Excessive abdominal fat content indicates poor prognosis in patients with newly diagnosed multiple myeloma

Li Bao (baolilq909@sina.com)
Beijing Jishuitan Hospital https://orcid.org/0000-0002-6436-1492
Yutong Wang
Beijing Jishuitan Hospital
Xiaoguang Cheng
Beijing Jishuitan Hospital
Bin Chu
Beijing Jishuitan Hospital
Minqiu Lu
Beijing Jishuitan Hospital
Lei Shi
Beijing Jishuitan Hospital
Kebin Cheng
Beijing Jishuitan Hospital

Research article

Keywords: visceral fat, subcutaneous fat, treatment response, newly diagnosed multiple myeloma

Posted Date: June 2nd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-31931/v1

Version of Record: A version of this preprint was published at Clinical Lymphoma Myeloma and Leukemia on October 1st, 2019. See the published version at https://doi.org/10.1016/j.clml.2019.09.139.

Abstract

Introduction: Obesity has been identified as risk factor for multiple myeloma (MM). Various indexes of body fat compartment make it difficult to assess the value of body fat compartment in predicting prognosis in MM patients.

Methods: 36 newly diagnosed MM (NDMM) patients underwent abdominal CT pre-chemotherapy, and 72 matched healthy people were included. Total fat area (TFA), visceral fat area (VFA) and subcutaneous fat area (SFA) were measured from T12 to S1 and analyzed at six slices of vertebral interfaces. The level of adiponectin was also detected.

Results: NDMM patients had larger TFA, VFA and SFA while significantly lower plasma adiponectin than healthy people. The percentage of bone marrow plasma cells was significantly inversely correlated with SAT, but positively correlated with VFA/SFA. A significant inverse correlation was observed between the high-risk cytogenetic abnormality gain 1q21 and VFA. SFA and VFA/SFA had a significant effect on treatment responses.

Conclusions: NDMM patients had higher abdominal fat content but lower adipokine levels than healthy people. Excessive subcutaneous fat might be a predictive factor for high tumor burden and poor treatment response. Visceral fat content may be correlated with high-risk cytogenetic abnormalities. However, further investigation in larger samples is necessary to verify this association.

Background

Multiple myeloma (MM) is a malignant monoclonal plasma cell disorder, ranking second in frequency of hematological malignancies.[1, 2] Nonetheless, the exact etiology and mechanism remain incompletely elucidated. Obesity has been identified as a risk factor for the development of many cancers including MM[3]. The mechanisms underlying the association between obesity and MM are incompletely understood, but may involve impaired glucose metabolism[4] and inappropriate secretion of adipokines, including decreased adiponection and up regulated leptin. [5] Epidemiological studies had suggested abdominal adiposity evaluated by body mass index (BMI) and waist circumference was more relevant in MM.[6] This pool analysis of 20 prospective studies found higher early-adult BMI was associated with elevated MM mortality.[6] Others reported the underweight MM patients (BMI<18.5kg/m2) had increased mortality, whereas overweight (BMI 25-29.9kg/m2) and obese MM patients (BMI>30kg/m2) had lower mortality compared with normal weight patients (BMI 18.5-24.9kg/m2).[7] These paradoxical results might lead by disease-related weight loss, as BMI was a surrogate of obesity that mainly affected by weight.[8] We speculated the BMI, which unable to describe the body fat content, was inappropriate to evaluate the prognosis of MM. Therefore, the quantitative indexes of abdominal adipose tissue were appropriate for assessment of association between obesity and MM.

Computed tomography (CT) is an available method which can obtain an accurate assessment of intra-abdominal fat by measuring the visceral fat area (VFA) and subcutaneous fat area (SFA) on multi-

sections and is routinely used to diagnose and assess treatment options for MM.[9] Clinical researches in solid tumor, including gastrointestinal cancer[10, 11], renal cell carcinoma[12] and melanoma[13], have shown a strong association between increased visceral fat and poor treatment response, decreased progression free survival (PFS) and overall survival (OS). Few studies had investigated the predictive effect of fat compartment on treatment response and survival outcomes. [14, 15] Research from Takeoka et al indicated low subcutaneous adipose tissue index (SAI) at baseline correlated to poor survival outcomes of MM patients,[14] while group from Janathan found reciprocal association between VFA of abdomen and pelvis and treatment outcome in GMMG M5 trail.[15] They took different approaches to calculate fat compartment and the detection compartment only involved two intervertebral spaces. Nonetheless, the exact relationship between fat compartment and MM remain incompletely elucidated. Besides, no one had compared the difference of fat compartment between MM patients and healthy people.

In this study, we compared abdominal fat compartment between MM patients and BMI-matched health persons for the first time. We also analyzed the VFA and SFA assessed by CT with MM baseline characteristics and prognostic factors including disease stage, adverse cytogenetics and treatment response in newly diagnosed MM (NDMM) patients.

Materials And Methods

Our study was approved by the ethics committee of Beijing Jishuitan Hospital. Written informed consent was obtained from each patient prior to performance of any study procedures in accordance with the Declaration of Helsinki.

