Clinical Neurology and Neurosurgery 185 (2019) 105480

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Spinal epidural lipomatosis is associated with liver fat deposition and dysfunction

Tetsutaro Abe[a], Masashi Miyazaki[a,*], Toshinobu Ishihara[a], Shozo Kanezaki[a], Naoki Notani[a], Masashi Kataoka[b], Hiroshi Tsumura[a]

[a] Department of Orthopaedic Surgery, Faculty of Medicine, Oita University, Oita, Japan
[b] Physical Therapy Course of Study, Faculty of Welfare and Health Sciences, Oita University, Oita, Japan

ARTICLE INFO

Keywords:
Lumbar spinal canal stenosis
Spinal epidural lipomatosis
Fatty liver
CT
Body weight
CRP
γ-GTP
Uric acid
Lifestyle diseases
Metabolic syndrome

ABSTRACT

Objective: This study examined the association of spinal epidural lipomatosis (SEL) with liver fat deposition and any other liver dysfunction, except steroid involvement.

Patients and Methods: We analyzed 102 patients (62 men and 40 women; mean age 73.3 years) who underwent spinal magnetic resonance imaging (MRI), computed tomography (CT), and myelography for the diagnosis of lumbar spinal canal stenosis between January 2014 and June 2018. Additional data collected included height, weight, body mass index, blood test results (C-reactive protein, albumin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase [γ-GTP], total cholesterol, neutral fat, amylase, urea nitrogen, creatinine, estimated glomerular filtration rate, uric acid, platelets), the epidural fat-occupying ratio in each vertebra from L1/2 to L5/S1 on MRI, and liver CT values.

Results: In 30 cases, the average occupying ratio of epidural fat was ≥40% (SEL), and in 45 cases, liver CT values were < 40 HU (fatty liver). Correlation analysis between average occupying ratio of epidural fat and various measurements showed liver CT value ($r = -0.574$, $P < 0.001$), body weight ($r = 0.304$, $P = 0.002$), γ-GTP ($r = 0.370$, $P = 0.01$), and uric acid ($r = 0.201$, $P = 0.04$) to be independent explanatory factors. Multivariate analysis revealed that SEL was associated with liver CT value (odds ratio 0.774, 95% confidence interval [CI] 0.689–0.871) and body weight (odds ratio 1.063, 95% CI 1.016–1.135).

Conclusion: There was a strong correlation between epidural fat and liver fat deposits suggesting an association between SEL and systemic fat deposition.

1. Introduction

Spinal epidural lipomatosis (SEL) is a condition characterized by over-deposition of epidural fat in the spinal canal. Hyperplasia of this adipose tissue occasionally causes neurological symptoms, such as back pain, radiculopathy, claudication, myelopathy, and cauda equine syndrome [1,2]. Idiopathic SEL predominantly affects male patients, and more than 75% of all reported patients were obese [3]. A recent large population study reported the prevalence of SEL to be approximately 2.5% and that the factors associated with SEL included male sex and obesity in addition to systemic corticosteroid use [4]. Because obesity in adults is usually accompanied by common non-communicable diseases, such as hypertension, type 2 diabetes mellitus, dyslipidemia, and arteriosclerosis [5–7], the high rate of obesity in patients with idiopathic SEL suggests that non-communicable diseases and SEL are causally related. Weight loss has been proposed as a primary treatment. However, the results from this intervention remain unclear [8]. While patients with worsening or persistent neurologic symptoms may warrant surgery [1].

Non-alcoholic fatty liver disease (NAFLD) is emerging as the most common chronic liver condition in developed countries. Disease presentation ranges from asymptomatic elevated liver enzyme levels to cirrhosis with complications of liver failure and hepatocellular carcinoma. Accumulating evidence supports an association between NAFLD and metabolic syndrome [9]; however, few studies have evaluated the association between SEL and NAFLD. The purpose of the present study was to examine the association of SEL with liver fat deposition and any other liver dysfunction, except steroid involvement.

* Corresponding author at: Department of Orthopaedic Surgery, Faculty of Medicine, Oita University, 1-1 Idaigaoka, Hasama-machi Yufu-shi, Oita, 879-5593, Japan.

E-mail address: masashim@oita-u.ac.jp (M. Miyazaki).

https://doi.org/10.1016/j.clineuro.2019.105480
Received 4 July 2019; Received in revised form 1 August 2019; Accepted 7 August 2019
Available online 10 August 2019
0303-8467/ © 2019 Elsevier B.V. All rights reserved.

