if $p<0.05$.

Ethical clearance: This was a single-blinded clinical trial conducted during 2016-2017. The study was approved by the Ethics Committee of Faculty of Medicine, Medical Faculty of Diponegoro University and Dr. Kariadi Hospital. The study protocol was performed according to the Declaration of Helsinki. A part of the data included in this publication was obtained from an umbrella study that evaluated curcumin in myeloma with Ethical Number: 48/EC/FK-RSDK/I/2016. Prior to being enrolled in the trial, each patient signed an informed consent form.

Results

A total of 35 subjects were clinically diagnosed with MM according to the IMWG 2014 criteria. Two subjects did not meet the inclusion criteria; therefore, 33 subjects continued to randomization which then assigned to MPC (n=17) and MP (n=16) groups. After the study concluded, a total of 24 patients were suitable for analysis (see the consort, figure 1). The median age of the MPC group was 52 (42-77) years and the MP group was 58.5 (31-74) years. The most common type of myeloma in this study was IgG myeloma. The percentage of IgG, IgA, IgM, and light chain myeloma in the treatment group was 42%, 17%, 17%, and 25%, respectively. The percentage of IgG, IgA, IgM, and light chain myelomas in the control group was 33%, 33%, 8%, and 25%, respectively. All subjects in both groups had stage IIIA or IIB according to the Durie-Salmon staging.

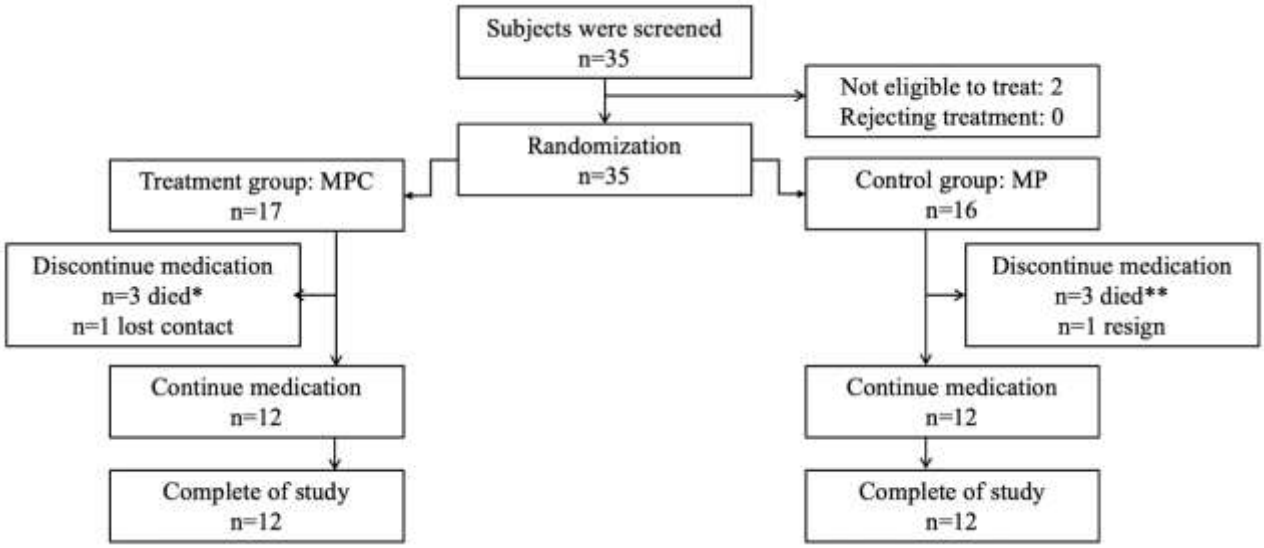

Figure 1. Study Flow. Description. MPC: melphalan, prednisone, and curcumin, MP: melphalan, prednisone. *In the first month of the treatment group, sepsis, thrombocytopenia, and anemia claimed the lives of four subjects. **In the first month of the control group, sepsis, anemia, and melena claimed the lives of three subjects. One participant in the control group quit taking the prescribed medicine because it gave him hot flashes. In the second month, we lost touch with one patient in the treatment group.