Patients

In this retrospective study, a total of 36 patients enrolled in, who were newly diagnosed with MM at the Department of Hematology, Beijing Jishuitan Hospital, during the period from October 2015 to March 2017. Diagnosis, staging, treatment and response evaluation of MM patients were performed according to the IMWG consensus.[16, 17] These patients received abdominal and pelvic CT before chemotherapy initiation or changed regimen when relapsed as part of the standardized staging examination. We followed these patients from diagnosed until the end of this study, unless the death or withdrawn. The median of follow- up of these NDMM patients was 677 days, range from 26 to 981.

For each NDMM case, 2 matched healthy people were randomly selected from the database supported by Radiology department of our hospital. The subjects included in this database were participants of an ongoing study since June 2014 investigating degeneration of the spine in the Department of Orthopedics, Beijing Jishuitan Hospital. These control cases were matched using the following criteria: age, sexual, height, weight and BMI.

Disease activity and treatment response

Patients received blood test including blood routine test, biochemistry (lactate dehydrogenase, calcium, creatinine), immune globulin and β2 globulin test et al for CRAB criteria and ISS staging. They also detected the bone marrow plasma by flowcytometry represented as tumor burden and cytogenetic detection including deletion 17p13, translocation t(4;14), translocation t(14;16) , translocation t(11;14) , deletion 13q14, gain 1q21 >3 copies by Fluorescence in situ hybridization (FISH) of $CD38^+$ purified plasma cells. Patients received chemotherapy based on the proteasome inhibitor and evaluated the effect post 4 cycles before autologous hematopoietic stem cell transplantation. Patients achieving at least a partial response (PR) after induction therapy were classified as treatment responders.[18] Treatment regimens and patients disposition are summarized in Figure 1.

Abdominal fat compartment quantitative assessment

All simulation scans were obtained in the supine position using a CT scanner compliant with five phantom (Mindways Software Inc., America) of Quantitative computed tomography (QCT) under whole abdomen. All studies were performed on an 80-slice CT scanner (Toshiba Medical Systems Corp., Tokyo, Japan) after an overnight fast. After generally calibration, the instrument parameters was setting as follows: 120 kV, 250 mA, 40 cm FOV, 120 cm bed height, 1 mm slice thickness, and 512 × 512 matrix. Scans generally extended from the last thoracic vertebrae (T12) to the sacrum (S1) and six slices of T12/L1, L1/L2, L2/L3, L3/L4, L4/L5 and L5/S1 vertebral interface used as anatomic markers. Visceral fat area (VFA) and total fat area (TFA) at each level were obtained, respectively, and the subcutaneous fat area (SFA) was calculated using the following equation: SFA = TFA -VFA.[19] These measurements and analysis were performed by a radiologist blinded to patient information.

Enzyme-Linked Immunosorbent Assay (ELISA) to Detect the Adiponectin in Plasma

Blood samples of 25 NDMM patients were collected to detect the baseline levels of total adiponectin. Plasma samples from 17 healthy people were used as normal controls which collected from the rest of their routine blood test. Adiponectin was measured using Human ELISA kit (Abcam Inc. Burlingame, CA) in accordance with the manufacturer's protocol. First, within 4 hours of collection, EDTA-anticoagulated blood was centrifuged at 1000g for 15 minutes. The separated plasma was centrifuged again at 10,000×g for 10 minutes at 4 °C to obtain platelet-poor plasma, which was then aliquotted and stored at -80 °C until testing. All samples were analysed in duplicate. Concentrations greater than 25 pg/ml for adiponectin were detectable. The color intensity was measured at 450 nm using a microplate reader (Bio-Rad, Berkeley, CA, USA), and the resulting data were analysed using CurveExpert 1.4. The personnel who performed the Elisa assays were blinded to the samples' clinical backgrounds

Statistical Analysis

The body mass index (BMI) was defined as the individual's body weight in kilograms divided by height squared in meters (kg/m^2). The ratio of VFA/SFA was calculated to display the distribution of abdominal fat. The median values and ranges are reported for continuous variables, and proportions are reported for categorical variables. Shapiro-Wilk tests were used to estimate the normality of the distribution of the

parameters. Variables with a normal distribution were then analyzed with a two-sided *t* test. None of the values of fat area followed a normal distribution. The comparison of NDMM and healthy people were conducted by Mann-Whitney U nonparametric tests. To analyze the association between baseline characteristics and abdominal fat compartment, Mann-Whitney U nonparametric tests were conducted for sex, DS stage, adverse cytogenetics and chemotherapy response with fat components. The correlation of fat area and continuously quantities like age, height, weight, BMI, BM stage, LDH were analyzed by Spearman test. All procedures were performed using a statistical package (SPSS 16.0, SPSS, Inc., Chicago, IL), with $P < 0.05$ regarded as significant.

