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Clinical Study

Spinal epidural lipomatosis is a previously unrecognized manifestation of metabolic syndrome

Shinichi Ishihara, MD[a,b], Nobuyuki Fujita, MD, PhD[a,*], Koichiro Azuma, MD, PhD[c], Takehiro Michikawa, MD, PhD[d], Mitsuru Yagi, MD, PhD[a], Takashi Tsuji, MD, PhD[e], Michiyo Takayama, MD, PhD[f], Hideo Matsumoto, MD, PhD[c], Masaya Nakamura, MD, PhD[a], Morio Matsumoto, MD, PhD[a], Kota Watanabe, MD, PhD[a]

[a] *Department of Orthopaedic Surgery, Keio University School of Medicine, 35 Shinanomachi, Shinjyuku-ku, Tokyo 160-8582, Japan*
[b] *Department of Orthopaedic Surgery, International University of Health and Welfare (IUHW), Mita Hospital, 1-4-3 Mita, Minato-ku, Tokyo 108-8329, Japan*
[c] *Institute for Integrated Sports Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan*
[d] *Environmental Epidemiology Section, Centre for Health and Environmental Risk Research, National Institute for Environmental Studies, 16-2 Onogawa, Tsukuba, Ibaraki 305-8506, Japan*
[e] *Department of Orthopaedic Surgery, Fujita Health University, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan*
[f] *Center for Preventive Medicine, Keio University Hospital, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan*
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Abstract

BACKGROUND CONTEXT: Spinal epidural lipomatosis (SEL) is a condition in which excess lumbar epidural fat (EF) deposition often leads to compression of the cauda equina or nerve root. Although SEL is often observed in obese adults, no systematic research investigating the potential association between SEL and metabolic syndrome has been conducted.
PURPOSE: To elucidate potential association between SEL and metabolic syndrome.
STUDY DESIGN: An observational study used data of a medical checkup.
PATIENT SAMPLE: We retrospectively reviewed data from consecutive subjects undergoing medical checkups. A total of 324 subjects (174 men and 150 women) were enrolled in this study.
OUTCOME MEASURES: The correlation of EF accumulation with demographic data and metabolic-related factors was evaluated.
METHODS: The degree of EF accumulation was evaluated based on the axial views of lumbar magnetic resonance imaging. Visceral and subcutaneous fat areas were measured at the navel level using abdominal computed tomography. Metabolic syndrome was diagnosed according to the criteria of the Japanese Society of Internal Medicine. The correlation of SEL with metabolic syndrome and metabolic-related conditions was statistically evaluated.
RESULTS: The degree of EF accumulation demonstrated a significant correlation to body mass index, abdominal circumference, and visceral fat area. However, age, body fat percentage, and subcutaneous fat area showed no correlation with the degree of EF accumulation. Logistic regression analysis revealed that metabolic syndrome (odds ratio [OR]=3.8, 95% confidence interval [CI]=1.5–9.6) was significantly associated with SEL. Among the diagnostic criteria for metabolic syndrome, visceral fat area $\geq$100 cm^2 (OR=4.8, 95% CI=1.5–15.3) and hypertension (OR=3.5, 95% CI=1.1–11.8) were observed to be independently associated with SEL.
CONCLUSION: This is the first study to demonstrate that metabolic syndrome is associated with SEL in a relatively large, unbiased population. Our data suggest that metabolic-related conditions

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* Corresponding author. Department of Orthopaedic Surgery, Keio University School of Medicine, 35 Shinanomachi, Shinjyuku-ku, Tokyo 160-8582, Japan. Tel.: (81) 3-5363-3812; fax: (81) 3-3353-6597.
E-mail address: nfujita@a7.keio.jp (N. Fujita).

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are potentially related to EF deposition and that SEL could be a previously unrecognized manifestation of metabolic syndrome.

