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Correlations between glucose metabolism of bone marrow on ^{18}F-fluoro-D-glucose PET/computed tomography and hematopoietic cell populations in autoimmune diseases

Tong Zhang, Jifeng Zhang, Hongjia Wang and Ping Li

Purpose **This study aims to investigate which hematopoieticcell populations, clinical factors, and laboratory values are associated with FDG uptake in bone marrow (BM) on FDG PET/CT in patients with autoimmune diseases.**

Methods **Forty-six patients with autoimmune disease who underwent FDG PET/CT and BM aspiration (BMA) between 2017 and 2022 were enrolled. The max and mean standard uptake values (SUVmax and SUVmean, SUVs) of FDG in BM, liver, and spleen were measured, and the bone marrow-to-liver SUVs ratios (BLRmax and BLRmean, BLRs) and spleen-to-liver SUVs ratios (SLRmax and SLRmean, SLRs) were calculated. BMA and clinical and laboratory parameters were collected and evaluated for association with BLRs and SLRs.**

Results **The patients were divided into the Grade II group (20; 43.5%) and Grade III groups (26; 56.5%) according to hemopoietic activity. The BLRmax ($P = 0.021$), proportion of granulocytes ($P = 0.011$), metamyelocytes ($P = 0.009$), myelocytes ($P = 0.024$), and monocytes ($P = 0.037$) in BM were significantly higher in the Grade II group. Multivariate (stepwise) linear regression analyses showed that the proportion of granulocytes in BM was the strongest and only independent factor ($P < 0.0001$) associated with BLRmax with an adjusted R^2 of 0.431 in model 1. In model 2, ferritin ($P = 0.018$), CRP ($P = 0.025$), and the proportion of metamyelocytes ($P = 0.043$) in BM were correlated with BLRmax with an adjusted R^2 of 0.414.**

Conclusion **The FDG uptake in BM is associated with hemopoietic activity and is regulated by hyperplastic granulocytes, particularly immature metamyelocytes, in patients with autoimmune diseases. Glucose metabolism in the BM correlates with the severity of systemic inflammation.** *Nucl Med Commun* **44: 212–218**

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Keywords: autoimmune disease, bone marrow, FDG PET/CT, hematopoiesis, inflammation

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Introduction

Bone marrow (BM) is a heterogeneous tissue, and actively hematopoietic BM is characteristically located in the central cavities of axial and long bones in adults [1]. As a major hematopoietic organ and primary lymphoid tissue, BM is a critical site for the production, differentiation, and maturation of blood cells and the immune response to inflammation or cancers [1]. Indeed, BM can be affected by various pathological conditions, including hematological diseases (not only malignancies but also benign disorders), the immune response, and inflammatory/infectious diseases.

In the last 2 decades, 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) PET/computed tomography (CT) has become a commonly used imaging technique for evaluating marrow diseases such as leukemia, multiple myeloma, lymphoma, and myelofibrosis [2,3]. However, FDG is not a specific malignancy agent; the imaging modality allows for accurate localization of accumulated FDG that may present inflammation or infection in parallel to neoplasia. The investigation of elevated FDG accumulation in BM in benign disorders is limited. Autoimmune disorders are a spectrum of systemic inflammation diseases with tissue damage induced by pathological autoantibodies and self-reactive lymphocytes [4]. Homogeneously increased FDG uptake of BM is commonly observed in some FDG PET/CT scans of patients with autoimmune disease. BM is generally defined as 'hypermetabolic' if its FDG avidity exceeds that in the liver [5]. Previous studies have indicated that increased FDG accumulation in BM was associated with WBC, neutrophil counts, and C-reactive protein (CRP) in patients with autoimmune diseases [6]. The FDG avidity of BM showed a significant correlation with the activity of Adult-onset Still's disease (AOSD) [7].

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Most previous studies have focused on investigating the adaption and response BM displayed on FDG PET/CT to various pathological conditions with indirect parameters such as peripheral blood cell counts and CRP, with few studies assessing the direct relationship between cytological alteration of BM and increased glucose metabolism. BM aspiration (BMA) is an essential and minimally invasive diagnostic intervention for evaluating hematologic abnormalities and suspected infection by providing accurate information regarding marrow cellularity and hematopoietic elements [8]. This study evaluated the correlation between FDG uptake by BM on PET/CT and hematopoietic cell populations through BMA parameters and further definite BM hematopoietic remodeling disclosed by diffusely hypermetabolic BM in autoimmune diseases.