Results

Abdominal fat of NDMM patients

NDMM patients had lager fat area of TFA (L4/L5, L5/S1), VFA (L4/L5, L5/S1) and SFA (T12/L1, L1/L2, L2/L3, L4/L5, L5/S1) than healthy people. The characters and values of fat area were shown in Table 1. We presented the fat distribution as VFA/SFA and found no significant difference between NDMM and healthy people.

Baseline characteristics

No correlation of parameters of body fat compartment and established factors for baseline charateristics (DS stages, monoclonal protein, LDH, hemoglobin, Creatinine, calcium light chain in urine and β2 microglobulin) were found. Regarding bone marrow (BM) plasma cells measured by flow cytometry, a reciprocal correlation was found with the SFA (L2/L3, p=0.018, r=-0.398), while positive correlation with VFA/SFA (T12/L1, p=0.047, r=0.338; L2/L3, p=0.039, r=0.351), visualized in Figure 2.

Adverse cytogenetics

A positive correlation was observed between adverse cytogenetic and VFA of the abdomen. The explored high risk cytogenetic of gain 1q21 (p=0.044) correlated with more VFA in slice of L4-L5 as shown in Table 3. Analysis of adipose tissue parameters and other adverse cytogenetics, consisting of Del 17p13 (n=11/36), Del 13q14 (n=10/36), T(14;16) (4/36), T(4;14) (7/36) and T(14/11) (n=4/36), showed no significant correlation.

Treatment response

As Figure 1 shown, 21 patients completed 8 cycles of chemotherapy. Above all, 7 patients achieved a VGPR or better and 9 patients showed a PR. The Overall treatment response (ORR) was defined as PR or better (n=16). Table 4 summarizes analysis of abdominal fat compartment and treatment response. ORR was negatively correlated to SFA of L4/L5 (p=0.025) and L5/S1 (p=0.044). Responders thus had a lower median SFA of the L4/L5 (169.97 cm^2) and L5/S1 (185.91 cm^2) than non-responders (262.19 cm^2 and 300.09 cm^2, respectively). The ration of VFA/SFA (L4/L5) was also showed a statistical significant effect

on treatment response (p=0.002). The small samples of this study remains as a limitation towards conducting further multivariate analysis.

Levels of adiponectin in plasma

Plasma level of adiponectin from NDMM and healthy people was measured by Elisa. As indicated in Figure 3, plasma adiponectin (1147.40pg/ml vs. 2077.10pg/ml, p=0.0368) level was significantly lower in NDMM group than in the healthy people group.

Discussion

With the current study we demonstrated that TFA and VFA of two intervertebral slices (L4/L5, L5/S1) were excessive, whereas levels of adiponectin in plasma was lower, in NDMM patients compared to BMI-matched healthy people. Moreover, we observed excessive SFA (L2/L3) and low ratio of VFA/SFA (T12/L1 and L2/L3) correlated with low levels of bone marrow plasma cells. In addition, an association of VFA (L4/L5) and the presence of a high-risk cytogenetic abnormality (Gain 1q21), while large SFA of the L4/L5 and L5/S1 were significantly associated with poor treatment response, which predicted poor prognosis of NDMM. Limitations of our pilot study include the small number of patients, single institution, and retrospective design.

To our knowledge, this study, for the first time, compared fat compartment assessed using CT scan between NDMM patients and healthy people. Based on the database containing abdominal fat compartment of healthy people from our radiology department, we found NDMM patients had higher abdominal fat, especially SFA, while had the similar compartment of VFA and SFA compared with BMI matched healthy population. One potential reason conferring excess fat content in NDMM patients is the obese people had higher risk in developing cancers. [3] Meta analysis of prospective studies reported the risk of MM was statistically significantly elevated among subjects categorized as overweight or obese. [20] Furthermore, the involuntary weight loss before MM diagnosed, which the loss of skeletal muscle and gain of adipose tissue occurred simultaneous,[21] may also result in excessive TFA, VFA and SFA in NDMM patients. Patients in our cohort had commonly normal weight, but they often harbored occult, severe preexisting fat excess. Diagnostic CT imaging provides additional important insight of intra-abdominal fat via measurements of SFA and VFA, especially for patients who are not overweight or obese in appearance and who may be normal weight, thin, or wasted.

Patients with excessive subcutaneous fat tissue (L2/L3) and low ratio of VFA/SFA (T12/L1 and L2/L3) correlated with low levels of baseline plasma cells in BM (Fig 2). As energy storage was the main functions of subcutaneous adipose tissue, low volume of SFA reflects the severe energy exhaustion caused by myeloma cells, indicating the advanced stage of the disease.[22] The adipose atrophy of cancer patients may caused by fat oxidation, decreased lipogenesis, impaired lipid depositionand adipogenesis, and browning of white adipose tissue. Inflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and interleukin-1 beta (IL-1β) produced by the tumor and host cells may direct contribute to lipolysis.[23] However, the pattern of loss has been incompletely characterized.