Keywords: Body mass index; Epidural fat; Metabolic syndrome; Medical checkups; Obesity; Spinal epidural lipomatosis; Visceral fat area.

Introduction

Fat tissue in the epidural space (epidural fat [EF]) is frequently observed in healthy people and is thought to serve as a cushion for the dural sac and nerve structures. However, overt and extended accumulation of EF, a condition referred to as spinal epidural lipomatosis (SEL), can compress the spinal cord, cauda equina, and nerve root. Consequently, patients with SEL often develop neurological symptoms, such as lower back pain, radiculopathy, and claudication.

The first case of SEL was described by Lee et al. in 1975 in a patient receiving corticosteroids after renal transplantation [1]. SEL is frequently associated with corticosteroid use and endocrine disorders with increased production of endogenous corticosteroids [2–4]. This suggests that SEL occurs secondary to hypercorticoidism. A case of SEL without a history of steroid use or endocrine disorders (idiopathic SEL, hereafter referred to as SEL) was first described by Badami et al. in 1982 [5]. Since then, several studies have shown that SEL most often occurs in obese people and has a male predominance [6–9]. We have previously demonstrated that the accumulation of lumbar EF is associated with obesity and hyperlipidemia (HL) in patients with lumbar spinal canal stenosis (LSS) [10,11]. Given that both obesity and HL are related to metabolic syndrome, it is conceivable that metabolic-related conditions are associated with the development of SEL.

According to the International Diabetes Federation [12], metabolic syndrome is defined as a condition with central obesity that is accompanied by any two of the following disorders: hypertension (HT), raised triglycerides, reduced HDL cholesterol, and raised fasting plasma glucose. Patients with metabolic syndrome have a higher risk for developing type-2 diabetes mellitus (T2DM), stroke, and cardiovascular diseases. The National Health and Nutrition Examination Survey revealed that the prevalence of metabolic syndrome is persistently increasing and that more than a quarter of adults in the United States are diagnosed with this condition [13]. These data and our previous observation indicate that there are number of patients with metabolic syndrome that are also at risk of developing SEL with symptomatic spinal stenosis and that SEL is posing a serious health issue in developed countries, especially in the United States. However, systematic studies exploring the association between metabolic syndrome and SEL have not been conducted, and only a few small-scale studies have examined this issue in patients with lumbar-related disorders [14,15].

At our facility, we offer medical examinations of the musculoskeletal system (including lumbar magnetic resonance imaging [MRI] scans). These examinations gave us an opportunity to systemically evaluate clinical data pertaining to both metabolic-related conditions and lumbar spine disorders from a relatively large and unbiased population. Using these clinical data, we aimed to elucidate potential associations between SEL and metabolic-related conditions.

Materials and methods

Subjects

We retrospectively reviewed the data from 333 consecutive subjects who underwent medical checkups including musculoskeletal examinations between July 2012 and November 2016. The medical checkup and musculoskeletal examination included blood tests, abdominal computed tomography (CT), dual X-ray absorptiometry (DXA), lumbar spine MRI, and a self-administered questionnaire for general and musculoskeletal complaints. We excluded subjects with missing data from any of the examinations. Table 1 summarizes the characteristics of the subjects enrolled in the current study. The procedures used in the current study were approved by our facility's institutional ethics committee (approval number 20160199). The subjects were notified of the study, and the data of those who declined to participate were excluded from the analysis to comply with the ethical guidelines of our facility.

CT

The visceral fat area (VFA) and subcutaneous fat area (ScFA) were measured at the level of the navel using CT (Aquilion CXL, Toshiba Medical Systems Corporation, Tochigi, Japan) (Fig. 1). Digital Imaging and Communication in Medicine (DICOM) data were analyzed using sliceOmatic software (TomoVision, Magog, Quebec, Canada). CT attenuation values were adjusted from −30 to −190 HU for adipose tissue [16,17].