Table 1. Characteristics and demographics of the study population

Characteristic	MPC group	MP group	P value
Subject (n=24)	12	12	
Age (year) (median; IQR)	52 (42-77)	58.5(31-74)	0.09
Sex [n (%)]			
Male	8 (66.7)	6 (50.0)	0.68
Female	4 (33.3)	6 (50.0)	

Characteristic	MPC group	MP group	P value
Recurrent infection [n (%)]			
Yes	3 (25)	2 (16.7)	0.62)
No	9 (75)	10 (83.3)	
Myeloma type [n (%)]			
Immunoglobulin G	5 (41.6)	4 (33.3)	
Immunoglobulin A	2 (16.6)	4 (33.3)	
Immunoglobulin M	2 (16.6)	1 (8.4)	0.77 ™
Light chain	3 (25)	3 (25)	
Nonsecretory	0	0	
Hypertension [n (%)]			
Yes	3 (25)	2 (16.7)	1.0™
No	9 (75)	10 (83.3)	
Obesity [n (%)]			
Yes	1 (8.3)	0	1.0 ™
No	11 (91.7)	12 (100)	
Dyslipidemia [n (%)]			
Yes	7 (58.3)	10 (83.3)	0.37™
No	5 (41.7)	2 (16.7)	
Diabetes Mellitus [n (%)]			
Yes	0	0	
No	12 (100)	12 (100)	
Thiazolidinedione Use [n (%)]			
Yes	0	0	
No	12 (100)	12 (100)	
Durie-Salmon Staging [n (%)]			
I	0	0	
II	0	0	
IIIA	6 (50)	9 (75)	0.40 ™
IIIB	6 (50)	3 (25)	
International Staging System (ISS) [n (%)]			
I	1 (8.3)	1 (8.3)	
II	0	1 (8.3)	0.59 ™
III	11 (91.7)	10 (83.3)	
Performance Status (ECOG) [n (%)]			
0	8 (66.7)	4 (33.3)	
1	3 (25)	4 (33.3)	
2	0	2 (16.7)	0.28 ™
3	1 (8.3)	2 (16.7)	
4	0	0	
Albumin serum (g/l, mean±SD)	2.79± 0.57	2.86±0.74	0.82 ¶

Characteristic	MPC group	MP group	P value
Hemoglobin (g/dL, mean±SD)	9.00±2.06	8.23±2.71	3.40 ¶
WBC (10^3/⌈l, mean±SD)	6.68±2.36	7.47± 4.79	0.55 ¶
Platelet (10^3/⌈l, mean±SD)	219.24±152.24	185.96±159.85	0.55 ¶
Urea (mg/dL, mean±SD)	59.18±58.16	65.00±37.59	0.74 ¶
Creatinine (mg/dl, mean±SD)	2.09±1.55	2.57±2.14	0.46 ¶
Calcium (mEq/L, mean±SD)	2.47±0.54	2.00±0.53	0.73 ¶
Protein M g/L, mean±SD)	5287±3171	5614±1938	0.80 ¶
Adiponectin ng/mL, mean±SD)	9288±5839	11313±7655	0.25 ¶

Notes: MPC, melphalan, prednisone, curcumin; MP, melphalan, prednisone; WBC, white blood cell; ™ Chi square test; Mann Whitney U test; ¶ Independent t-test.

According to the ISS staging, most subjects presented with stage III. Most of the patients came to the hospital with a good performance status (ECOG 0 and 1). All of the participants had no history of diabetes type 2 and were not medicated with thiazolidinediones. The MPC and MP groups did not vary significantly in terms of obesity, dyslipidemia, staging, hemoglobin, WBC, platelets, urea, creatinine, or calcium levels. After four cycles of treatment, the patients were re-evaluated for hemoglobin, WBC, platelet, urea, creatinine, calcium, protein M, and adiponectin levels (table 2). No significant changes are found in hemoglobin, WBC, platelet, urea, creatinine, calcium, and protein M levels in the MPC compared to MP groups. The serum adiponectin levels at baseline in the MPC and MP groups were 9288.5±5839 ng/mL and 11313.5±7655.5 ng/mL respectively (table 1). The serum adiponectin levels after four cycles of treatment in the MPC group were higher than in the MP group (12227.1±5748.3 ng/mL as compared to 11365.4± 9175.5 ng/mL) but not statistically significant (P = 0.78, figure 2, table 2). There were no statistical differences between baseline and post-treatment values of adiponectin within the MPC group (9288.5±5839.4 ng/mL vs 12227±5748. 3 ng/mL, *P* = 0.75). There were no serious adverse events related to the protocol during the study. Excessive mortality or major adverse events were not found. One subject of the MP control group halted taking his medication because he felt hot flushes when taking the medication.

