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Clinical significance of increased peripheral venous blood adipocyte-specific protein FABP4 after joint replacement

Zhuo Wang, MD[a,*], Na Buqi, MD[a], Pingji Zhang, BS[a], Yanxun Wang, MD[a], Yanwei Lv, MS[b], Guisheng An, BS[c]

Abstract

A new method of diagnosing fat embolism (FE) at the molecular level was proposed, and the diagnostic value of adipocyte-specific protein fatty acid-binding protein 4 (*Homo sapiens* [human]) gene ID = 2167 (FABP4) for FE was preliminarily explored. Eight joint replacement patients, 5 internal medicine patients, and 6 healthy persons were recruited. Serum of internal medicine patients, healthy people, and patients before and 24 hours after joint replacement were taken as study samples. Subcutaneous adipose, intra-articular adipose and intramedullary yellow bone marrow of patients undergoing joint replacement were taken as study samples. The level of FABP4 in the above samples was detected by enzyme-linked immunoassay. Normal distribution was tested. Paired sample *T* test was used for self-control. Univariate analysis of variance was used for multigroup comparison.

There was no significant difference in serum FABP4 level between healthy persons, medical patients, and preoperative patients. The FABP4 level in yellow bone marrow and subcutaneous adipose was significantly higher than that in serum of healthy people, medical patients, and preoperative patients. FABP4 level in the serum after joint replacement was significantly higher than that before joint replacement. FABP4 may be a specific indicator of FE diagnosis, but further studies are needed to confirm its clinical value.

Abbreviations: CT = computer tomography, FABP4 = fatty acid-binding protein 4 (*Homo sapiens* [human]) gene ID = 2167, FE = fat embolism, FES = fat embolism syndrome.

Keywords: adipocyte, diagnosis, embolism, fat, protein

1. Introduction

Fat embolism (FE) is a syndrome caused by fat globules entering the circulatory system, with or without clinical manifestations.[1] Fat embolism syndrome (FES) is a clinical syndrome in which fat globules enter the bloodstream and cause a range of clinical symptoms and signs. Thus, FES is a serious consequence of FE.[2] Due to the lack of sensitive diagnostic indicators of FE, the incidence of FE is underestimated. FE and FES often occur after trauma, fracture, orthopedic surgery, liposuction, and fat autotransplantation. The incidence of FE in patients with trauma and long bone fractures was reported as high as 90%,[3–5] and 22.5% to 29% of them developed FES.[6,7] It was reported that the mortality rate of FE varied greatly. Some authors reported mortality rates up to 60%.[8] At present, clinical diagnosis of FE mainly depends on pathologic diagnosis. There is no gold standard for diagnosis of FES.[2] The widely used diagnostic criteria of FES were derived from the framework proposed by Gurd and Wilson in 1974.[9] Though some authors added some new diagnostic indicators, such as fat droplets found in urine, sputum, or alveolar lavage fluid.[10–12] But no diagnostic parameter of them was unique to FE. At present, laboratory tests of FE and FES show poor specificity and sensitivity leading to high rate of misdiagnosis.[13] It is difficult to distinguish FE or FES from traumatic brain injury, lung injury, and other diseases. Over the past 40 years, the diagnostic criteria of FE and FES have rarely changed, resulting in a large number of patients being misdiagnosed and missed. Therefore, it is an urgent need to search for FE and FES diagnostic indicators with high sensitivity and specificity.

There are 2 main sources of embolus for FE: bone marrow source, and the source of adipocyte around the subcutaneous or visceral organs.

Adipocytes contain triglycerides. Triglycerides and chyle particles are also present in normal blood circulation, but there is no adipocyte-specific component. If the adipocyte-specific component is found in circulating blood, it indicates that the adipocyte component enters the blood circulation, which can prove the occurrence of FE. Therefore, the idea of diagnosing FE at the molecular level was proposed. To confirm the above hypothesis, we selected human adipocyte-specific protein FABP4

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

[a] Department of Respiratory and Critical Care Medicine, [b] Clinical Epidemiology Laboratory, [c] Department of Traumatic Orthopaedic, Beijing Jishuitan Hospital, Beijing, China.