Materials and methods

Patients

The BMA reports, medical records, and FDG PET/CT examinations of patients who underwent FDG PET/CT at the Second Affiliated Hospital of Harbin Medical University (Harbin, China) from September 2017 to March 2022 were reviewed. The inclusion criteria were: (a) patients with available PET/CT imaging; (b) patients underwent BMA examinations within 1 week of PET/CT examination; (c) patients with a definite diagnosis of autoimmune diseases. The exclusion criteria were: (a) patients administered hematopoietic cytokines within 1 week before PET/CT examination; (b) patients with hematopoietic disorders including hematological malignancies, iron-deficiency anemia (IDA), hemolytic anemia, etc. The diagnosis of AOSD was according to the American Cush criterion. This retrospective study was approved by the Human Research Protection Office at our institution. Patient informed consent was waived due to the retrospective nature of the study. All data were acquired from the Second Affiliated Hospital of Harbin Medical University.

Bone marrow aspiration data collection

All patient's BMA anatomic sites were the bilateral posterior iliac crest, and BMA parameters collected included hematopoietic activity assessed by BM nucleated differential cell count (NDC), the proportion of granulocytes, erythrocytes, lymphocytes, promyelocytes, myelocytes, metamyelocytes, band forms neutrophils, segmented neutrophils, and monocytes. The proportion of neutrophils was calculated by adding promyelocytes, myelocytes, metamyelocytes, band forms neutrophils, and segmented neutrophils. According to NDC, BM hemopoietic activity was defined as Grades I–V from extremely active hematopoiesis to extremely decreased hematopoiesis. The patients in this study were only involved in Grade II and Grade III.

Clinical and laboratory data collection

Clinical data collected included age, sex, and glucose level before PET/CT, with a fever or not within 1 week of PET/CT examination. Laboratory data included hemoglobin, CRP, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, albumin, and alkaline phosphatase level, which all were measured within 5 days of the PET/CT.

Fluoro-D-glucose PET/computed tomography image acquisition

PET/CT images were acquired with a PET/CT system (Biograph 64 mCT, Siemens Healthcare, Berlin, Germany) combining a full-ring PET scanner at Harbin Medical University, 2nd affiliated Hospital. Patients fasted for 6 h before intravenous injection of 18F-FDG (4.07 MBq/kg, 0.11 mCi/kg). Blood glucose levels of all patients were less than 11 mmol/l before the procedure using a glucometer (Bayer Company, Leverkusen, Germany). FDG dose and uptake time were 169–469 MBq (295.8 ± 64.8 MBq) and 27–171 min (70.4 ± 24.9 min), respectively. ^{18}F-FDG with a minimum radiochemical purity of 95% was provided. PET images were generated at one site using a similar protocol. Patients were allowed to breathe normally during PET and CT acquisitions. Three-dimensional (3D) emission and transmission scanning were acquired from the base of the skull to the mid-femur approximately 60 min after FDG injection. The PET images were reconstructed via the TrueX TOF method with a slice thickness of 1 mm.

Assessment of fluoro-D-glucose PET/computed tomography scans

Semiquantitative analysis of the FDG accumulation was quantified by both mean (SUVmean) and maximum (SUVmax) standardized uptake values (SUV). The liver and spleen SUVmax and SUVmean (SUVs) were obtained, respectively, by drawing three spherical volumes of interest (VOI) of 1 cm on different slices of liver and spleen, excluding large vessels and lesions, and then calculating the average. BM SUVs were obtained separately from thoracic vertebra 8 to lumbar vertebra 5 and averaged (except for compression fractures, severe osteoarthritis changes, or lesions). The plane VOI was measured at the vertebral center level, excluding the cortical bone. Pelvis SUVmax was measured by manually drawing the outline on the central level of the second sacral vertebra. The liver was used as a reference organ for FDG uptake in the BM and spleen. Then, bone marrow SUVs-to-liver SUVs ratio (BLRmax and BLRmean, BLRs), spleen SUVs-to-liver SUVs ratio (SLRmax and SLRmean, SLRs), and pelvis SUVmax-to-liver SUVmax ratio (PLRmax) were calculated. The observers were blinded to the BM biopsy and laboratory results.