Table 2. Laboratory data analysis after four treatment cycles

Variable	MPC group (mean±SD)	MP group (mean±SD)	P value
Hemoglobin (g/d)	10.23± 2.04	10.07±2.39	0.87¶
WBC (10^3/□l)	4.37±1.92	4.53±1.00	0.84¶
Platelet (10^3/□l)	154.42± 89.32	207.55±167.07	0.35¶
Urea (mg/dL)	35.58±21.77	27.82 ±16.13	0.35¶
Creatinine (mg/dl, mean ± SD)	1.47±0.93	1.20 ±0.75	0.45¶
Calcium (mEq/L,)	2.09±0.16	2.03 ±0.20	0.48¶
Protein M (g/L)	3139±2277	4724 ±2426	0.17¶
Adiponectin (ng/mL)	12227 ± 5748	11365 ± 9175	0.78¶

Notes; MPC, melphalan, prednisone, curcumin; MP, melphalan, prednisone; WBC, white blood cells, ¶ Independent t-test.

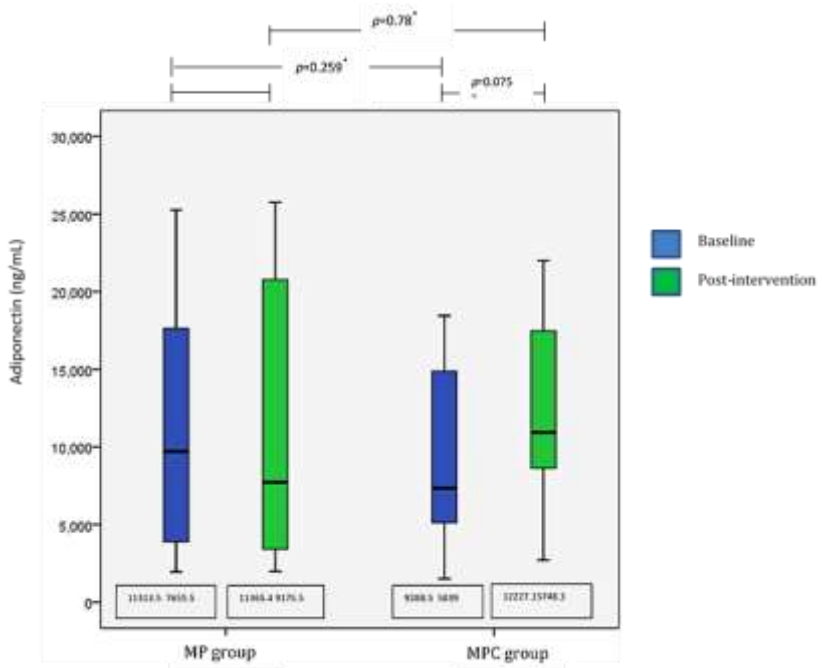

Figure 2. Comparison between adiponectin level at baseline and post-intervention 4-cycles treatment. The value of adiponectin showed as [mean±SD], Note; * Independent T test

Discussion

As far as our knowledge, this study is the first investigation of MPC regimen treatment to patients with transplant-ineligible myeloma, studying the circulating adiponectin levels of the patients. We found that curcumin supplementation increases adiponectin levels in myeloma patients. This increase in adiponectin levels may have a good clinical impact on the progression of myeloma patients' disease, as there is evidence that higher adiponectin levels protect against myeloma development and may reduce the risk of MGUS progression to myeloma. The current epidemiologic evidence that is available now suggests that adiponectin has the capability of protection to multiple myeloma progression, mainly among individuals with visceral fat accumulation (15). Our findings are consistent with the previous study in this field, which found that curcumin increases serum adiponectin levels. Curcumin suppresses angiogenesis in adipose tissue and affects lipid metabolism in adipocytes (16).A randomized clinical trial by Panahi, Y et al. demonstrated that curcumin improved adiponectin and leptin levels in serum of patients with metabolic syndrome (17). Further, an in vitro study has shown that curcumin induces preadipocyte apoptosis and inhibits adipocyte differentiation (18). The increase in adiponectin levels in the treatment group has been adjusted with other variables such as hypertension, dyslipidemia, and obesity, as it is known that these conditions correlate with adiponectin levels and interfere with the results of the analysis. Adiponectin has a variety of protective effects against obesity and its complications including hypertension, metabolic dysfunction, atherosclerosis, and ischemic heart disease (19, 20). The adiponectin serum level is a biomarker of, and possible mediator in the development of adiposity-related hypertension (21). Adiponectin in low levels has association with atherogenic lipoprotein levels such as elevation of triglycerides, decreased HDL cholesterol, and small dense LDL cholesterol (22). Adiponectin is a major circulating adipokine. Its role in tumorigenesis is multifaceted and has potential contradictory functions. In cancer epidemiology, several factors such as dysregulation of adipocyte-secreted factors and its associated changes from homeostatic metabolisms are found to be critical. Adiponectin has been linked to leukemia, lymphoma, and myeloma, myelodysplasia syndrome (MDS), chronic myeloid leukemia (CML) (6). Evidence exists that adipocytes and adipocytokines are as pathogenic in hematological malignancy as they are in solid tumors (23). Connections between serum adiponectin and risk of cancer are found to be negative correlation (24). The adiponectin's ability in becoming anti-proliferative for MM cells are due to mediation of the protein kinase A/adenosine monophosphate-activated protein kinase (AMPK) signaling pathway. Adiponectin also has a role in inhibiting osteoclast differentiation and maturation by targeting the mechanism of rapamycin kinase (mTOR) pathway (23-25). Adiponectin may stunt the growth of malignant cells by