Table 1
Characteristics of the participants

Age (y)	n (%)	Body mass index	n (%)
≥ 75	77 (23.8%)	≥25.0	88 (27.2%)
65–74	84 (25.9%)	18.5–24.9	209 (64.5%)
50–64	112 (34.6%)	<18.5 kg/m^2	27 (8.3%)
<50	51 (15.8%)	Comorbidities	n (%)
Sex	n (%)	Hypertension	149 (46.0%)
Male	174 (53.7%)	Hyperlipidemia	118 (36.4%)
Female	150 (46.3%)	Diabetes mellitus	95 (29.3%)

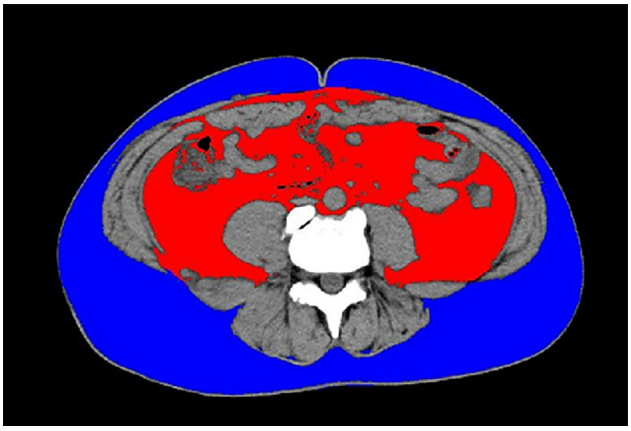

Fig. 1. Computed tomographic image of the visceral adipose area (red) and subcutaneous fat area (blue) at the level of the navel.

MRI

We measured the cross-sectional area of EF and the spinal canal (SC) from L1/2 to L5/S1 using the axial images of lumbar MRIs (Fig. 2). The ratio of EF to SC area (defined as EF/SC) was calculated at each intervertebral level. The mean value of EF/SC from L1/2 to L5/1 was calculated and defined as the EF/SC index. The MRI parameters used were as follows: T1-weighted sagittal images (TR/TE, 470/8.0; echo train length, 2; thickness of slice, 4/5 mm; field of view, 30 cm; matrix size, 384 × 224; NEX, two times), T2-weighted sagittal images (TR/TE, 3000/100; echo train length, 16; NEX, two times; the remaining parameters were the same as those used for the T1-weighted sagittal images), and T2-weighted axial images (TR/TE, 5000/102; thickness of slice, 5/6 mm; field of view, 16 cm; the remaining parameters were the same as used for the T2-weighted sagittal images).

Data collection

The following clinical data were collected: age, gender, BMI, abdominal circumference, blood pressure, body fat percentage measured by DXA (Lunar Prodigy Advance Encore 10X, GE Healthcare, Madison, WI, USA), smoking habits, alcohol consumption, and histories of common noncommunicable diseases, including HTN, T2DM, and HL.

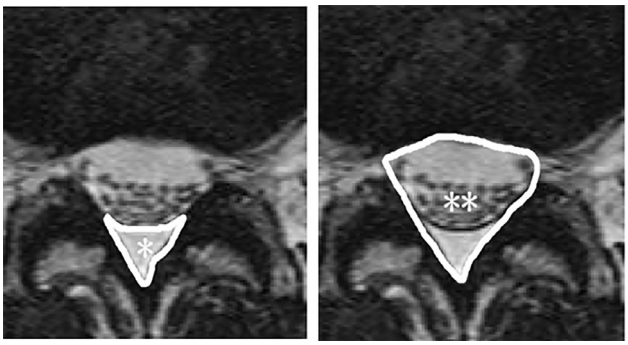

Fig. 2. Cross-sectional area of epidural fat (EF)* and the spinal canal (SC)**.

Furthermore, we reviewed blood tests, including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), high molecular weight adiponectin, high sensitivity C-reactive protein (CRP), blood glucose, glycated hemoglobin (HbA1c), and homeostasis model assessment (HOMA), which refers to insulin resistance calculated using a previously described formula [18]. Blood samples were obtained under fasting conditions.