Statistical analysis

For baseline data, all continuous variables were checked for normal distribution by Shapiro–Wilk tests and were presented as mean ± SD or median with interquartile

range (IQR) for normally or nonnormally distributed data, respectively. Categorical variables were expressed as frequencies(percentages). Normally distributed variables were compared with the Student's *t*-test, nonnormally distributed variables were compared with the Rank sum test, and categorical data were compared using the Chi-square test. The comparison of PET/CT and BMA variables was performed in the Grade II and Grade III groups (classified by hematopoietic activity). The population was divided into BM-uptake quintiles (Q1–Q5) according to BLRmax to explore the association between the degree of glucose metabolism in BM and participant characteristics. Rank correlation analysis and multivariate (stepwise) linear regression analyses were performed to investigate the correlation between dependent variables (BLRs, SLRs, and PLRmax) and independent variables, including BMA, clinical, and laboratory variables. *P*-values <0.05 were considered statistically significant. All statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) version 26.

Results

Baseline characteristics

After a review of the inclusion and exclusion criteria, 46 FDG PET/CT scans from 46 patients were analyzed, of which 15 men and 31 women had a mean age of 45.9 years. The mean proportion of granulocytes in BM was 68.2 ± 10.5%, erythrocytes were 17.8 ± 8.4%, and lymphocytes were 10.9 ± 7.3%. The median CRP was 39.9 (22.1,102.9) mg/L, with median hemoglobin of 104.0 (91.5,121.0) g/L. In total, 37 (80.4%) patients had a fever within 1 week of PET/CT examination (Tables 1 and 2). Systemic lupus erythematosus/Sjogren syndrome (SLE/SS) was the most common disease (14/46), followed by AOSD (12/46) (Table 3).

Quantitative analysis of ^{18}F-fluoro-D-glucose PET/computed tomography parameters

The median SUVmax of FDG in the BM was 3.91 (3.12,4.89), 3.42 (2.55,4.20) in the pelvis, and 2.89 (2.33,3.62) in the spleen. The median BLRmax was 1.65 (1.29,2.02), the median SLRmax was 1.16 (1.01,1.47), and the median PLRmax was 1.46 (1.09,1.86). Also, 42 (91.3%) patients showed hypermetabolic BM (BLRmax > 1), and 35 (76.1%) patients showed increased FDG uptake in the spleen (SLRmax > 1) (Table 2).

The comparison of PET/computed tomography and bone marrow aspiration variables between Grade II and Grade III groups

The patients were classified as Grade II (20; 43.5%) and Grade III (26;56.5%) according to NDC (expressed by hematopoietic activity). The BLRmax was significantly higher in the Grade II group than the Grade III group (Grade II vs. Grade III: 2.01 ± 0.79 vs. 1.55 ± 0.45, $P = 0.018$). The comparison of BLRmean ($P = 0.021$), BM SUVmax ($P = 0.026$), BM SUVmean ($P = 0.026$), pelvis SUVmax ($P = 0.029$), and PLRmax ($P = 0.023$) between two groups were similar to BLRmax (Table 2). Meanwhile, the proportion of granulocytes ($P = 0.011$), metamyelocytes ($P = 0.009$), myelocytes ($P = 0.024$), and monocytes ($P = 0.037$) in the BM were significantly higher in the Grade II group (Table 2 and Fig. 1).

Variables associated with bone marrow-to-liver SUVs ratios

The cohort was divided into BM-uptake quintiles according to the BLRmax, showing that the increase in FDG uptake of the BM was accompanied by elevated granulocytes ($P < 0.001$), neutrophils ($P < 0.001$), and metamyelocytes ($P = 0.031$) in BM, ferritin ($P = 0.005$) and CRP ($P = 0.027$). The characteristics of each BM-uptake subgroup are presented in Supplementary Table 4, Supplemental Digital Content 2, *http://links.lww.com/NMC/A237*, and Fig. 2. Representative maximal intensity projection (MIP) images of Q1–Q5 are displayed in Fig. 3.