2. Materials and methods

2.1. Participants

The current study was approved by the Ethics Committee of Oita University, and all methods were in accordance with the relevant guidelines and regulations. Written and/or oral informed consent was obtained from each of the patients. The study design was a retrospective study. We retrospectively reviewed 102 patients (62 men and 40 women) who underwent spinal magnetic resonance imaging (MRI), computed tomography (CT), and myelography for the diagnosis of lumbar spinal canal stenosis between January 2014 and June 2018. CT was taken for the evaluation of lumbar spinal canal stenosis after myelography and liver CT Hounsfield Units (HU) value was measured. Spine specialists evaluated each patient and confirmed that the symptoms originated from the lumbar spinal canal based on the patient's symptoms (pain or numbness from the hip to lower extremity caused or exacerbated by standing or walking and improved by forward bending or sitting), neurological examination findings, and stenosis in the spinal canal as detected on MRI. Patients with foraminal stenosis and disc herniation on MRI were excluded. Patients with a history of long-term steroid administration or history of liver disease, such as acute or chronic viral hepatitis, autoimmune liver disease, alcoholic liver disease, or disorders that can influence the levels of corticosteroids were excluded. Additional data collected included height, weight, body mass index (BMI), blood test results (C-reactive protein [CRP], albumin, total bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyltransferase [γ-GTP], total cholesterol, triglycerides [TG], amylase, urea nitrogen, creatinine, estimated glomerular filtration rate [eGFR], uric acid, and platelet), and liver CT value. The diameter of epidural fat/anteroposterior diameter of the spinal canal (EF/SpiC) index at L1/2 to L5/S1 levels was assessed on the basis of lumbar T2-weighted axial MRI (Fig. 1). Those with liver CT values < 40 HU were diagnosed with fatty liver [10]. Presence of hypertension, hyperlipidemia, and diabetes mellitus was determined based on medical history and laboratory examination at the time of the present study. Those with TG of ≥150 mg/dL and/or total cholesterol < 220 mg/dL were diagnosed as having hyperlipidemia. Those with hemoglobin A1c of ≥6.5% were diagnosed as having diabetes mellitus. Participants with a medical history of hyperlipidemia were all on cholesterol-lowering medications.

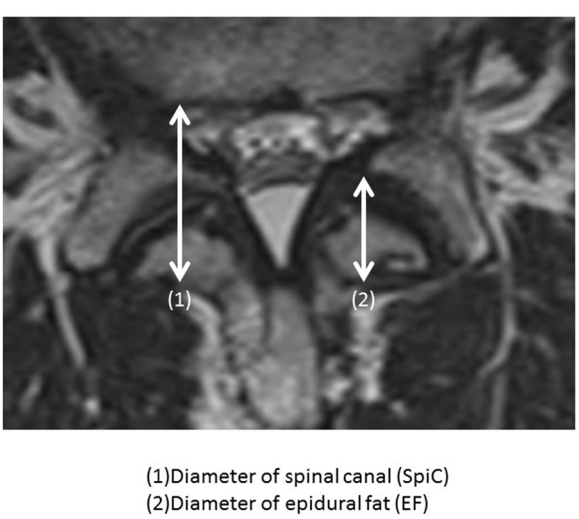

Fig. 1. The diameter of epidural fat/spinal anteroposterior diameter of the spinal canal index was assessed on the basis of lumbar magnetic resonance axial images. (1) diameter of spinal canal (SpiC), (2) diameter of epidural fat (EF).

2.2. Grouping of participants

Participants were divided into two groups according to the EF/SpiC index. According to the Borré et al. classification [11], those with L1/2 to L5/S1 average EF/SpiC index < 0.4 were defined as patients without SEL (non-SEL group, n = 72). Those with EF/SpiC index ≥0.4 were defined as patients with SEL (SEL group, n = 30). The SEL and non-SEL groups were compared with respect to clinical features as well as blood and image examinations.