Diagnostic criteria for metabolic disorders

Obesity was defined as a BMI ≥25 kg/m^2. Presence of HTN, HL, and T2DM was determined by medical history and clinical examination during medical checkups. HTN was defined as systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP ≥90 mmHg [19]. HL was defined as LDL-C ≥140 mg/dL and/or TG ≥150 mg/dL and/or HDL-C <40 mg/dL [20]. T2DM was defined as HbA1c ≥6.5% [21]. Metabolic syndrome was diagnosed according to the diagnostic criteria of the Japanese Society for Internal Medicine [22]. These criteria were as follows: VFA ≥ 100 cm^2 with any of the following two conditions: (1) TG ≥150 mg/dL and/or HDL-C <40 mg/dL, (2) systolic BP ≥130 mmHg and/or diastolic BP ≥85 mmHg, or (3) fasting plasma glucose ≥110 mg/dL.

Definition of SEL

Patients with 0.6≤ anteroposterior distance ratio of EF to SC at least at one lumbar level on MRI were diagnosed with SEL [10,11].

Statistical analysis

Data are presented as mean ± standard deviations. Pearson's correlation coefficients (r) were calculated to examine the correlation between the EF/SC index and each parameter (Figs. 4 and 5 and Supplementary Table 1). Student's *t*-test was used to evaluate the statistical differences of the EF/SC index between genders (Fig. 3). To examine the

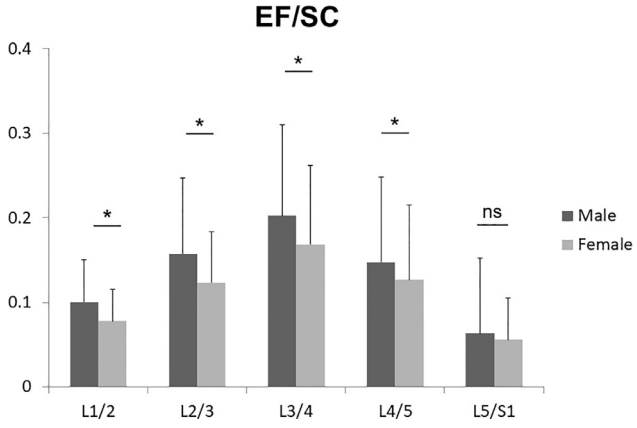

Fig. 3. Ratio of EF to SC area (EF/SC) from L1/2 to L5/S1. *p<.05; ns, not significant.

association of metabolic syndrome and each metabolic-related condition with SEL, we applied a logistic regression model and estimated odds ratios (ORs) and 95% confidence intervals (95% CIs) for SEL (Tables 3 and 4). Logistic regression was performed using STATA14 software (Stata Corporation, College Station, TX). In this study, $p<.05$ was considered statistically significant.

Results

A total of 324 subjects (mean age, 63.3 years; 174 men and 150 women) were enrolled in the current study (Table 1).

Using the clinical images collected from the subjects in the current study, we first determined the lumbar level where EF was most frequently observed. As shown in Fig. 3, the EF/SC value was greatest at L3/4, followed by L2/3, L4/5, L1/2, and L5/S1. Men had a greater EF/SC values than women at all the lumbar levels. The EF/SC index, which reflects the overall deposition of EF in the lumbar SC, demonstrated a significant correlation with BMI (r=0.37, $p<.0001$), abdominal circumference (r=0.33, $p<.0001$), and VFA (r=0.33, $p<.0001$) (Fig. 4). On the contrary, age (r=.09), body fat percentage (r=0.14), and ScFA (r=0.18) showed no correlation with the EF/SC index. Laboratory tests revealed no significant correlation of TG