CT image analysis of recently diagnosed solid tumor patients with cachexia revealed that patients were losing visceral fat more than subcutaneous fat.[24] Since we found the ratio of visceral to subcutaneous positive correlated to plasma cells in BM of newly diagnosed MM patients, further studies of clinics and experimental models are warranted examining the changes of compartment of abdominal fat in MM patients.

Besides the observed link between fat compartments and tumor load, we observed a correlation of excessive SFA with worse treatment response. Gonzalez C et al reported that nuclear factor-κB p65 (NF-κBp65) and expressions of its pro-Inflammatory target genes (IL-1β, IL-6, INF-γ, TNF-α, MCP-1) were up regulated in the subcutaneous adipose tissue of cachectic cancer patients.[25] Previous studies had demonstrated strong IL-6R expression of baseline is associated with poor response to thalidomide in MM patients.[26] The proteasome inhibitor bortezomib treated MM patients by addiction to NF-κB-induced survival signals in differentiated plasma cells.[27] The relationship between inflammatory cytokines and treatment response of bortezomib remains unelucidated. Due to the small number of enrolled patients, we put together an analysis of MM patients treated with bortezomib and thalidomide. The subgroup analysis based on chemotherapy regiments and multivariate analyses to various factors were needed to elucidated the direct effects of subcutaneous fat on treatment response of MM patients.

For all high-risk cytogenetic abnormalities, gain1q21 had a positive correlation with VFA (L4-L5) in our analysis, while Maximilian group reported less VFA associated with cytogenetic abnormalities t(4;14) and gain1q21.[15] We had claimed MM patients had excessive visceral adipose tissue (L4/L5 and L5/S1) compared with healthy people, which suggested VFA might correlated with disease. Otherwise, Joyc et al detected fat metabolic activity by FDG-PET/CT and found patients with recently diagnosed MM had higher visceral tissue metabolic activity compared to patients with MGUS.[28] Visceral adipose tissue appears to be different metabolic and endocrine contributor than subcutaneous adipose tissue that was associated with obesity and cancer.[29] Increased visceral adipose tissue with active metabolism leads to increased circulation of a number of bioactive compounds such as IL-6, TNF-α, leptin and insulin-like growth factor-1 (IGF-1). [29, 30] Binding of these compounds to their respective receptors on tumour cells activated signalling pathways including the phosphatidylinositol 3-kinase (PI3K), mitogen activated protein kinase (MAPK), signal transducer and activator of transcription 3 (STAT3) and IkB kinase (IKK) pathways and leads to increased cell survival and proliferation thus promoting tumour progression.[31, 32]

In summary, we had stated for the first time a differentiation of abdominal fat distribution between NDMM and healthy people. We also demonstrated the subcutaneous fat correlated with tumor burden and poor treatment response, while visceral fat to high risk cytogenetic. The CT scan of adipose tissue measurement at the baseline might have prognostic implications and application for clinics should be on the basis of large-scale clinical trials.

Tables

Table 1. Demographics and fat distribution of MM patients and healthy people

	MM patients (N=36)	Healthy donor (N=72)	P value
Age, year	62(27-74)	59(27-82)	0.420
Sex, male/female	15/21	34/38	0.586
BMI, kg/m^2	24.02(19.75-30.12)	25.14(18.03-30.84)	0.211
Height, m	1.66(1.48-1.8)	1.68(1.44-1.73)	0.173
Weight, kg	64(46.5-82)	65(45-100)	0.514
TFA, cm^2			
T12-L1	238.78±83.37	217.76±82.50	0.447
L1-L2	279.08±83.09	237.08±83.91	0.062
L2-L3	307.17±80.63	276.67±93.26	0.132
L3-L4	306.21±82.66	291.74±110.33	0.442
L4-L5	328.03±86.51	262.14±76.22	0.001
L5-S1	328.66±96.57	262.94±78.80	0.001
VFA, cm^2			
T12-L1	152.78±72.57	148.28±71.90	0.945
L1-L2	179.95±68.04	154.08±69.91	0.418
L2-L3	175.52±63.01	166.45±69.53	0.755
L3-L4	149.56±59.55	143.08±52.41	0.732
L4-L5	142.95±42.26	110.27±31.79	0.002
L5-S1	134.40±36.32	101.39±26.60	0.000
SFA, cm^2			
T12-L1	86.00±34.35	69.48±35.95	0.026
L1-L2	108.11±44.43	83.01±36.16	0.014
L2-L3	131.65±47.55	110.21±44.29	0.028
L3-L4	156.65±67.73	148.66±76.02	0.314
L4-L5	185.08±69.09	151.87±61.14	0.025
L5-S1	194.25±81.52	160.56±68.87	0.049
VFA/SFA			

T12-L1	1.58(0.37-6.59)	2.14(0.52-6.14)	0.191
L1-L2	1.60(0.44-4.14)	2.03(0.48-4.68)	0.413
L2-L3	1.45(0.54-3.77)	1.46(0.62-5.38)	0.588
L3-L4	1.05(0.01-2.41)	1.00(0.53-2.57)	0.931
L4-L5	0.79(0.35-2.36)	0.77(0.31-2.03)	0.579
L5-S1	0.74(0.29-1.94)	0.68(0.23-1.99)	0.338

The Age, BMI, Height, Weight and V/S were shown as median (range). The value of TFA, VFA and SFA were shown as mean±SD. BMI, Body Mass Index; TFA, Total Fat Area; VFA, Visceral Fat Area; SFA, Subcutaneous Fat Area; T, thoracic vertebra; L, lumbar vertebra; S, sacral vertebra.