2.3. Statistical analysis

The data were collected prospectively after appropriate informed consent was obtained. Data are presented as mean ± standard deviation. Statistical analyses were performed using an unpaired two-tailed Student's *t*-test or an analysis of variance. To assess correlations between independent variables (height, weight, BMI, CRP, albumin, total bilirubin, AST, ALT, γ-GTP, total cholesterol, TG, amylase, urea nitrogen, creatinine, eGFR, uric acid, and platelets) and the dependent variable (EF/SpiC index), we used Pearson correlation coefficients. Variables with a P value less than 0.05 in univariate analysis were considered for multivariate linear analysis. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) are presented with their respective P values. All analyses were performed using SPSS (version 13; SPSS, Chicago, IL). P values of less than 0.05 were considered statistically significant.

3. Results

There were 30 cases in which the EF/SpiC index ≥0.4 (SEL). Fig. 2 showed the distribution of EF/SpiC index and the Kolmogorov–Smirnov test showed that the data had a normal distribution. 45 cases with liver CT values < 40 HU (fatty liver).

3.1. Comparison between SEL and non-SEL groups for clinical features, and blood and image examinations

Table 1 shows the demographic data for the 102 subjects included in this study. There were 62 men and 40 women. The mean age overall was 73.3 years (range, 50–89 years) and 73.4 years and 73.1 years for men and women, respectively. The SEL group comprised 30 subjects (29.4%; 24 men, 6 women), and the non-SEL group comprised 72 subjects (70.6%; 38 men, 34 women). There were no significant differences in age, height, BMI, CRP, albumin, total bilirubin, AST, ALT, total cholesterol, TG, amylase, urea nitrogen, creatinine, platelets, eGFR, and incidence of co-morbidities such as hypertension, hyperlipidemia, and diabetes mellitus. However, the SEL group had significantly more male patients (80.0%, $P = 0.02$); higher body weight

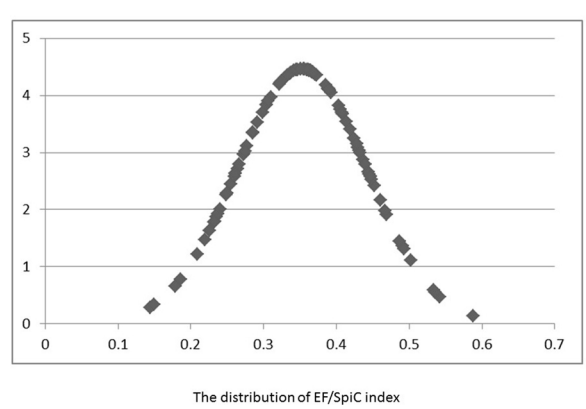

Fig. 2. The distribution of EF/SpiC index was shown and the Kolmogorov–Smirnov test showed that the data had a normal distribution.

Table 1
Comparison of SEL and non-SEL group characteristics.

	SEL (n = 30)	Non-SEL (n = 72)	*p*
age	73.1 ± 9.3	73.6 ± 5.8	0.74
Height	159.7 ± 7.68	155.6 ± 10.7	0.07
Body weight	62.8 ± 9.21	58.3 ± 12.1	**0.04***
BMI	24.5 ± 2.58	24.2 ± 3.86	0.68
Male: Female ratio	24:6	38:34	**0.02***
CRP	0.49 ± 0.96	0.21 ± 0.12	0.06
Alb	4.08 ± 0.48	4.21 ± 0.33	0.17
T-bil	0.65 ± 0.27	0.67 ± 0.27	0.72
AST	26.1 ± 9.51	24.7 ± 7.55	0.46
ALT	20.4 ± 9.57	20.7 ± 10.8	0.88
γ-GTP	58.6 ± 5.39	28.1 ± 2.62	**0.01***
TC	177.6 ± 45.7	182.5 ± 33.4	0.59
TG	148.6 ± 64.5	132.4 ± 57.5	0.24
Amy	97.2 ± 47.1	91.5 ± 34.5	0.55
BUN	18.9 ± 7.16	17.8 ± 4.72	0.43
Cr	0.88 ± 0.184	0.91 ± 0.28	0.84
UA	5.81 ± 1.65	5.17 ± 1.35	**0.04***
Plt	18.4 ± 7.04	20.8 ± 5.91	0.10
eGFR	58.5 ± 19.3	67.2 ± 12.1	0.06
Liver CT value	44.67 ± 5.06	56.7 ± 8.46	**0.03***
HL	13(43.3%)	19(30.6%)	0.11
HTN	17(56.6%)	26(41.9%)	0.06
DM	11(36.6%)	14(22.6%)	0.09

HL; hyperlipidemia, HTN; Hypertension, DM; diabetes mellitus.
* $p < 0.05$.