inhibiting the mTOR cell pathway, as this pathway is involved in the function of controlling cell proliferation, growth, differentiation, migration, and survival. One crucial role of the phosphoinositide-3-kinase/protein kinase B/mTOR pathway is to downregulate bone mineralization. Based on this theory, adiponectin may inhibit the differentiation of osteoclasts, a disease process that results in mineral bone disease in MM patients (5). A low serum adiponectin correlates with tumors' increase in numbers and the size of tumor foci. The roles of adiponectin in cancer are multifactorial. Multiple contexts need to be considered, such as adipocyte's dysfunction leading to disrupted metabolic homeostasis, activation of epigenetic cell neoplastic pathways, and the microenvironment of tumor. The effect of low adiponectin levels on tumorigenesis and progression is correlated to the disturbance of adiponectin. This is due to normal cells. AMPK signals halt the proliferative pathways signaling (6, 25).

Curcumin has anti-angiogenesis, anti-inflammatory, and anti-carcinogenic activity, and inhibits adipogenesis (17, 26). Adiponectin levels differ in various stages of MM, and it appears that high adiponectin levels protect against MM and MM complications (4). Curcumin inhibits adipogenesis through several inhibitory mechanisms, including downregulated preadipocyte differentiation, dephosphorylation of AMPK, transcription factor induction, PPAR ɣ and enhanced binding protein α (C / EBP α), and through inhibiting the Wnt / β catenin signal pathway (27). Curcumin also altered the key factors in adipogenesis and lipogenesis. As we have discussed, adiponectin causes enhancement of insulin-like growth factor-1 (IGF-1) and production of estradiol, and protects against inflammatory cytokine secretion, hyperinsulinemia, insulin resistance, oxidative stress, and hypoxic status. Different studies have addressed the effects of adipose tissue released pro-inflammatory cytokines in inhibiting adiponectin synthesis, such as tumor necrosis factor α (TNFα) and IL-6. This process in the microenvironment appears to have an important impact on tumor development and myeloma progression (28, 29). Limitations of this study is due to its small sample size and the restriction to a single hospital center. The findings may not be generalizable to a broader population, and the limited participant pool might not fully capture the variability in responses to curcumin supplementation. Additionally, the use of a single hospital center introduces the potential for selection bias, as the characteristics of patients in that specific center may differ from those in other healthcare settings. Additional investigation is warranted to evaluate the effect of curcumin on other factors associated with adipogenesis, include leptin and resistin. Adiponectin levels should also be correlated with other pro-inflammation cytokines.The consumption of curcumin in their daily food intake, in low doses, is common among the population of Indonesia. Thus, food analysis must be a part of re-assessing the results of this study in further research. This study showed that supplementation of a four-cycle MP regimen with 8000 mg curcumin daily for 28 days in multiple myeloma patients increases serum adiponectin levels after four cycles of treatment.

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Ethical approval: This clinical trial has been registered on the ISRCTN registry with study ID ISRCTN14131419. The protocol of the study was approved by the Ethics Committee of the Faculty of Medicine, Diponegoro University, and Dr. Kariadi General Hospital (48/EC/FK-RSDK/I/2016).

Conflict of interests: The writers attest that none of the information in this article is the subject of a conflict of interest.

Authors' contribution: Every author made an equal contribution to the manuscript's composition.

Data availability statement: The ethics committee has placed restrictions on the study data to preserve patient privacy. Requests for data from researchers who satisfy the requirements for access to the confidential data will be taken into consideration by the corresponding author once this paper is published.

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