According to Rank correlation analysis, the proportion of granulocytes ($P < 0.001$), neutrophils ($P < 0.001$), metamyelocytes ($P = 0.024$) in BM, CRP ($P = 0.005$), ferritin ($P = 0.001$), ALT ($P = 0.044$), and AST ($P = 0.023$) in peripheral blood and fever ($P = 0.046$) were positively associated with the BLRmax, whereas the proportion of lymphocytes ($P = 0.001$), erythrocytes ($P = 0.001$) in BM and total protein ($P = 0.038$) in peripheral blood were

Table 1 Baseline characteristics

Variables	Value
Clinical variables	
Age (years)	45.9 ± 17.1[a]
Sex (male)	15 (32.6%)[b]
Fever frequency	37 (80.4%)[b]
Glucose level (mmol/l)	5.5 ± 1.0[a]
Laboratory variables	
WBC count (×10^9/l)	10.6 (6.6,15.3)[c]
Neutrophil count (×10^9/l)	8.5 (4.3,12.2)[c]
Erythrocyte count (×10^9/l)	3.7 (3.2,4.2)[c]
Lymphocyte count (×10^9/l)	1.4 (0.9,2.1)[c]
Monocyte count (×10^9/l)	0.4 (0.2,0.6)[c]
Platelet count count (×10^9/l)	254.5 (130.0,389.2)[c]
Hemoglobin (g/l)	104.0 (91.5,121.0)[c]
CRP (mg/l)	39.9 (22.1,102.9)[c]
Ferritin (ng/ml)	2000 (675,2000)[c,d]
Alkaline phosphatase (U/l)	97.5 (66.5,121.2)[c]
Total protein (g/l)	62.8 (59.7,72.0)[c]
Albumin (g/l)	32.7 (29.4,35.9)[c]
ALT (U/l)	45.5 (13.8,64.2)[c]
AST (U/l)	36.5 (17.8,59.8)[c]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; WBC, white blood cell.
[a]Mean ± SD.
[b]Frequencies (percentages).
[c]Median (P_{25},P_{75}).
[d]Number confined to patients who underwent test ($N = 33$) and the level was recorded 2000 ng/ml when it exceed 2000 ng/ml.

Table 2 The comparison of PET/computed tomography and bone marrow aspiration variables between the Grade II and III groups

Variables	Total	Grade II ($n = 20$)	Grade III ($n = 26$)	*P*-value
BM SUVmax	3.91 (3.12,4.89)	4.53 ± 1.75	3.57 ± 1.04	0.026
BM SUVmean	3.13 (2.44,4.05)	3.81 ± 1.52	2.97 ± 0.94	0.026
Pelvis SUVmax	3.42 (2.55,4.20)	4.12 ± 1.76	3.17 ± 1.05	0.029
Liver SUVmax	2.27 (2.00,2.53)	2.30 ± 0.42	2.34 ± 0.47	0.763
Liver SUVmean	1.82 (1.59,2.05)	1.83 ± 0.31	1.90 ± 0.38	0.513
Spleen SUVmax	2.89 (2.33,3.62)	2.90 ± 0.86	2.93 ± 0.93	0.918
Spleen SUVmean	2.26 (1.81,2.92)	2.38 ± 0.72	2.36 ± 0.78	0.934
BLRmax	1.65 (1.29,2.02)	2.01 ± 0.79	1.55 ± 0.45	0.018
BLRmean	1.72 (1.27,2.06)	2.13 ± 0.92	1.58 ± 0.46	0.021
SLRmax	1.16 (1.01,1.47)	1.28 ± 0.39	1.26 ± 0.36	0.826
SLRmean	1.14 (1.01,1.56)	1.32 ± 0.43	1.24 ± 0.36	0.503
PLRmax	1.46 (1.09,1.86)	1.83 ± 0.81	1.38 ± 0.45	0.023
Granulocytes (%)	68.2 ± 10.5	72.6 ± 8.3	64.8 ± 10.9	0.011
Erythrocytes (%)	17.8 ± 8.4	16.3 ± 7.2	19.0 ± 9.2	0.277
Lymphocytes (%)	10.9 ± 7.3	8.9 ± 4.5	12.4 ± 8.6	0.099
Monocytes (%)	2.4 ± 1.7	1.8 ± 1.3	2.8 ± 1.9	0.037
Promyelocytes (%)	1.5 ± 1.8	2.0 ± 2.3	1.2 ± 1.4	0.154
Myelocytes (%)	9.6 ± 4.6	11.3 ± 4.6	8.3 ± 4.2	0.024
Metamyelocytes (%)	11.1 ± 4.1	12.9 ± 3.6	9.7 ± 4.1	0.009
Band forms neutrophils (%)	17.3 ± 6.5	17.5 ± 5.0	17.0 ± 7.6	0.807
Segmented neutrophils (%)	25.0 ± 11.1	23.9 ± 9.5	25.9 ± 12.4	0.545
Neutrophils (%)	64.8 ± 11.5	68.1 ± 11.6	62.3 ± 11.1	0.094