(62.8 ± 9.21 kg, $P = 0.04$), γ-GTP (58.6 ± 5.39 IU/l, $P = 0.01$), and uric acid (5.81 ± 1.65 mg/dl, $P = 0.04$); and lower liver CT value (44.67 ± 5.06 HU, $P = 0.03$). In the SEL group, the liver CT value < 40 HU (fatty liver) in 23 cases.

3.2. Correlation analysis between the EF/Spic index and each factor

On correlation analysis of the EF/SpiC index and body weight, height, and BMI, only body weight was statistically significant (Table 2). Laboratory examination showed that serum γ-GTP and uric acid levels were correlated with the EF/SpiC index (Table 3). Incidence of co-morbidities such as hypertension, hyperlipidemia, or diabetes mellitus had no correlation with EF/SpiC. Liver CT value had a very strong correlation with the EF/SpiC index (Table 4).

3.3. Multivariate analyses of factors associated with the EF/SpiC index

We further performed a Pearson correlation test to investigate the factors related to SEL using the explanatory variables that were significant in the univariate analysis (Table 5).

Thus, Body weight, γ-GTP, uric acid levels and Liver CT value were entered in the multivariate linear regression analysis, which confirmed that liver CT value (OR 0.774, 95% CI 0.689–0.871) and body weight (OR 1.063, 95% CI 1.016–1.135) to be significant explanatory variables.

Table 2
Correlation analysis results between EF/Spic index and factors (patient's characteristics).

	Correlation coefficient	*p*
Age	−0.098	0.32
Height	0.231	0.19
Body weight	0.304	**0.02***
BMI	0.208	0.36

* $p < 0.05$.

Table 3
Correlation analysis results between EF/Spic index and factors (blood examinations).

	Correlation coefficient	*p*
CRP	0.201	0.43
Alb	−0.101	0.31
T-bil	−0.030	0.76
AST	0.139	0.16
ALT	0.069	0.49
γ-GTP	0.370	**0.01***
TC	−0.035	0.72
TG	0.193	0.06
Amy	0.028	0.77
BUN	0.057	0.56
Cr	0.055	0.58
UA	0.201	**0.04***
Plt	−0.188	0.06
eGFR	−0.188	0.06

* $p < 0.05$.

Table 4
Correlation analysis results between EF/Spic index and factors (medical history).

	Correlation coefficient	*p*
HL	0.042	0.67
HTN	0.122	0.22
DM	0.089	0.37
Liver CT value	−0.574	< 0.001

HL; hyperlipidemia, HTN; Hypertension, DM; diabetes mellitus.

Table 5
Multivariate analysis of factors associated with EF/SpiC index.

	Odds rations	95% confidence intervals	*p*
Body weight	1.063	(1.016)-(1.135)	**0.04***
γ-GTP	1.013	(0.995)-(1.031)	0.17
UA	1.017	(0.614)-(1.682)	0.49
Liver CT value	0.774	(0.689)-(0.871)	< **0.001****

* $p < 0.05$.
** $p < 0.001$.

4. Discussion

SEL is a rare condition in which a pathological overgrowth of fat tissue occurs in the epidural space and causes dural impingement. In symptomatic SEL, the overgrowth of fat tissue leads to encroachment on the spinal canal and compression of the spinal cord, cauda equine, or nerve root. SEL is commonly observed in patients receiving exogenous steroid agents and in patients with endogenous overproduction of steroids due to endocrine diseases [2,12]. However, a number of non-steroid-related cases have been reported [13] and the mechanism of epidural fat hyperplasia in SEL is still not fully understood. Consistent with previous studies [4,14,15], there was positive correlation between the degree of obesity and severity of SEL. In the present study, we focused on the relationship between liver fat deposition and SEL because obesity is a common feature in patients with SEL. Our data showed that liver CT values were significantly decreased in patients with SEL, suggesting that aberrant lipid metabolism is potentially related to the pathogenesis of idiopathic SEL.