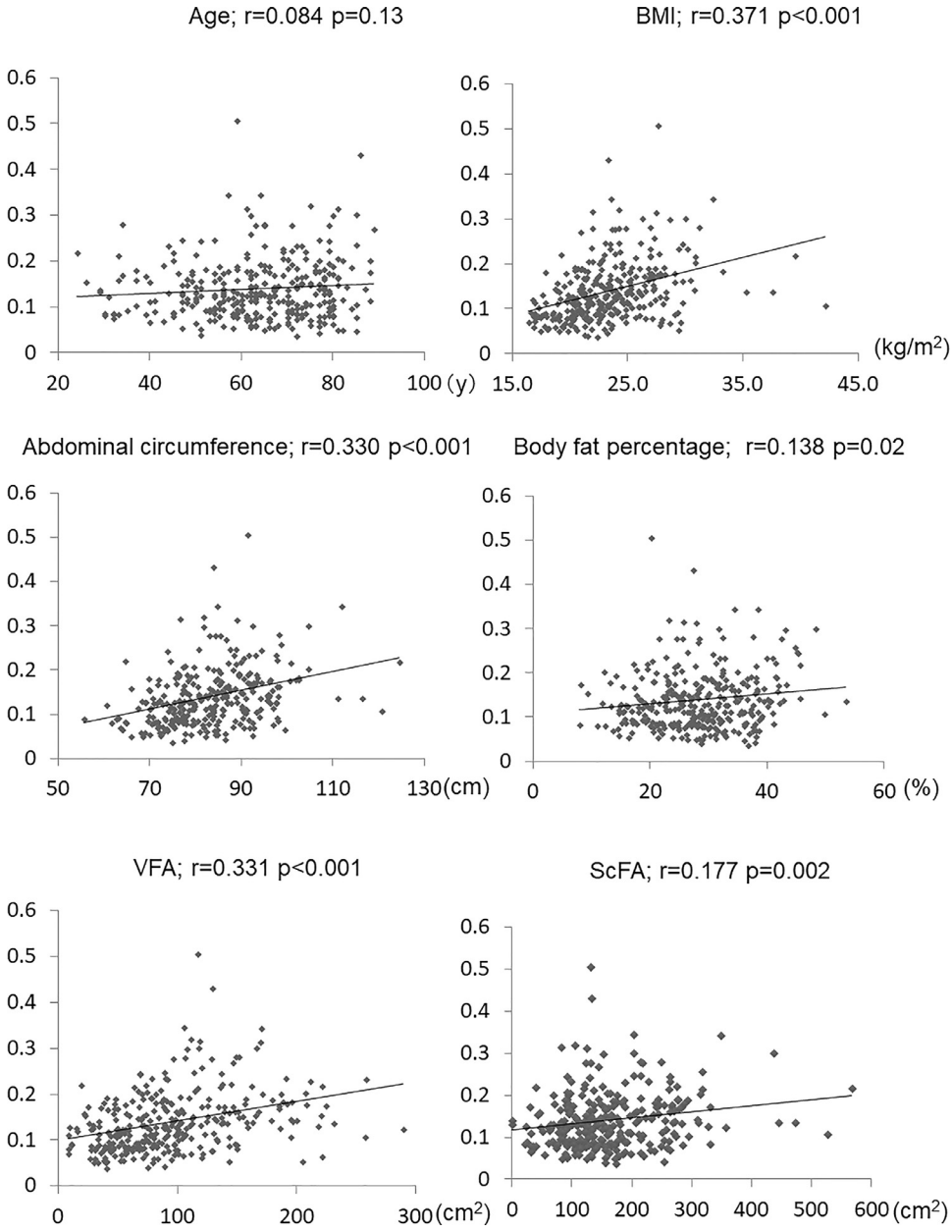

Fig. 4. Correlation between EF/SC index and metabolic parameters. r, correlation coefficient; BMI, body mass index; VFA, visceral fat area; ScFA, subcutaneous fat area.