Table 2. Baseline characteristics of involved MM patients

	MM patients (n=36)
Plasma cells in BM, %	19(0-96)
Hemoglobin, g/L	114(48-156)
Serum creatinine, umol/L	71(31-444)
Serum calcium after correction, mmol/L	2.36(1.8-3.53)
Lactate dehydrogenase, LDH, IU/L	160(98-388)
Light chain in urine, g/24h	0.35(0-33.4)
Serum β2 microglobulin, mg/L	3(2-12.65)
DS stage, I/II/III	1/0/34
Cholesterol, mmol/L	4.18(1.4-8.23)
Triglycerides, mmol/L	1.34(0.38-3.77)
High-density lipoprotein, mmol/L	1.21(0.7-2.33)
Low-density lipoprotein, mmol/L	2.38(0.49-4.68)
Fasting glucose,mg/dL	5.6(3.9-8.9)
Adverse cytogenetics	
Del 17p13	11 (30.6%)
Del 13q14	10 (27.8%)
Gain 1q21	5 (13.9%)
T(14;16)	4 (11.1%)
T(4;14)	7 (19.4%)
T(11;14)	4 (11.1%)

Data was shown as median (range) and number (percentage). BM, bone marrow; DS, Durie-Salmon; Del, delet; T, translocation.

Table 3. Mean of adipose tissue values which statistically significant to the presence of baseline cytogenetic abnormalities.

	Absent of Gain 1q21 (N=31)	Present of Gain 1q21 (N=5)	*P* value
VFA·L4-L5, cm^2	127.20	167.96	0.044

VFA, Visceral Fat Area; L, lumbar vertebra.

Table 4. Mean of adipose tissue values which statistically significant to the overall response post 8 cycles of chemotherapy.

	Overall response (N=16)	No response (N=5)	*P* value
SFA·L4-L5, cm^2	169.97	262.19	0.025
SFA·L5-S1, cm^2	185.91	300.09	0.044
VFA/SFA·L4/L5	0.78	0.53	0.020

VFA, Visceral Fat Area; SFA, Subcutaneous Fat Area; L, lumbar vertebra; S, sacral vertebra.

Declarations

Author's contributions

Contributions: L.B designed the study; Y.-T.W. and S.G. collected the data; Y.-T.W. and L.B analyzed the data and wrote the manuscript; and all authors contributed to the interpretation of the data, prepared the manuscript, and approved the final version.

Acknowledgements

This work was supported by Wu Jieping Medical Foundation (grant no. 320-6750-18309) and Beijing JST Research Funding (grant no. QN-201908& ZR-201909).

Competing interests

The authors have disclosed no conflicts of interest

.

Consent for publication

Written informed consent for publication was obtained from all participants.