[*] Correspondence: Zhuo Wang, Department of Respiratory and Critical Care Medicine, Beijing Jishuitan Hospital, No 31 Xinjiekoudong Street, Xicheng District, Beijing 100035, China (e-mail: grace_wang358@hotmail.com).

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(fatty acid-binding protein 4, *Homo sapiens* [human], gene ID: 2167) as the biomarker for FE, designed the following experiments, to explore a new diagnostic method of molecular level. FABP4 is present in adipocyte cytoplasm and adipocyte nucleus, and is a lipid transporter in adipocytes. Although FABP4 can be secreted outside the adipocytes, it is found in adipocytes in much higher quantities than in other cells and tissues. In this study, we hypothesized that FABP4 exists in high amounts in adipose tissue and yellow bone marrow, and the content of FABP4 is significantly higher than that of normal blood. If FABP4 level in peripheral blood of patients after joint replacement surgery is significantly higher than that in peripheral blood before surgery, it can indicate the occurrence of FE. To exclude the interference of other factors, FABP4 level in peripheral blood of patients with internal diseases and without trauma, surgery, or other surgical conditions in the past 2 years was detected.

The aim of the study was to find out the biomarker of diagnosis for FE/FES, and explore the correlation between the biomarker and the FE/FES.

2. Materials and methods

This study was consistent with the Helsinki declaration. This study was approved by the Ethics Committee of Beijing Jishuitan Hospital. And project approval number is "Ethics Committee of Beijing Jishuitan Hospital, No. 201811-08-01." All enrolled patients in this study signed informed consent (see also the Appendix, http://links.lww.com/MD/E375).

Healthy people were included from the physical examination center of Beijing Jishuitan hospital, and were named healthy control group. Patients hospitalized in internal medicine department were named internal medicine group. Patients who needed hip or knee replacement due to osteoarthritis or old fractures were named operation group. Inclusion criteria: age: more than 14 years, gender: unlimited; informed consent; and the ability to act independently. Exclusion criteria: patients undergoing joint replacement and were suffering from brain diseases and injuries, respiratory diseases and chest injuries, cardiac dysfunction, abnormal coagulation function, pleural effusion; in the healthy control group, there were consciousness disorder, dyspnea, cardiac insufficiency, various trauma, abnormal coagulation function, and surgical operation within the past 2 years; about the internal medicine inpatient, fracture, operation, and trauma occurred in the past 2 years; refuse to participate in the project; patients with various tumors; and pregnant or lactating women.

Serum and adipose tissue samples were collected and divided into healthy control serum, internal medicine patient serum, preoperative patient serum, postoperative 24-hour patient serum, subcutaneous adipose, intra-articular adipose, and yellow bone marrow group.

2.1. Specimen collection

The blood samples (3 mL) were taken before and 24 hours after hip arthroplasty or knee arthroplasty. The blood sample (3 mL) was taken at the time of admission to the hospital from the internal medicine patients and healthy subjects. Without anticoagulation, blood was naturally coagulated at room temperature for 10 to 20 minutes, 1300*g*, and centrifugation for 10 minutes. Serum was isolated and preserved at −80°C refrigerator.

The yellow marrow samples (1 cm^3) and adipose samples (1 cm^3) were taken from of patients with hip arthroplasty or knee arthroplasty, and were preserved at −80°C refrigerator.

2.2. Processing of adipose and yellow bone marrow

One hundred millgrams of specimens were weighed. Cut them into small pieces and washed twice with 1 mL phosphate-buffered saline. After centrifuging for 5 minutes at 500*g*, the supernatant was discarded carefully. One milliliter total protein extraction buffer (Beijing Solarbio Biological Technology Company Ltd, Beijing, China) was added to tissue samples, after mixed by oscillation, and the tissue suspension was transferred to the precooled glass to homogenate for 6 to 10 times. The tissue suspension of homogenate was transferred to a new 1.5-mL centrifuge tube, incubated on ice for 30 minutes, and mixed with oscillations every 10 minutes centrifuged for 10 minutes (4°C, 1400*g*). Then supernatant was collected for subsequent experiments or preserved at −80°C.

