Lumbar Spinal Canal Stenosis from the Perspective of Locomotive Syndrome and Metabolic Syndrome: A Narrative Review

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Abstract:
Patients with lumbar spinal canal stenosis (LSS) have impaired activities of daily living because of pain or motor paralysis, but no effective preventive treatment is currently available. The number of patients with LSS is predicted to continually increase as the average age of the global population increases. To provide a conceptual framework for improving healthy life expectancy, the Japanese Orthopaedic Association introduced the concept of locomotive syndrome, to which LSS is related. Ours and other studies have shown that LSS exacerbates locomotive syndrome and that surgical treatment is one method for improving it. Furthermore, we propose that the two-step test, a locomotive syndrome risk test, is effective for assessing the risk for falls and severity of LSS. Meanwhile, lumbar spinal epidural lipomatosis (LSEL), which is a manifestation of LSS, has been shown to be related to metabolic syndrome. Previous studies have suggested that the whole LSS can be also associated with metabolic syndrome. Although locomotive syndrome is very different from metabolic syndrome, which involves lipid metabolism, these two syndromes overlap, such as in LSS. Conducting research on LSS from the perspectives of both locomotive syndrome and metabolic syndrome may lead to novel methods for prevention and treatment of LSS and, conversely, may yield clues for resolving symptoms of the two syndromes. This review provides an overview of LSS from the perspective of locomotive syndrome and metabolic syndrome, along with findings from our research group.

Keywords:
lumbar spinal canal stenosis, locomotive syndrome, metabolic syndrome
healthy life expectancy, the Japanese Orthopaedic Association in 2007 introduced the concept of locomotive syndrome, to which LSS is related\textsuperscript{17-19}. Locomotive syndrome is defined as a state of decreased mobility due to musculoskeletal organ impairment. As locomotive syndrome progresses, the risk of needing long-term care increases.

Locomotive syndrome differs markedly from metabolic syndrome, which involves lipid metabolism. However, these two syndromes overlap, such as in LSS. This review aimed to provide an overview of LSS from the perspective of locomotive syndrome and metabolic syndrome, along with findings by our research group.

2. Lumbar Spinal Canal Stenosis from the Perspective of Locomotive Syndrome

2.1. Locomotive syndrome

Functional mobility impairment can greatly affect health and happiness. Japan has seen an increase in the number of patients complaining of symptoms associated with disorders of the joints, spine, and other musculoskeletal organs as the average age of its population has increased. Thus, prevention, early detection, and early treatment of these disorders are needed. The locomotive syndrome concept can be shown by systematic monitoring of relevant features. Diagnosis of locomotive syndrome is made by conducting locomotive syndrome risk tests, including the stand-up test, two-step test, and self-administered 25-question Geriatric Locomotive Function Scale (GLFS)\textsuperscript{20}. Patients who exceed the reference value for at least one of the above three tests are diagnosed as having locomotive syndrome. Locomotive syndrome has two stages. Stage 1 is indicated by the beginning of a decline in mobility function, and Stage 2 is defined by a progressive decrease in mobility and an increased risk of losing the ability to live independently. Osteoarthritis and osteoporosis are two other major musculoskeletal diseases that cause locomotive syndrome.

2.2. Lumbar spinal canal stenosis and locomotive syndrome

We previously performed locomotive syndrome risk tests for 200 patients aged \(\geq 65\) years with LSS who were scheduled to undergo surgery\textsuperscript{21}. All 200 patients were diagnosed as having locomotive syndrome, and 97\% of the patients were Stage 2. As LSS became more severe, their locomotive syndrome risk test scores worsened, demonstrating a correlation between the stage of locomotive syndrome and severity of LSS\textsuperscript{21}; this relationship was also observed by Kasukawa et al.\textsuperscript{22} and is consistent with the correlation between the 25-question GLFS and the Zurich Claudication Questionnaire reported by Araki et al.\textsuperscript{23}. We determined that among the locomotive syndrome risk tests, the two-step test is particularly strongly correlated with the severity of LSS\textsuperscript{24}. Importantly, we and others recently found that surgical treatment improves locomotive syndrome severity in patients with LSS\textsuperscript{24,25}, with Shimizu et al. noting that risk factors associated with non-improvement of neurological symptoms by surgical treatment were late elderly age and postoperative sagittal imbalance\textsuperscript{25}. To summarize, LSS exacerbates locomotive syndrome, whereas surgical treatment is one method for improving it.