(r=0.19), HDL-C (r=−0.18), LDL-C (r=0.03), high sensitivity CRP (r=0.06), adiponectin (r=−0.16), or HOMA (r=0.18) with the EF/SC index (Fig. 5).

Based on MRIs, 30 out of 324 subjects were diagnosed with SEL (9.3%). Table 2 shows the results of the self-administered questionnaire for evaluating neurological symptoms in the subjects with SEL. The data suggest that SEL is highly associated with neurogenic symptoms that are related to lumbar spinal canal stenosis. The potential association of metabolic syndrome (as defined by the Japanese Society for Internal Medicine [20]) with SEL was independently evaluated to avoid collinearity arising from other metabolic-related conditions (such as HTN, T2DM, and obesity). For these data, we divided the subjects into following two groups: those with metabolic syndrome (n=57; 17.6%) and those without (n=267; 82.4%) (Table 3). Logistic regression analysis of variables demonstrated that metabolic syndrome was significantly associated with SEL (OR=3.9, 95% CI=1.5−9.8, adjusted for age, gender, smoking habits, and alcohol consumption) (Table 3). To evaluate the association of SEL with each metabolic-related condition, a logistic regression model was generated using the following variables: obesity, VFA ≥100 cm^2, HL, HTN, and T2DM.

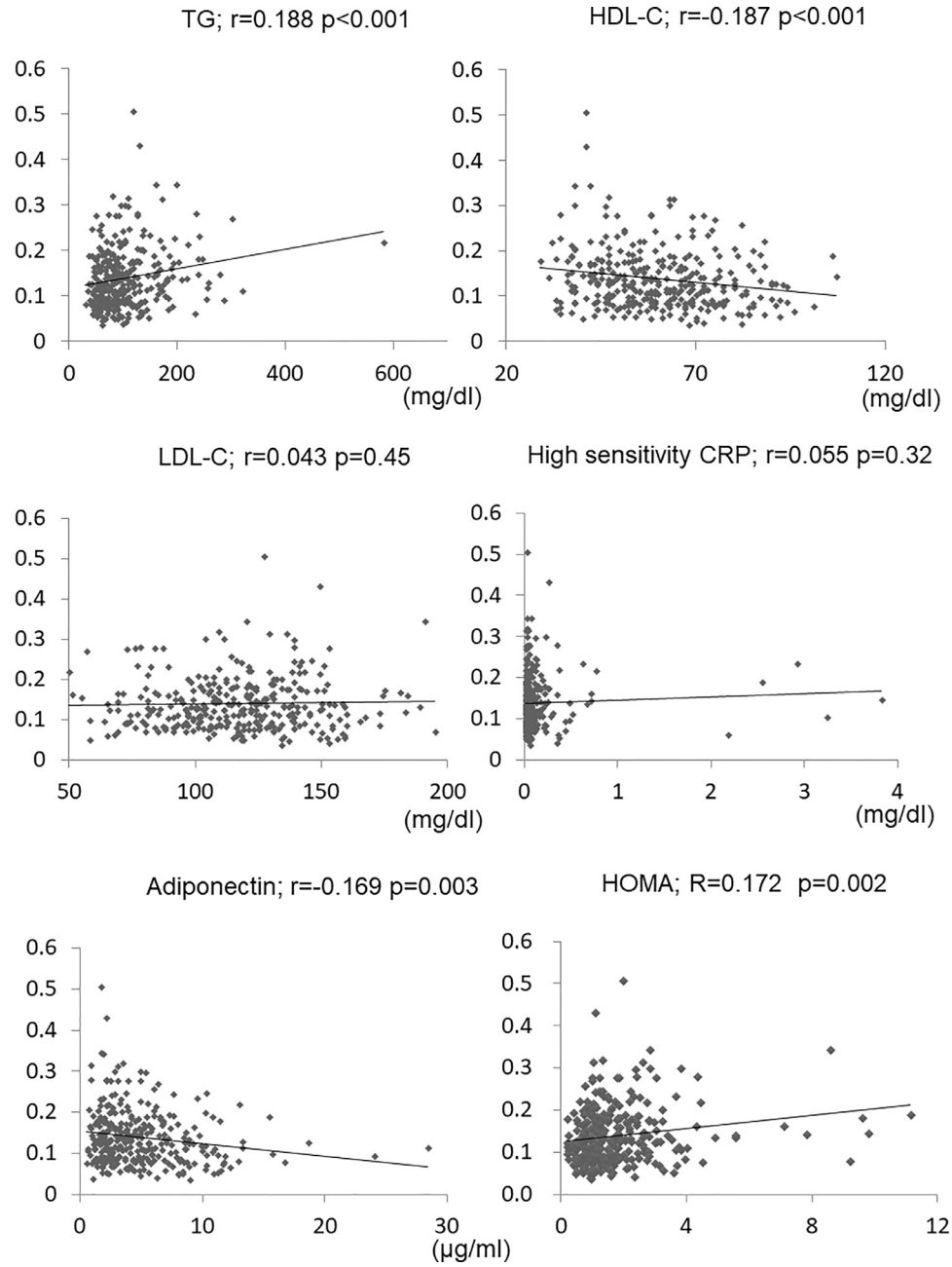

Fig. 5. Correlation between EF/SC index and blood parameters. r, correlation coefficient; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein; HOMA, homeostasis model assessment.

Table 2
Neurological symptoms of the subjects with SEL

	Questionnaire items	SEL (n=30) Yes	No