Melted and remained at 2°C to 8°C temperature, a certain amount of phosphate-buffered saline (pH 7.4) was added to the specimen after homogeniting thoroughly, it was centrifuged at 1300*g* for 20 minutes. The supernatant was collected and subpacked.

2.3. FABP4 detection

Human FABP4 enzyme-linked immunoassay kit produced by ABCAM was used. Detection sensitivity 2.7 pg/mL. Test type: sandwich (quantitative).

2.4. Statistical methods

Data are presented as mean ± standard error mean. All statistical analyses were performed using SPSS 11.0. Normal distribution of samples was tested, where appropriate, to select parametric or nonparametric tests as indicated in the figure legends. The paired *t* test or 1-way analysis of variance for multiple comparisons was used to determine *P*-values, unless indicated differently in the figure legend.

3. Results

Nineteen subjects were recruited, including 6 healthy subjects, 5 internal medicine patients, and 8 operation patients (2 patients only provided discarded adipose tissue in joint cavity). General information is shown in Table 1.

The major diagnoses of the patients in the medical group were: 2 patients of community-acquired pneumonia, 1 patient of bronchiectasis combined with infection, 1 patient of acute

Table 1

General condition data of subjects.

Items groups	Healthy control group	Internal medicine group	Operation group
Number	6	5	8
Male (n)	3	3	2
Female (n)	3	2	6
Age, yr	46–63	45–86	54–67
Height, cm	154–176	148–180	155–170
Weight, kg	60–78	68–90	50–82

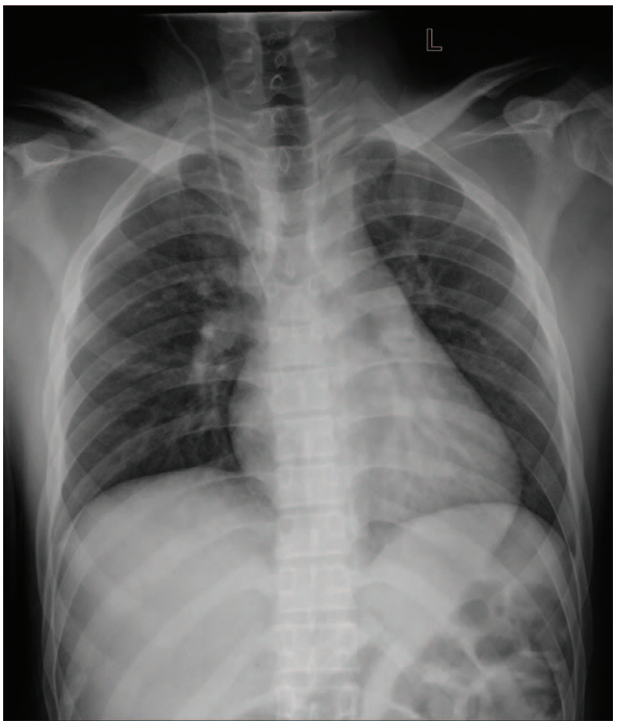

Figure 1. Bedside chest X-ray showed coarsening of lung texture.

exacerbation of chronic obstructive pulmonary disease, and 1 patient of bronchial asthma combined with pulmonary infection. The main diagnoses of the patients in the operation group on admission were: 2 patients of old femoral neck fracture and 6 patients of knee osteoarthritis. Total-hip arthroplasties were performed in 2 patients and total-knee arthroplasties in 6 patients. No skin petechiae and ecchymosis were found except near the wound. All the 8 patients presented increased blood leukocyte, increased neutrophils, decreased hemoglobin, decreased platelet, and postoperative low fever for 2 to 3 days. All the 7 patients had no other complaints of discomfort except the pain at the surgical site. One patient (male, 65 years old, right hip replacement) presented dyspnea on the day after the operation, with respiratory rates of 25 to 35 bpm, heart rates of 100 to 120bpm, clear consciousness, breathing sounds in both the lungs,