2.3. Short stride length and risk for falls

Among the elderly, fractures sustained in falls can lead to the necessity of long-term care\textsuperscript{26}. Short stride length is correlated with the risk for falls among the elderly\textsuperscript{27,28} and is a clinical symptom of LSS\textsuperscript{29,30}; consistent with this correlation, the risk for falls increases in LSS\textsuperscript{31,32}. We examined the risk for falls in 357 LSS patients aged \(\geq 65\) years by conducting the two-step test\textsuperscript{33}, which is a very simple test for measuring maximum stride length and is part of the locomotive syndrome examination\textsuperscript{20}. In this test, the patient stands and moves two strides forward with maximum stride from a start line, after which the distance is normalized by the patient’s height (Fig. 1). We found strong associations of the two-step test results for the risk for falls with age of \(\geq 80\) years, motor deficits of the lower extremities, and forward-bent posture\textsuperscript{33}. Our previous study also showed that the results of the two-
Lumbar Spinal Canal Stenosis from the Perspective of Metabolic Syndrome

3.1. Lumbar spinal epidural lipomatosis

LSEL was first reported by Lee et al. in 1975 in patients who were continuously administered steroids as immunosuppressants following kidney transplantation. Subsequently, steroid use and endocrine disorders that result in an excess of endogenous steroids have been suggested to be involved in causing LSEL. In 1982, Badami et al. reported a case of idiopathic LSEL unrelated to steroids. Since then, LSEL has frequently been reported in obese patients, mostly men. A diagnosis of LSEL is mainly based on MRI. Abnormally large masses with high signal intensity on both T1- and T2-weighted MRIs are observed in the spinal epidural space of LSEL patients. The characteristic “Y-sign” is often seen on axial MRI. When we examined epidural fat tissues from 16 patients with LSEL, histological analysis revealed hypertrophy of adipocytes in LSEL patients who demonstrated a significantly larger area of adipocytes than the control group. In a case report, Ohba et al. also histologically examined the epidural fat of a patient with LSEL under obesity and reported adipocyte hypertrophy, a finding that is consistent with our own results. In our study, we used real-time polymerase chain reaction to examine mRNA expression levels of cytokines in adipocytes. Although we did not observe significant differences for the adipocytokines adiponectin or leptin, expressions of the inflammatory cytokines TNF-α and IL-1β were significantly elevated in LSEL patients. Visceral fat in obese patients with metabolic syndrome also demonstrates adipocyte hypertrophy and elevated expressions of inflammatory cytokines, a pathology known to be involved in chronic inflammation. The above findings indicate that epidural and visceral fat may share similar cellular biological properties. Given that inflammatory cytokines are involved in discogenic low back pain and that inflammatory cytokines induce expression of molecules involved in pain, such as prostaglandin E2 and substance P, elevated expressions of inflammatory cytokines are presumed to be involved in pain in patients with LSEL.

3.2. Epidural fat accumulation and pain

In our previous study, we used epidural fat thickness as the basis to create three groups from 166 male patients with LSS who had undergone surgery and retrospectively compared body mass index (BMI), blood test results (including lipid markers), and ankle-brachial pressure index among these groups. We found that as the epidural fat thickened, BMI significantly increased, as did total cholesterol and triglyceride levels. We also found that, as epidural fat thickened, scores worsened for the pain-related disorder and walking ability domains of the self-administered Japanese Orthopedic Association Back Pain Evaluation Scale. These results suggest that, in patients with LSEL, obesity and hyperlipidemia are related to epidural fat thickness and that thicker epidural fat further exacerbates clinical symptoms. The exacerbation of pain associated with thicker epidural fat may be caused in part by elevated expression of inflammatory cytokines produced by hypertrophic adipocytes. In obese patients with LSEL, however, mechanical stress on the lumbar spine associated with a high BMI is commonly viewed as the cause of their pain. However, based on the above results, pain in obese patients with LSEL may be caused not only by mechanical stress but also by chronic inflammation associated with hypertrophic adipocytes. Further basic research is required regarding the relationship between pain and epidural fat hypertrophy in patients with LSEL.

3.3. Lumbar spinal epidural lipomatosis and metabolic syndrome

In a previous study we conducted, multivariate analysis of LSEL and lifestyle-related diseases demonstrated an association between LSEL and hyperlipidemia. The subjects participating in this study were LSS patients, and the number of subjects was relatively low, meaning that the relationship between LSEL and hyperlipidemia remains debatable. However, the results suggested that LSEL may be associated with metabolic syndrome. Thus, we examined the correlations among epidural fat accumulation in the lumbar spinal...
Figure 3. Schematic representation of ectopic fat.