Although the accumulation of epidural fat tissue can be readily assessed on MRI, the diagnostic criteria and definition of idiopathic SEL remain ill defined. Ishikawa et al [13] reported a grading system based on sagittal and axial MR images; however, the diagnostic criteria for SEL were not defined in their grading system. According to the histological and clinical findings of previous [16] and present studies, we

propose that SEL be defined as an EF/SpiC index value of > 40% at the average epidural fat-occupying ratio in each vertebra from L1/2 to L5/S1 on MRI, which is responsible for SEL symptoms, and suggest that idiopathic SEL be defined as SEL without any history of steroid use or endocrine disorders that can potentially increase the serum corticosteroid levels. However, additional studies are required to establish a standardized definition and diagnostic criteria for SEL.

Metabolic syndrome is an important systemic disorder characterized by increased fat and insulin resistance due to the accumulation of visceral fat, abnormal lipid metabolism, hyperglycemia, and hypertension [17]. These factors are associated with onset of cardiovascular disorders and reduced life expectancy [18]. Previous reports have shown that intra-abdominal fat volume has a correlation with visceral fat area when measured from cross-sectional views taken at the level of the umbilicus [19] and it is well known that metabolic syndrome is closely associated with visceral fat area rather than subcutaneous fat area [20]. From the CT evaluations in the present study, the patients with SEL had significantly lower liver CT values. Furthermore, multivariate analysis showed that the liver CT value was a significant explanatory variable for SEL, indicating that SEL may have a relationship with metabolic disorders, especially fatty liver. In addition, NAFLD is a clinic pathologic entity increasingly recognized as a major health burden in developed countries. It includes a spectrum of liver damage ranging from simple steatosis to nonalcoholic steatohepatitis, advanced fibrosis, and rarely, progression to cirrhosis [8]. Our study supports an association between NAFLD and metabolic syndrome.

In addition to subcutaneous and visceral fat, the concept of ectopic fat has recently been proposed [21]. Ectopic fat is excess adipose tissue found in organs that normally contain little or no fat. In humans, ectopic fat is found in the liver, skeletal muscle, pancreas, heart, and other organs. In metabolic disorders, as visceral fat exceeds normal limits, excess energy is passively stored in the liver and skeletal muscle, leading to ectopic fat deposition [18]. The epidural space normally contains no more than a small amount of fat and there is a possibility that the epidural fat in patients with SEL is increased by a similar mechanism. In addition, fat content in the liver and skeletal muscle is known to be related to insulin resistance. It has also been reported that there is a stronger correlation between insulin resistance and visceral adipose tissue than with subcutaneous adipose tissue [22]. Ectopic fat in organs causes insulin resistance, with accumulation of high levels of TG, leading to hypertension and cardiovascular disease [21]. The accumulation of epidural ectopic fat in patients with SEL may be explained by a similar pathological mechanism as metabolic syndrome and fatty liver.

The present study has several limitations. This was a single-center study with a small patient population due to the relatively low incidence of SEL, and we did not perform long-term evaluation. Additionally, we only included neurologically symptomatic patients whose pathology was located in the lumbar spine.

5. Conclusion

The present study is the first report investigating the association between liver CT value and SEL focusing on visceral fat and related laboratory data. There was a strong correlation between epidural fat and liver fat deposits, suggesting an association between SEL and systemic fat deposition. The effectiveness of methods such as lipid control and weight loss might be considered for treatment of SEL. Although further studies are required to clarify the potential role of fatty liver in patients with SEL, we believe that the present study provides important insight into the pathogenesis of SEL. The results of the present study may help to understand the causes of SEL and there is a possibility that prevention of metabolic syndrome may have a prophylactic effect for SEL.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None.

Acknowledgement

None.