Reference

1. Kyle RA RS: Multiple myeloma. *N Engl J Med* 2004, 351:1860–1873.
2. Siegel R, Naishadham D, Jemal A: Cancer statistics, 2013. *CA: a cancer journal for clinicians* 2013, 63(1):11-30.
3. Yang L, Drake BF, Colditz GA: Obesity and Other Cancers. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2016, 34(35):4231-4237.
4. Becker S, Dossus L, Kaaks R: Obesity related hyperinsulinaemia and hyperglycaemia and cancer development. *Archives of physiology and biochemistry* 2009, 115(2):86-96.
5. Reseland JE, Reppe S, Olstad OK, Hjorth-Hansen H, Brenne AT, Syversen U, Waage A, Iversen PO: Abnormal adipokine levels and leptin-induced changes in gene expression profiles in multiple myeloma. *European journal of haematology* 2009, 83(5):460-470.
6. Teras LR, Kitahara CM, Birmann BM, Hartge PA, Wang SS, Robien K, Patel AV, Adami HO, Weiderpass E, Giles GG *et al*: Body size and multiple myeloma mortality: a pooled analysis of 20 prospective studies. *British journal of haematology* 2014, 166(5):667-676.
7. Beason TS, Chang SH, Sanfilippo KM, Luo S, Colditz GA, Vij R, Tomasson MH, Dipersio JF, Stockerl-Goldstein K, Ganti A *et al*: Influence of body mass index on survival in veterans with multiple myeloma. *The oncologist* 2013, 18(10):1074-1079.
8. Jung SH, Yang DH, Ahn JS, Lee SS, Ahn SY, Kim YK, Kim HJ, Lee JJ: Decreased body mass index is associated with poor prognosis in patients with multiple myeloma. *Annals of hematology* 2014, 93(5):835-840.
9. Yoshizumi T, Nakamura T, Yamane M, Islam AH, Menju M, Yamasaki K, Arai T, Kotani K, Funahashi T, Yamashita S *et al*: Abdominal fat: standardized technique for measurement at CT. *Radiology* 1999, 211(1):283-286.
10. Guiu B, Petit JM, Bonnetain F, Ladoire S, Guiu S, Cercueil JP, Krause D, Hillon P, Borg C, Chauffert B *et al*: Visceral fat area is an independent predictive biomarker of outcome after first-line bevacizumab-based treatment in metastatic colorectal cancer. *Gut* 2010, 59(3):341-347.
11. Miyato H, Kitayama J, Hidemura A, Ishigami H, Kaisaki S, Nagawa H: Vagus nerve preservation selectively restores visceral fat volume in patients with early gastric cancer who underwent gastrectomy. *The Journal of surgical research* 2012, 173(1):60-67.
12. Keehn A, Srivastava A, Maiman R, Taylor J, DiVito J, Ghavamian R, Stern JM: The relationship between visceral obesity and the clinicopathologic features of patients with small renal masses. *Journal of endourology* 2015, 29(3):372-376.
13. Grignol VP, Smith AD, Shlapak D, Zhang X, Del Campo SM, Carson WE: Increased visceral to subcutaneous fat ratio is associated with decreased overall survival in patients with metastatic melanoma receiving anti-angiogenic therapy. *Surgical oncology* 2015, 24(4):353-358.
14. Takeoka Y, Sakatoku K, Miura A, Yamamura R, Araki T, Seura H, Okamura T, Koh H, Nakamae H, Hino M *et al*: Prognostic Effect of Low Subcutaneous Adipose Tissue on Survival Outcome in Patients

With Multiple Myeloma. *Clinical lymphoma, myeloma & leukemia* 2016, 16(8):434-441.

15. GroDelta JP, Nattenmuller J, Hemmer S, Tichy D, Krzykalla J, Goldschmidt H, Bertsch U, Delorme S, Kauczor HU, Hillengass J *et al*: Body fat composition as predictive factor for treatment response in patients with newly diagnosed multiple myeloma - subgroup analysis of the prospective GMMG MM5 trial. *Oncotarget* 2017, 8(40):68460-68471.
16. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, Kumar S, Hillengass J, Kastritis E, Richardson P *et al*: International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* 2014, 15(12):e538-548.
17. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, Munshi N, Lonial S, Blade J, Mateos MV *et al*: International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *The Lancet Oncology* 2016, 17(8):e328-e346.
18. Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, Gertz M, Dimopoulos M, Westin J, Sonneveld P *et al*: International uniform response criteria for multiple myeloma. *Leukemia* 2006, 20(9):1467-1473.
19. Yu AH, Duan-Mu YY, Zhang Y, Wang L, Guo Z, Yu YQ, Wang YS, Cheng XG: Correlation between Non-Alcoholic Fatty Liver Disease and Visceral Adipose Tissue in Non-Obese Chinese Adults: A CT Evaluation. *Korean journal of radiology* 2018, 19(5):923-929.
20. Wallin A, Larsson SC: Body mass index and risk of multiple myeloma: a meta-analysis of prospective studies. *European journal of cancer* 2011, 47(11):1606-1615.
21. Baumgartner RN: Body composition in healthy aging. *Annals of the New York Academy of Sciences* 2000, 904:437-448.
22. Fearon KC, Moses AG: Cancer cachexia. *International journal of cardiology* 2002, 85(1):73-81.
23. Ebadi M, Mazurak VC: Evidence and mechanisms of fat depletion in cancer. *Nutrients* 2014, 6(11):5280-5297.
24. Agustsson T, Wikrantz P, Ryden M, Brismar T, Isaksson B: Adipose tissue volume is decreased in recently diagnosed cancer patients with cachexia. *Nutrition* 2012, 28(9):851-855.
25. Camargo RG, Riccardi DM, Ribeiro HQ, Carnevali LC, Jr., de Matos-Neto EM, Enjiu L, Neves RX, Lima JD, Figueredo RG, de Alcantara PS *et al*: NF-kappaBp65 and Expression of Its Pro-Inflammatory Target Genes Are Upregulated in the Subcutaneous Adipose Tissue of Cachectic Cancer Patients. *Nutrients* 2015, 7(6):4465-4479.
26. Bedewy AM, El-Maghraby SM: Do baseline Cereblon gene expression and IL-6 receptor expression determine the response to thalidomide-dexamethasone treatment in multiple myeloma patients? *European journal of haematology* 2014, 92(1):13-18.
27. Nencioni A, Grunebach F, Patrone F, Ballestrero A, Brossart P: Proteasome inhibitors: antitumor effects and beyond. *Leukemia* 2007, 21(1):30-36.
28. Veld J, O'Donnell EK, Reagan MR, Yee AJ, Torriani M, Rosen CJ, Bredella MA: Abdominal adipose tissue in MGUS and multiple myeloma. *Skeletal radiology* 2016, 45(9):1277-1283.