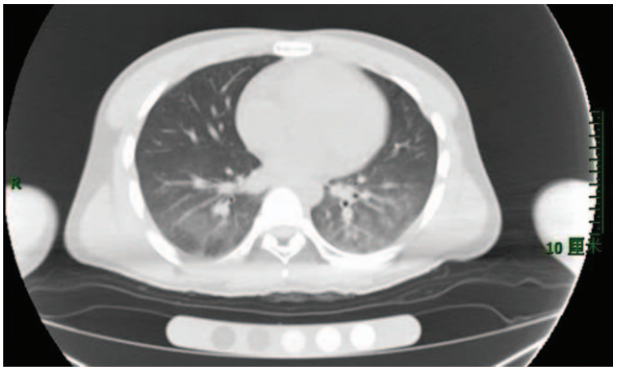

Figure 2. Computed tomography showed ground glass opacity of bilateral lower lungs.

no dry and wet rales, and no heart murmur. Blood gas analysis: FiO_2 100%, pH 4.405, CO_2 28.5 mm Hg, PO_2 188.6 mm Hg, lactic acid 3.9 mmol/L. N-Terminal pro-brain natriuretic peptide (Nt-proBNP) 1854 pg/mL. Bedside chest X-ray showed increased bronchovascular shadows (Fig. 1), and lung computer tomography (CT) showed ground-glass shadows of both lower lungs (Fig. 2). Preoperative peripheral venous blood FABP4 concentration was 314.04 pg/mL, and postoperative 489.13 pg/mL. FES and cardiac insufficiency were suspected. Dexamethasone 10 mg, intravenous input, once a day was given for 3 days. Albumin 20 g, intravenous drip, once a day for 3 days, furosemide 20 mg, albumin intravenous input, once a day, after albumin for 3 days. The symptoms gradually improved and the patient was discharged. No abnormality was found at follow-up outside the hospital.

There were 23 serum samples: healthy control serum, serum of internal medicine patients, serum of preoperative patients, serum of postoperative patients. There were 20 adipose tissue specimens: subcutaneous adipose, intra-articular adipose, and yellow bone marrow. FABP4 concentration of each group is shown in Table 2. There was no significant difference in serum FABP4 levels between healthy controls, internal medicine patients, and preoperative patients. FABP4 levels of subcutaneous adipose and yellow bone marrow were significantly higher than serum FABP4 levels of healthy controls, internal medicine patients and preoperative patients. FABP4 levels of intra-articular adipose tissue were significantly lower than serum FABP4 levels of healthy controls, internal medicine patients, preoperative patients and postoperative patients, as well as subcutaneous adipose and yellow bone marrow FABP4 levels.

4. Discussion

The diagnosis of FE mainly relies on pathologic examination of the lung, brain, kidney, and other parts to discover the presence of fat emboli in small blood vessels. However, this method is mostly used for postmortem autopsy of patients, which greatly limits its application. Unlike thromboemboli, fat emboli are small and dispersed, mostly in the blood circulation in the form of fat droplets or incarcerated in small blood vessels. Therefore, radiologic examination, neither CT nor magnetic resonance imaging are able to demonstrate specific manifestations.[14] Fat droplets were also found in blood, sputum, alveolar lavage fluid, and urine of healthy people.[8,15] Because under normal circumstances, the human blood circulation also contains triglycerides, cholesterol and chylous particles, and other components. At present, there is no simple and convenient method with high specificity and sensitivity to diagnose FE.

Diagnostic standard of FES proposed by Gurd and Wilson in 1974 is generally adopted in clinic. A positive diagnosis was made on finding of least 1 major feature and 4 minor features.[9] Main criteria: respiratory insufficiency; cerebral involvement; petechial rash; minor criteria: pyrexia; tachycardia; retinal changes; jaundice; and renal changes. Laboratory features: anemia; thrombocytopenia; high erythrocyte sedimentation rate; and fat macroglobulemia.[9] As the standard is mainly based on clinical manifestations, all the indicators examined in laboratory lack specificity and the rate of missed diagnosis is high. Also, many patients are misdiagnosed as traumatic brain injury, lung injury, and other diseases. Some authors had tried to improve the diagnosis of FES,[16–18] and others used a scoring system to evaluate high-risk patients to assist the diagnosis of FES, but the

Table 2

FABP4 concentrations in each group.