BLR, bone marrow-to-liver SUVs ratio; BM, bone marrow; PLR, pelvis SUVmax-to-liver SUVmax ratio; SLR, spleen-to-liver SUVs ratio; SUV, standard uptake value.

Table 3 Diseases spectrum of final diagnosis

Type of autoimmune disease	*n* (%)
Systemic lupus erythematosus/Sjogren syndrome	14 (30.4)
Adult-onset Still's disease	12 (26.1)
Hemophagocytic lymphohistiocytosis	6 (13.0)
Vasculitis	5 (10.9)
Inflammatory myositis	4 (8.7)
IgG4-related disease	2 (4.3)
Kikuchi disease	1 (2.2)
Rheumatoid arthritis	1 (2.2)
Polymyalgia rheumatica	1 (2.2)
Total	46

negatively associated with the BLRmax (Supplementary Table 5, Supplemental Digital Content 2, *http://links.lww.com/NMC/A237*).

In model 1, we explored which variables are associated with BLRmax, including BMA variables (the proportion of granulocytes, lymphocytes, erythrocytes, and monocytes in BM), laboratory variables, and clinical variables. The multivariate linear regression analysis revealed that the proportion of granulocytes in BM was the strongest and only independent factor($P < 0.001$) with an adjusted R^2 of 0.431. In model 2, the BMA variables were replaced with the proportion of promyelocytes, myelocytes, metamyelocytes, band forms, and segmented neutrophils in BM, and the multivariate linear regression analysis showed that ferritin ($P = 0.018$), CRP ($P = 0.025$) and the proportion of metamyelocytes ($P = 0.043$) correlated with BLRmax. These variables had an adjusted R^2 of 0.414 (Supplementary Table 6, Supplemental Digital Content 2, *http://links.lww.com/NMC/A237*).

Variables associated with spleen-to-liver SUVs ratios

According to the Rank correlation analysis, the proportion of granulocytes ($P = 0.002$), neutrophils ($P = 0.007$), myelocytes ($P = 0.026$), metamyelocytes ($P = 0.034$) in BM, CRP ($P = 0.025$), ferritin ($P = 0.024$), and AST ($P = 0.002$) in peripheral blood and fever ($P = 0.003$) were positively associated with SLRmax, whereas the proportion of lymphocytes ($P = 0.002$) in BM and hemoglobin ($P = 0.036$) in peripheral blood were negatively associated with SLRmax (Supplementary Table 5, Supplemental Digital Content 2, *http://links.lww.com/NMC/A237*).