Excess accumulation of epidural fat can also be considered as a type of ectopic fat.

canal and BMI, abdominal circumference, visceral fat area by computed tomography, and blood test results in 324 healthy subjects who underwent medical checkups. Such analysis demonstrated the following: BMI, abdominal circumference, and visceral fat area were all significantly correlated with epidural fat accumulation, and the incidence of LSEL was significantly higher in the individuals with metabolic syndrome than in those without metabolic syndrome. Other research groups also have investigated such correlations, with Morishita et al. reporting that LSEL was strongly correlated with visceral fat and Abe et al. reporting that epidural fat accumulation was strongly correlated with accumulation of fat in the liver. Recently, the concept of ectopic fat has been proposed as a third type of fat, separate from subcutaneous fat and visceral fat, and excessive storage of ectopic fat in organs can diminish their functions. Ectopic fat primarily occurs in the pancreas, muscles, liver, and heart. Because LSEL is also associated with lifestyle-related diseases and metabolic syndrome, excess accumulation of epidural fat may also be considered a type of ectopic fat (Fig. 3). Intriguingly, quite unlike ectopic fat in other organs, ectopic fat in the epidural space appears to be associated with pain.

3.4. Treatment for lumbar spinal epidural lipomatosis

Treatments for LSEL include conservative approaches, such as weight reduction, and surgical treatments, such as decompression surgery. Given the pathology of LSEL combined with obesity, weight reduction would be predicted to reduce the excess epidural fat. In fact, weight reduction has been shown to be effective in reducing symptoms of LSEL in several case reports. Regarding the efficacy of weight reduction in treating LSEL with obesity, prospective interventional studies will be critical for establishing strategies.

The efficacy of surgical treatment on patients with LSEL was indicated by Ishikawa et al. and Ferlic et al. in retrospective studies. However, in both studies, the sample size was limited and no control group was included. By conducting a case-control study, Bayerl et al. demonstrated that the effect of surgical treatment on LSEL was nearly identical to its effect in patients with LSS without LSEL. Recently, we also conducted a multicenter retrospective study on the efficacy of surgical treatment for LSEL. Unlike the results from Bayerl et al., ours demonstrated that, although surgical treatment significantly improved clinical symptoms in patients with LSEL, the outcomes of surgical treatment for LSEL were significantly inferior to therapeutic outcomes among patients with LSS without LSEL. The differences between the results in these two studies are conceivably due to differences in the definition of LSEL and the methods of statistical analysis between the groups. However, importantly, the results of both studies show that surgical treatment can be recommended for patients with LSEL. If chronic inflammation is involved in LSEL, then biopharmaceuticals that target inflammatory cytokines could be used to treat LSEL in the future. However, because of their adverse drug reactions and relatively high cost, biopharmaceuticals are unlikely to become a first-line treatment for LSEL. Presently, weight reduction, combined with surgical treatment, is likely the most reasonable treatment for LSEL with obesity or metabolic syndrome.

3.5. Lumbar spinal canal stenosis and metabolic syndrome

As mentioned above, LSEL has been demonstrated to be associated with lifestyle diseases and metabolic syndrome. As other research groups have reported, the whole LSS is also associated with lifestyle-related diseases, such as diabetes and hypertension. In a basic study, Luo et al. demonstrated that ligamentum flavum hypertrophy, a cause of LSS, was affected with hyperglycemia. Given that blood glucose is included in the diagnostic criteria for metabolic syndrome, these study results suggest that the whole LSS also can be associated with metabolic syndrome. Although the causal relationship remains unclear, it can be inferred that LSS and metabolic syndrome mutually affect each other.
LSS, which includes elements of locomotive syndrome and metabolic syndrome, can be viewed as an interaction between the two (Fig. 4). We and others have demonstrated that LSS was associated with locomotive syndrome and that surgical treatment for LSS was effective in decreasing the severity of locomotive syndrome. However, there has not yet been a direct assessment of (i) the extent to which LSS affects healthy life expectancy and (ii) whether surgical treatment for LSS extends healthy life expectancy. In the future, large-scale study data should be used to determine the relationship between LSS and healthy life expectancy.

Although LSEL has been recognized as being associated with lifestyle-related diseases and metabolic syndrome, a consistent definition or diagnosis of LSEL is still needed. A standardized LSEL definition would likely accelerate basic and clinical research. Furthermore, large-scale studies must be conducted to investigate the extent to which not only LSEL but also the whole LSS is involved with metabolic syndrome. Going forward, approaching LSS from the perspectives of both locomotive syndrome and metabolic syndrome may lead to novel methods for prevention and treatment of LSS. Conversely, research on LSS is anticipated to yield clues useful in developing treatments for both syndromes.

Conflicts of Interest: The author declares that there are no relevant conflicts of interest.

Ethical Approval: unnecessary

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