Items	Groups						
	Serum of healthy control subjects	Serum of internal medicine patients	Serum of preoperative patients	Serum of postoperative patients	Subcutaneous adipose	Intra-articular adipose	Yellow bone marrow
Number	6	5	6	6	6	8	6
FABP4 (maximum)	415.17	446.87	435.55	489.13	565.23	164.35	547.25
FABP4 (minimum)	307.25	281.58	314.04	395.55	512.93	9.32	402.72
FABP4 (mean ± standard deviation, pg/mL)	363.47 ± 41.65	357.51 ± 74.39	381.96 ± 44.49	442.21 ± 36.49Δ	538.83 ± 17.17*,†,‡,§,‖	77.93 ± 63.52*,†,‡,‖	507.96 ± 54.02*,†,‡,§,‖
t/*F*				2.53[1]/70.16[2]/75.75[3]			
P				0.05[1]/0.00[2]/0.00[3]			

[1]Because the serum was from the same patient before and after surgery, the 2 groups were compared by paired *T* test. The data in this table are analyzed [2]by multigroup 1-way analysis of variance (ANOVA) for serum of preoperative patients and other 5 groups, and [3]by multigroup 1-way ANOVA for serum of postoperative patients and other 5 groups, which are combined in this table to save space.

FABP4 = fatty acid-binding protein 4 (*Homo sapiens* [human]) gene ID = 2167.

* There was a significant difference compared with healthy people serum, $P < .05$.

† There was a significant difference compared with serum of preoperative patients, $P < .05$.

‡ There were significant differences compared with serum of internal medicine patients, $P < .05$.

§ There was significant difference compared with intra-articular adipose, $P < .05$.

‖ There was a significant difference compared with serum of postoperative patients, $P < .05$.

¶ There was a significant difference between preoperative and postoperative patients, $P = .05$.

lack of specificity and effectiveness has limited the clinical application.[19]

There are 2 main sources of embolus for FE:

1. Bone marrow source: After 18 years of age, the body's long bones are almost full of yellow bone marrow. The yellow bone marrow is mainly composed of adipose tissue. When a long bone fracture occurs, the adipocytes in the bone marrow cavity are squeezed and damaged and enter the blood circulation through the damaged blood vessels and FE happens. During hip and knee replacement, one end of the prosthesis should be firmly inserted into the bone marrow cavity to fix the artificial joint. In the process of embedding and fixation, the pressure in the bone marrow cavity is very high, and it is very easy to crush the yellow bone marrow in the bone marrow cavity, squeezing adipocytes into blood vessels, and enter the blood circulation, and FE occurs immediately. Therefore, the adipocytes in the yellow bone marrow in the marrow cavity are the main source of FE emboli. Therefore, patients with long bone fracture and joint replacement are at high risk of FE.
2. The source of adipocyte around the subcutaneous or visceral organs: When trauma occurs, the soft tissue is squeezed and damaged, and adipocytes are pushed through the damaged vessels and into blood circulation, causing FE. Fat droplets were found in the peripheral blood of 100% of animals during liposuction.[20] During liposuction, small vessels were damaged. Adipocytes and lipid were pushed into the blood circulation.[21–23] Fat particles were visible in all peripheral blood samples taken at the middle and end process of liposuction. These blood samples showed different patterns of fat particles. The number of fat particles in blood samples at the end of liposuction was significantly higher than that at the middle process of liposuction.[20] When fat transplantation was performed, adipocytes were injected into the target site. The local pressure or tension was so high that adipocytes were pushed into damaged vessels. FE occurred. The adipocytes around the subcutaneous or visceral organs are other major sources of the FE embolus. Patients with trauma and fat transplantation were also at high risk for FE.[5,8]