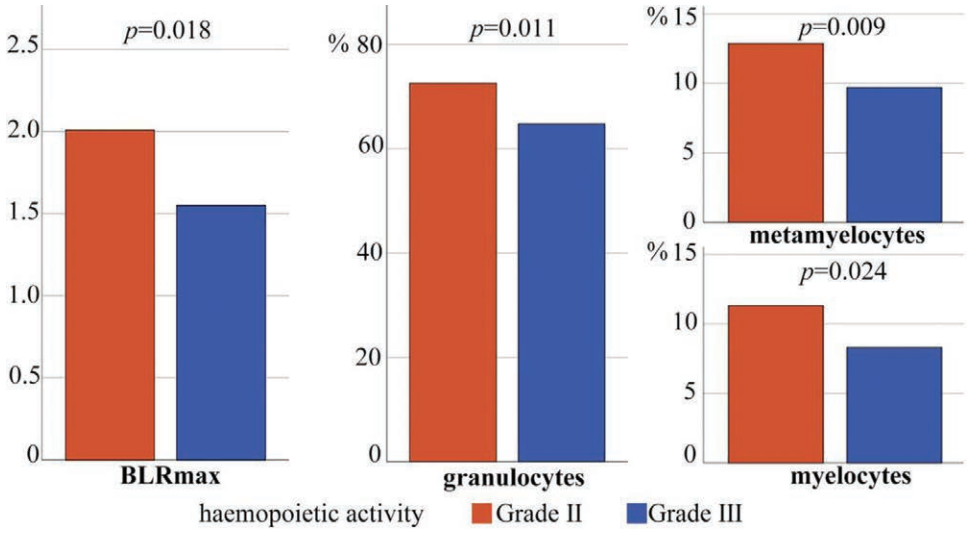
Multivariate linear regression analysis to explore which variables are associated with SLRmax showed that the ferritin level showed the strongest positive association with SLRmax ($P = 0.004$), and hemoglobin was negatively associated with SLRmax ($P = 0.035$). Although the BMA variables were replaced with the proportion of promyelocytes, myelocytes, metamyelocytes, band forms, and segmented neutrophils, the result did not change. These variables had an adjusted R^2 of 0.235 (Supplementary Table 7, Supplemental Digital Content 2, *http://links.lww.com/NMC/A237*). Supplementary Tables 4–7 are presented as Supplementary Data, Supplemental Digital Content 2, Supplemental Digital Content 2, *http://links.lww.com/NMC/A237*.

Discussion

In the present study, the percentage of hypermetabolic BM and median BLRmax were significantly higher than in previous studies [6], possibly due to the inclusion criteria of available BMA examination, which is usually applied to patients with fever of unknown origin and an abnormal leucocyte count. Our study indicated that fever and increased myeloid hematopoiesis were positively associated with hypermetabolic BM.

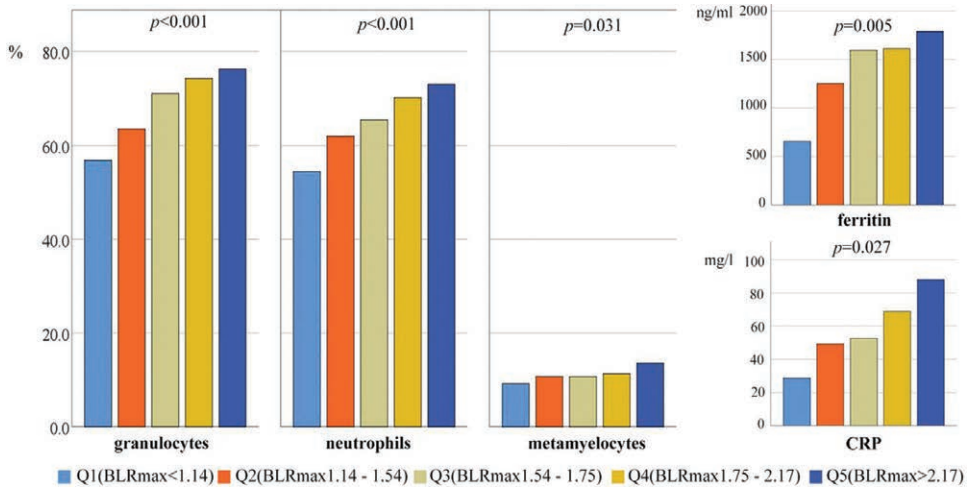
As a primary hematopoietic and immune organ, metabolic information of BM on FDG PET/CT is usually neglected and underestimated. In this study, the FDG activity of BM was significantly higher in the Grade II group than in the Grade III group, which might be due to the elevated hematopoietic activity and the generation of granulocytes, metamyelocytes, and myelocytes (Fig. 1). Estimating hematopoietic changes using FDG metabolic activity in BM was supported by physiopathology. In healthy adults, the FDG accumulation and age-related FDG metabolic changes throughout the skeleton were compatible with the normal distribution of hematopoietic marrow and age-related BM conversion [9]. Diffusely increased FDG uptake in BM has been described in patients treated with BM stimulation, such as granulocyte colony-stimulating factors (G-CSF) and erythropoietin (EPO), and patients with G-CSF–producing gallbladder cancer as a result of stimulative hematopoiesis [10,11]. These findings support that the physical glucose metabolism in BM was caused by

Fig. 1



The comparison of participant variables between the Grade II and Grade III groups. The patients in the Grade II group showed higher BLRmax ($P = 0.018$). The proportion of granulocytes ($P = 0.011$), metamyelocytes ($P = 0.009$), and myelocytes ($P = 0.024$) in BM were significantly higher in the Grade II group. BLRmax, maximum bone marrow-to-liver SUVs ratio; BM, bone marrow.