References

[1] P.W. Ferlic, A.F. Mannion, D. Jeszenszky, F. Porchet, T.F. Fekete, F. Kleinstuck, et al., Patient-reported outcome of surgical treatment for lumbar spinal epidural lipomatosis, Spine J. 16 (2016) 1333–1341.
[2] G.R. Fogel, P.Y. Cunningham 3rd, S.I. Esses, Spinal epidural lipomatosis: case reports, literature review and meta-analysis, Spine J. 5 (2005) 202–211.
[3] S.C. Robertson, V.C. Traynelis, K.A. Follett, A.H. Menezes, Idiopathic spinal epidural lipomatosis, Neurosurgery 41 (1997) 68–74.
[4] N.C. Theyskens, N.R. Paulino Pereira, S.J. Janssen, C.M. Bono, J.H. Schwab, T.D. Cha, The prevalence of spinal epidural lipomatosis on magnetic resonance imaging, Spine J. 17 (2017) 969–976.
[5] M.P. Canale, S. Manca di Villahermosa, G. Martino, V. Rovella, A. Noce, A. De Lorenzo, et al., Obesity-related metabolic syndrome: mechanisms of sympathetic overactivity, Int. J. Endocrinol. 2013 (2013) 865965.
[6] S.W. Rabkin, The relationship between epicardial fat and indices of obesity and the metabolic syndrome: a systematic review and meta-analysis, Metab. Syndr. Relat. Disord. 12 (2014) 31–42.
[7] M. Takahara, I. Shimomura, Metabolic syndrome and lifestyle modification, Rev. Endocr. Metab. Disord. 15 (2014) 317–327.
[8] E. Noh, An unusual complication of morbid obesity: epidural lipomatosis, Am. J. Emerg. Med. 33 (742) (2015) e3-742.e4..
[9] H. Yki-Jarvinen, Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome, Lancet Diabetes Endocrinol. 2 (2014) 901–910.
[10] C.J. Boyce, P.J. Pickhardt, D.H. Kim, A.J. Taylor, T.C. Winter, R.J. Bruce, et al., Hepatic steatosis (fatty liver disease) in asymptomatic adults identified by unenhanced low-dose CT, AJR Am. J. Roentgenol. 194 (2010) 623–628.
[11] D.G. Borre, G.E. Borre, F. Aude, G.N. Palmieri, Lumbosacral epidural lipomatosis: MRI grading, Eur. Radiol. 13 (2003) 1709–1721.
[12] M. Lee, J. Lekias, S.S. Gubbay, P.E. Hurst, Spinal cord compression by extradural fat after renal transplantation, Med. J. Aust. 1 (1975) 201–203.
[13] Y. Shimada, Y. Ishikawa, N. Miyakoshi, T. Suzuki, M. Hongo, Y. Kasukawa, et al., Decompression of idiopathic lumbar epidural lipomatosis: diagnostic magnetic resonance imaging evaluation and review of the literature, J. Neurosurg. Spine 4 (2006) 24–30.
[14] K. Kumar, R.K. Nath, C.P. Nair, S.P. Tchang, Symptomatic epidural lipomatosis secondary to obesity. Case report, J. Neurosurg. 85 (1996) 348–350.
[15] H. Mishima, H. Sugaya, T. Tanaka, T. Ogawa, Spinal epidural lipomatosis in lumbar magnetic resonance imaging scans, Orthopedics 37 (2014) e362–e366.
[16] N. Hosogane, N. Fujita, T. Hikata, A. Iwanami, K. Watanabe, Y. Shiono, et al., Potential involvement of obesity-associated chronic inflammation in the pathogenesis of idiopathic spinal epidural lipomatosis, Spine (Phila Pa 1976) 41 (2016) E1402–E1407.
[17] S. Morishita, Y. Arai, T. Yoshii, K. Sakai, T. Hirai, A. Okawa, Lumbar epidural lipomatosis is associated with visceral fat and metabolic disorders, Eur. Spine J. 27 (2018) 1653–1661.
[18] Y. Matsuzawa, T. Funahashi, T. Nakamura, The concept of metabolic syndrome: contribution of visceral fat accumulation and its molecular mechanism, J. Atheroscler. Thromb. 18 (2011) 629–639.
[19] H. Kvist, B. Chowdhury, L. Sjostrom, U. Tylen, A. Cederblad, Adipose tissue volume determination in males by computed tomography and 40K, Int. J. Obes. 12 (1988) 249–266.
[20] I. Zajac-Gawlak, B. Klapcinska, A. Kroemeke, D. Pospiech, J. Pelclova, M. Pridalova, Associations of visceral fat area and physical activity levels with the risk of metabolic syndrome in postmenopausal women, Biogerontology 18 (2017) 357–366.
[21] M. Shimabukuro, C. Kozuka, S. Taira, K. Yabiku, M. Dagvasumberel, M. Ishida, et al., Ectopic fat deposition and global cardiometabolic risk: new paradigm in cardiovascular medicine, J. Med. Invest. 60 (2013) 1–14.
[22] R. Oka, K. Yagi, M. Sakurai, K. Nakamura, S.Y. Nagasawa, S. Miyamoto, et al., Impact of visceral adipose tissue and subcutaneous adipose tissue on insulin resistance in middle-aged Japanese, J. Atheroscler. Thromb. 19 (2012) 814–822.