1	Do you have a back, buttock, or leg pain?	27 (90%)	3 (10%)
2	Does your back, buttock, or leg pain get worse while walking or standing?	15 (50%)	15 (50%)
3	Do you have numbness in your buttock, legs, or feet?	18 (60%)	12 (40%)

SEL, spinal epidural lipomatosis.

Our analysis revealed that VFA ≥100 cm^2 (adjusted OR=5.1, 95% CI=1.6–16.2) and HTN (adjusted OR=3.7, 95% CI=1.1–12.3) were significantly correlated with SEL. On the contrary, obesity (adjusted OR=1.1, 95% CI=0.3–3.5), HL (adjusted OR=0.4, 95% CI=0.1–1.0), and T2DM (adjusted OR=0.9, 95% CI=0.3–2.3) did not reach a level of statistical significance with SEL in the subjects of the current study (Table 4).

Discussion

We used a dataset consisting of a relatively large population of adults who underwent medical checkups at our facility to demonstrate that metabolic syndrome has a significant correlation with SEL. Furthermore, among the criteria for metabolic syndrome, we found that VFA ≥100 cm^2 and HTN were statistically associated with SEL. These results suggest that SEL represents a previously unappreciated manifestation of metabolic syndrome.

Several past surgical case reports suggest that SEL often occurs at L5/S1 [8,14,23]; however, our analysis revealed that L3/4, but not L5/S1, had the greatest EF/SC values among the lumbar levels. A recent retrospective study analyzing 93 subjects showed a similar result that SEL most frequently occurs at L3/4 [24]. Moreover, in accordance with the male prevalence of SEL, the current study also showed that EF/SC values were greater in men than in women at all lumbar levels [6,10,25].