29. Doyle SL, Donohoe CL, Lysaght J, Reynolds JV: Visceral obesity, metabolic syndrome, insulin resistance and cancer. *The Proceedings of the Nutrition Society* 2012, 71(1):181-189.
30. Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G: Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. *American journal of physiology Endocrinology and metabolism* 2001, 280(5):E745-751.
31. Park EJ, Lee JH, Yu GY, He G, Ali SR, Holzer RG, Osterreicher CH, Takahashi H, Karin M: Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. *Cell* 2010, 140(2):197-208.
32. van Kruijsdijk RC, van der Wall E, Visseren FL: Obesity and cancer: the role of dysfunctional adipose tissue. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2009, 18(10):2569-2578.

Figures

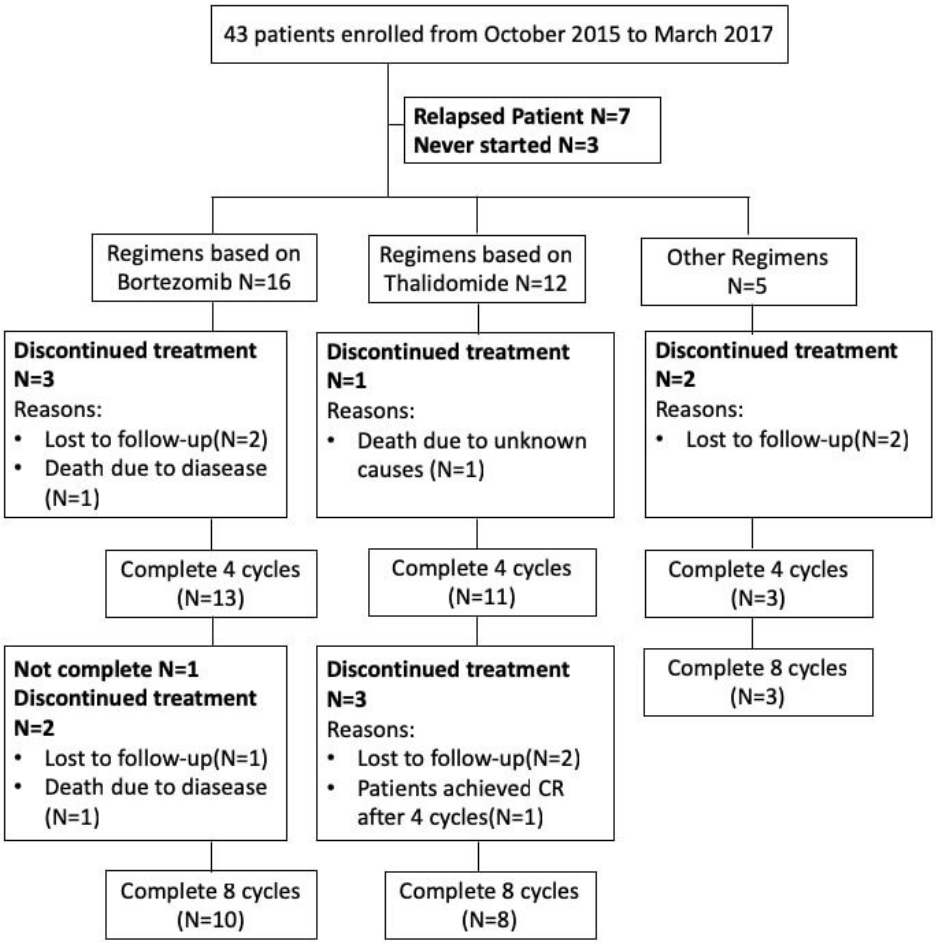

Figure 1

Patient disposition.