Normally, triglycerides and chylous granules are present in the blood circulation, but there is no adipocyte-specific component in the blood circulation. If adipocyte-specific components are found in the blood circulation, indicating that adipocyte components outside the circulation enter the blood circulation. And the occurrence of FE can be proved. If the adipocyte-specific component (biomarker) can be found, the occurrence of FE can be confirmed as long as such biomarkers are detected in peripheral blood. Therefore, the author proposes this idea of diagnosing FE at the molecular level. To verify the above hypothesis, the author chose protein FABP4 as the marker. FABP4 is found in the cytoplasm and nucleus of adipocytes, and it is a specific marker of adipocytes, participating in lipid metabolism. Although FABP4 can be detected in peripheral blood of normal people, FABP4 can still be used as candidate diagnostic indicators of FE because the content of FABP4 in adipocytes is much higher than that in other tissues. When FE occurs, smaller fragments can travel through the pulmonary circulation to the systemic circulation,[14,15] so adipocyte-specific proteins can be detected in the peripheral blood. Therefore, the author proposed the hypothesis: if the adipocyte-specific protein FABP4 was detected in the peripheral blood of the high-risk group with FE, and the content of this protein was significantly higher than that in the peripheral blood of normal people, it shows the occurrence of FE. When the concentration of FABP4 reaches a certain level, there will be clinical symptoms, namely FES. If this hypothesis can be verified, only a small amount of peripheral blood of patients can be used for diagnosis. The results can be used to distinguish FES from brain injury and lung injury.

To test this hypothesis, we conducted a preliminary exploration in a small number of subjects. The results of this study showed that: the content of FABP4 in subcutaneous adipose and yellow bone marrow was very high, and significantly higher than the content of FABP4 in serum of the normal control group, internal medicine patients, and preoperative patients; there was no significant difference in FABP4 content in serum of normal control group, internal medicine patients, and preoperative patients; and the serum FABP4 content of postoperative patients

was significantly higher than that of preoperative patients. The results are encouraging. It is proved that FABP4 could be used as FE-specific diagnostic indicators. A total of 8 joint replacement patients were recruited in this study, 7 of whom had no obvious complaints of discomfort except wound pain postoperation. All the 8 patients showed increased leukocyte, decreased platelet counts, and decreased hemoglobin levels in routine blood test 24 hours after operation. The body temperature was 1 to 3 days low-grade fever after the operation, and 7 patients were discharged 3 to 4 days after the operation. After discharge, no obvious abnormality was found. One patient developed dyspnea postoperatively and was diagnosed with FES. Although this patient met the diagnostic criteria of FES proposed by Gurd and Wilson in 1974, because the clinical symptoms and auxiliary examination of this patient were difficult to exclude the common perioperative complications of cardiac dysfunction, the doctor made the diagnosis of FES and cardiac dysfunction, then took targeted treatment. Anticoagulation therapy was not given because the thromboembolism was not found and the risk of bleeding was high. The patient's symptoms improved significantly after treatment. FABP4 was detected in the later, and the results showed that the content of FABP4 in the blood postoperation was significantly higher than that before operation, further confirming the diagnosis of FES. Less than 2% of FES patients have typical dyspnea, delirium, and skin petechiae.[24] A large number of FE patients are missed. Therefore, it is speculated that other patients are likely to have asymptomatic FE. The study also found that the FABP4 content in the adipose tissue in the articular cavity was very low, which was significantly lower than that in other groups. Some studies have shown that the source of bone marrow adipose tissue is different from the source of subcutaneous adipose tissue, but whether the source of intra-articular adipose tissue is different from the source of bone marrow adipose tissue and subcutaneous adipose tissue is still unclear, and further research is needed.

The advantage of this study is that it provides a new way to diagnose FE at molecular level, and provides a possibility to search for sensitive and specific diagnostic indicators of FE. The disadvantage is that due to the lack of previous relevant studies, this study is an initial exploratory study with few patients.

5. Conclusion

1. This study provides preliminary research data for the diagnosis of FE at the molecular level.
2. Adipocyte-specific protein FABP4 may be an indicator of FE diagnosis, but further studies are needed to confirm its clinical application value.

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Author contributions

Dr. Zhuo Wang designed and organized the study. Other authors participated in and conducted the study.

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