Fig. 2

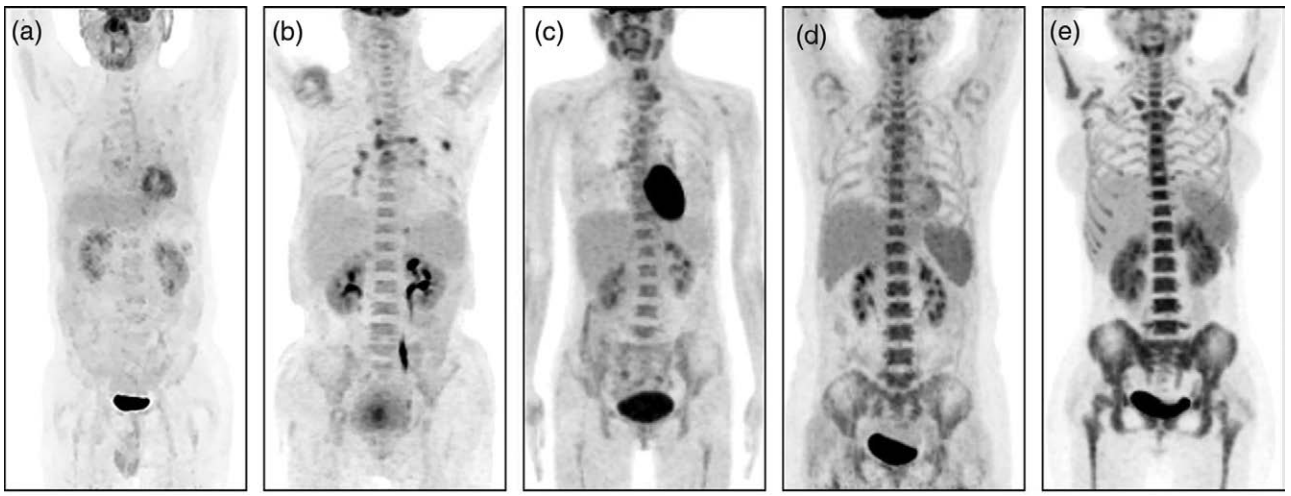


Participant variables stratified by quintiles of BLRmax. The increase in FDG uptake of bone marrow accompanied with elevated proportion of granulocytes ($P < 0.001$), neutrophils ($P < 0.001$), and metamyelocytes ($P = 0.031$) in BM, ferritin ($P = 0.005$) and CRP ($P = 0.027$). BLRmax, maximum bone marrow-to-liver SUVs ratio; BM, bone marrow; CRP, C-reactive protein; FDG, fluoro-D-glucose.

hematopoietic activity and regulated by hematopoietic stimulants.

It was significant that the proportion of granulocytes, particularly immature metamyelocytes, in BM were significantly associated with BLRs in autoimmune diseases. Hematopoiesis is a process of hematopoietic stem cell (HSC) self-updating giving rise to a range of mature blood cells. In systemic inflammation induced by autoimmune disorders, the tremendous demand for mature myeloid cells, particularly neutrophils, resulted in specific hematopoietic stress, further promoting urgent myeloid proliferation and differentiation of HSCs (termed emergency myelopoiesis) displacing steady-state hematopoiesis [12,13]. This process is associated with increased glucose flux through glycolysis and the pentose phosphate pathway. During the proliferation from HSCs to downstream progenitor cells, the metabolic way rapidly switches from glycolysis to oxidative phosphorylation to adapt to the higher energy input, driving an increase in both mitochondrial mass and membrane potential

Fig. 3



(a–e) Representative maximal intensity projection (MIP) images of Q1–Q5. (a) A 61-year-old man with BLRmax of 0.81 and the proportion of granulocytes in BM of 45.5%. (b) A 71-year-old woman with BLRmax of 1.39 and the proportion of granulocytes in BM of 62.5%. (c) A 36-year-old woman with BLRmax of 1.62 and the proportion of granulocytes in BM of 68.5%. (d) A 52-year-old woman with BLRmax of 2.01 and the proportion of granulocytes in BM of 73.0%. (e) A 54-year-old woman with BLRmax of 4.00 and the proportion of granulocytes in BM of 80.0%. BLRmax, maximum bone marrow-to-liver SUVs ratio; BM, bone marrow.

associated with increased glucose metabolism [14,15]. Furthermore, to prepare for terminal maturation, immature myeloid cells also exhibit high glucose consumption rates via active glycolysis [16].