In agreement with previous studies [6–10], we found that BMI was positively correlated with EF deposition in the lumbar spine (i.e., EF/SC index). Notably, our analysis revealed that VFA, but not ScFA, was significantly associated with the EF/SC index. This indicates that visceral obesity, but not subcutaneous obesity, is causally related to EF deposition. Interestingly, recent studies have shown that ectopic fat deposition occurs in various organs in patients with metabolic syndrome including the pancreas, liver, heart, and skeletal muscle [26–28], besides the viscera [29]. The accumulation of fat in these organs leads to chronic inflammation and ultimately results in organ dysfunction [26–28]. These observations indicate that metabolic syndrome is associated with systemic fat deposition and further support our hypothesis that SEL is not an independent pathological entity but one of the accompanying symptoms of metabolic syndrome. If this is the case, it may be possible to treat neurological symptoms of patients with SEL by targeting the underlying metabolic-related

Table 3
Association of metabolic syndrome with SEL

		Prevalence of SEL	p Value by chi-square test	Odds ratio*	95% CI	p Value*
Metabolic syndrome	No (N=267)	7.1% (N=19)	**<.01**	Ref.		**.01**
	Yes (N=57)	19.3% (N=11)		**3.9**	1.5–9.8	

CI, confidence interval; SEL, spinal epidural lipomatosis.
* Adjusted by age, gender, smoking habit, and drinking history.

Table 4
Association of metabolic-related disorders with SEL

		Prevalence of SEL	p value by chi-square test	Odds ratio*	95% CI	p Value*
Body mass index	<18.5 (N=27)	0.0% (N=0)		NA		
	18.5–24.9 (N=209)	9.1% (N=19)	.15	Ref.	0.3–3.5	.87
	≥25.0 kg/m^2 (N=88)	12.5% (N=11)		1.1		
Visceral fat area	<100 cm^2 (N=200)	3.5% (N=7)		Ref.		
	≥100 cm^2 (N=124)	18.6% (N=23)	**<.01**	**5.1**	1.6–16.2	**.01**
Hyperlipidemia	No (N=206)	9.7% (N=20)		Ref.		
	Yes (N=118)	8.5% (N=10)	.71	0.4	0.1–1.0	.05
Hypertension	No (N=175)	3.4% (N=6)		Ref.		
	Yes (N=149)	16.1% (N=24)	**<.01**	**3.7**	1.1–12.3	**.03**
Type-2 diabetes mellitus	No (N=229)	8.3% (N=19)		Ref.		
	Yes (N=95)	11.6% (N=11)	.35	0.9	0.3–2.3	.76

CI, confidence interval; SEL, spinal epidural lipomatosis.
* Adjusted for age, gender, smoking habit, drinking history, and all above items.

conditions that compromise fat metabolism and lead to ectopic fat deposition [14,30,31]. Nevertheless, further clinical and basic studies are warranted to address these issues.

The current study had several limitations. First, the reason for the lack of statistical correlation of BMI and body fat percentage with EF/SC index is not fully understood. Given that these two factors are apparently associated with increased abdominal circumference (and consequently with the EF/SC index), these results seem counterintuitive. However, we found that in our subjects the association of BMI and body fat percentage to VFA was lower compared with that to abdominal circumference (Supplementary Table 1). This may explain, at least in part, the aforementioned discrepancy. Second, although our multivariate analysis demonstrated that HTN was significantly associated with SEL, the causal relationship between HTN and SEL remains unclear. Third, there was a discrepancy regarding the association of HL and SEL between our current and past studies [11]. In the past study, we solely enrolled male patients with LSS [11], whereas in the current study, we enrolled both men and women who underwent medical checkups, irrespective of the presence of spine-related disorders. Therefore, it is possible that the subject-related differences between these two studies led to these discrepancies.

Conclusion

In summary, to the best of our knowledge, this is the first study to systematically evaluate the potential association between metabolic-related disorders and EF deposition in a relatively large unbiased population. Most importantly, the present study clearly demonstrated that metabolic syndrome is associated with the development of SEL. Because the number of patients with metabolic syndrome is increasing globally [13,32,33], it is most likely that the number of SEL patients with symptomatic spinal stenosis is also on the rise. This raises a serious concern that SEL could pose a significant health issue in developed countries, especially in the United States. In this regard, SEL may need to be considered as one of manifestations of metabolic syndrome (along with HT, T2DM, and HL) and be treated as such.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.spinee.2018.07.022.

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