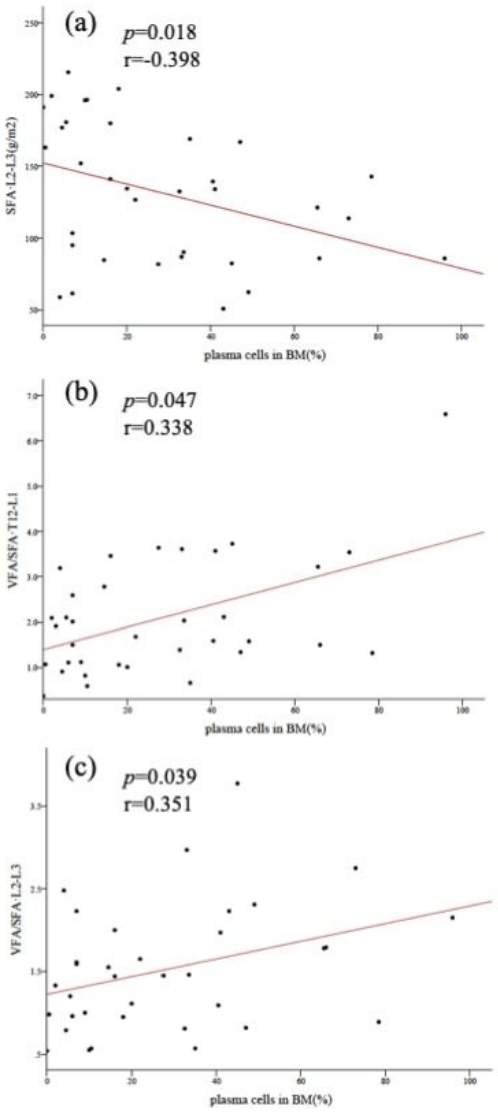

Figure 2

Correlation of percentage of plasma cells in BM and SFA (L2-L3) (r=-0.398, p<0.05) (A), VFA/SFA (T12-L1) (r=0.338, p<0.05) (B), VFA/SFA (L2-L3) (r=0.335, p<0.05) (C).

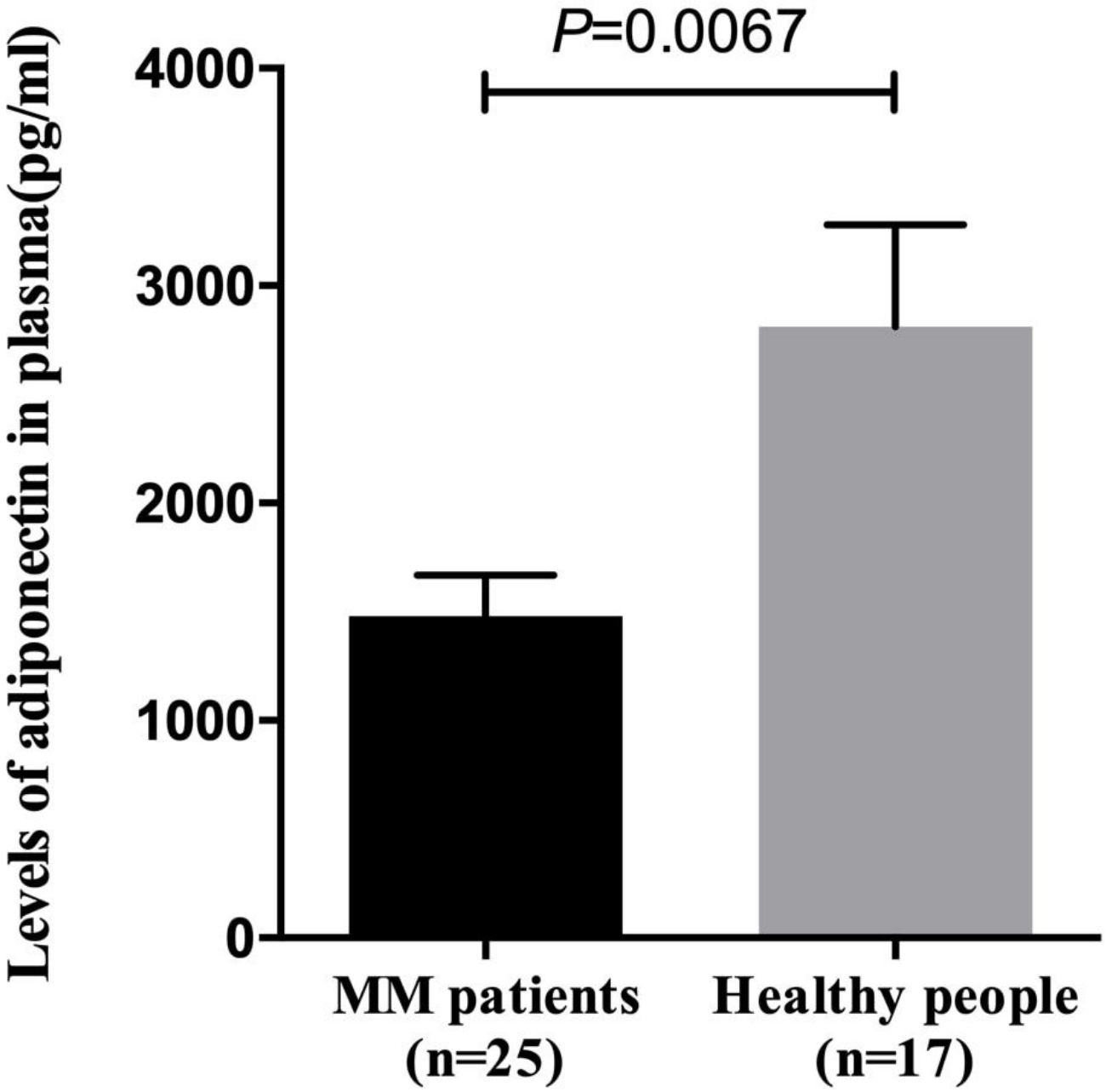

Figure 3

Adiponectin levels in plasma, as measured by Elisa assay. The NDMM patients exhibited significantly decreased plasma levels of adiponectin compared with healthy people.