Patients with hematopoietic diseases, including malignancies and benign disorders, were excluded from our study since they may interfere with glucose metabolism by BM. Leukemia cells could elevate glucose consumption by switching to glycolysis from aerobic oxidation to produce energy [17]. FDG uptake in BM decreased homogeneously as the aggravation of myelofibrosis because of the lower inflammatory activity and advanced BM exhaustion [3]. Hyperplastic BM induced by EPO and decreased ferritin is characteristics of IDA. Sustained erythropoiesis and erythroid hyperplasia also exist in chronic hemolytic anemia [18] and anemia associated with alcoholism [19]. This compensated BM response might influence and conceal actual hematopoietic activity in autoimmune diseases.

Unexpectedly, although common anemia was observed in autoimmune diseases, the hemoglobin level and the proportion of erythroid cell populations did not correlate with the BLRmax. This may be explained by 'hyporegenerative anemia', which is characteristic of inflammation-induced anemia. Anemia of inflammation (AI), also referred to as anemia of chronic disease (ACD), is associated with chronic systemic inflammatory disorders generated by the activation of the immune system by autoantigens, microbial molecules, or tumor antigens [20,21]. Autoimmune diseases, malignant disorders, and acute or chronic infections are the principal disease types in AI. Erythropoietic drive was suppressed in patients with AI due to the downregulation of the EPO receptor on erythroid progenitor cells and lower serum EPO concentrations [20,21]. There was indeed no correlation between hemoglobin and the proportion of erythroid cells in BM in our study, so it is not surprising that erythroid cells did not contribute to the glucose consumption of BM despite anemia persisting in autoimmune patients.

We also found that FDG accumulation in BM was related to inflammatory markers reflecting the severity of systemic inflammation, such as ferritin and CRP. With emergency myelopoiesis regulated by inflammatory cytokines and factors, systemic inflammation promoted the expansion of granulocytes in BM. In turn, inflammation depends on developing proinflammatory granulocytes [12].

The glucose metabolism of BM is a significant and promising field in inflammatory derangement, and these results can explain why glucose metabolism in BM of AOSD correlated with disease activity [7]. Hematopoiesis-related BM activation is associated with inflammatory markers and further subclinical atherosclerosis in patients with psoriasis [22]. Furthermore, although our research involved only autoimmune diseases, the correlation may also apply to other systemic inflammatory diseases, such as some cancers and infections, because of the same pathological alteration in BM. Previous studies have indicated elevated glucose uptake in BM correlated with host systemic inflammation in patients with some solid tumors and infection [23,24], and BM activation on PET/CT is also an indirect indicator of infective endocarditis [25].

Splenic glucose metabolism is also of interest in autoimmune diseases. Ahn *et al*. [6] reported that splenic FDG uptake might provide useful information in differentiating autoimmune disease from infectious disease since immune-cell activation in the spleen is more specific in febrile autoimmune diseases. In our study, SLRmax was associated with ferritin and hemoglobin. However, the potential association between systemic inflammation and splenic metabolism remains unclear and requires further exploration.

The strength of our study is evaluating every PET/CT scan with a definite diagnosis by correspondent cytology of BM through recent BMA examinations. To our knowledge, a similar study remained rare. Limitations to our study include bias in patient selection and analysis due to single-institution retrospective observational studies and small samples. In addition, with strict inclusion and exclusion criteria, the range of applications in clinical practices and evaluation to scans still require prudent filtration and analysis.

Conclusion

FDG uptake in BM is associated with hemopoietic activity and is regulated by hyperplastic granulocytes, particularly immature metamyelocytes, instead of erythroid or lymphoid cells in autoimmune diseases. The glucose metabolism of BM and spleen correlates with systemic inflammation severity. The index of BLRmax on FDG PET/CT is a reliable and noninvasive imaging measure in evaluating the adaptive hematopoiesis of BM to systemic inflammation.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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