Obesity is a Risk Factor for Epidural Lipomatosis: A Meta-analysis

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Abstract

Background: Many studies have investigated the relationship between spinal epidural lipomatosis and obesity, no meta-analysis of studies have provided definitive evidence. To summarize the evidence of associations between obesity factors and spinal epidural lipomatosis (SEL) and to evaluate the strength and validity of these associations.

Methods: Electronic databases such as Wiley Online Library, PubMed, Embase, Cochrane Library were searched and manual retrieval of references, the time limit was from the establishment of the database to May 2020. The included literature was case-control studies that reported body mass index (BMI) and SEL correlation, and excluded any primary and secondary tumors or other compression diseases in the spinal canal. Methodological quality evaluations of the included studies were assessed using the bias risk assessment tool recommended by the Cochrane Guidelines. The RevMan 5.3 software was used for meta-analysis.

Results: Finally, ten studies were included for systematic review, all of which were observational studies with mixed bias risk. These studies involved 1,541 patients, with an average age of 54.9 to 73.6 years, and 60.2 percent of the participants were male. The sample sizes for the included studies ranged from 28 to 398. The results of meta-analysis showed that high BMI was one of the factors affecting SEL. All reviews had a high risk of bias, and the most common source of bias was that there was no strict unified case diagnosis standard between researches, and some studies (four items) did not clearly describe the confounders that they controlled.

Conclusions: We suggest that physicians should consider obesity as a factor leading to SEL, and to control body mass index actively should be considered as the preferred treatment strategy before surgical intervention is conducted.

Background

It is reported that the incidence of low back pain has been linked to obesity or high body mass index (BMI). The probability of people of overweight or obesity presenting with back pain has been reported as high as three times as likely as those who are not obese [1, 2]. The cause of back pain is often the compression of the spinal cord or nerves. Spinal epidural lipomatosis (SEL) is characterized by hypertrophy of unwrapped adipose tissue in the epidural space of the spinal canal, which most often occurs in the lumbosacral segment, followed by the thoracic segment, and the cervical spine is rare [3]. The clinical symptoms caused by SEL include low back pain, radiculopathy, claudication, cauda equina syndrome, etc. [4], which can also lead to failure of epidural analgesia [5]. The pathological manifestations are mostly mature adipocyte tissue, and there are few naive adipocytes with no biological characteristics of malignant tumors. Akhaddar et al [6] saw lobulated fat masses without sheath during the operation, speculating that it may be a hamartia tissue caused by the developmental disorder of the mesenchymal tissue in the spinal canal. Although SEL has been described as a rare disease by many scholars, the recent literature shows that the prevalence of SEL is between 6.2% and 8.6%, far more than previously reported [7]. This may be due to the combined effects of the development of imaging technology, the increase in obesity, and the aging of the population [8]. MRI is the most sensitive diagnostic method, and treatment strategies to relieve symptoms, including conservative treatment and surgical decompression have also been reported many times. However, the reasons for the formation and development of SEL are still unclear. There are currently several hypotheses to explain the pathological mechanism of epidural fat accumulation. The widely evaluated factors are the use of exogenous steroids and the endogenous steroid overproduction caused by endocrine diseases such as Cushing's disease, etc. [3, 9]. Fogel [3] suggested that exogenous steroids group represents 55.3% of cases, 3.2% of the patients are due to the existence of diseases that increase endogenous steroid secretion, and obesity-associated disease represents 24.5% of cases. Another patients without steroid hormone interference is considered to be idiopathic SEL, and these patients often have increased BMI; The high obesity rate of patients with idiopathic SEL suggests that obesity and SEL have a causal relationship. Other factors include that men are more likely to suffer from SEL than women [10, 11].

In some cases, weight loss alone was sufficient to alleviate the clinical symptoms and reduce the volume of epidural adipose tissue [12, 13]. Some scholars have suggested that for every percentage point increase in body weight, the likelihood of suffering from SEL increases by 13% [14]. Up to now, although many literature has shown that obesity has a clear correlation with SEL, most of them are isolated case reports and small sample case series. In general, whether obesity is an influencing factor is still controversial. Some reported studies showed that there is no significant correlation between SEL and BMI [15]. It has also been suggested that patients

with SEL have a high BMI [16, 17]. We hope to clarify the correlation between obesity and SEL through systematic search and review of the literature, to provide a reference for further discussion of the etiology and mechanism of SEL.

Methods

We conducted a systematic review of reviews in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (<http://www.prisma-statement.org/>).

Search strategy

A comprehensive search was conducted in the electronic databases such as Wiley Online Library, PubMed, Embase, Cochrane Library, the time limit was from the establishment of the database to May 2020. Taking PubMed as an example, the specific search strategy is shown in Table 1. In addition, the related review literature is consulted, and the references of the included literature are manually searched.

Table 1
Search strategy

Search Set	Terms	Results
#1	(((SEL[Title/Abstract]) OR ("spinal epidural lipomatosis"[Title/Abstract])) OR ("Idiopathic spinal epidural fat accumulation"[Title/Abstract])) OR ("Lumbosacral Epidural Lipomatosis"[Title/Abstract])) OR ("Epidural fat mass"[Title/Abstract])	1,521
#2	(((((((Obesity[Title/Abstract]) OR (Obese[Title/Abstract])) OR (Adiposity[Title/Abstract])) OR (Overweight[Title/Abstract])) OR ("body mass index"[Title/Abstract])) OR (BMI[Title/Abstract])) OR ("body fat"[Title/Abstract])) OR ("waist circumference"[Title/Abstract])	485,609
#3	#1 AND #2	89

Inclusion and exclusion criteria

We applied specific inclusion criteria in the selection process. (a) All studies that report the correlation between BMI and SEL (as a relative risk, or the assessment of sensitivity and specificity, or sufficient evidence can be obtained from the article); (b) The diagnosis of SEL is derived from the symptoms and signs displayed by the patient or from the imaging findings; (c) The experimental design was a cross-sectional study, a cohort study, a case-control experiment, and a prospective or retrospective analysis experiment.

The main exclusion criteria that were applied during the selection process were as follows: (a) Studies that participants have a long history of systematic steroid injections (≥ 3 months); (b) Participants have other pathological features: any primary or secondary tumor in the spinal canal, abscess, hemangioma, and epidural hematoma; (c) Non-chinese or English literature; (d) Repeated publications of the same data; (e) Animal experiments, meeting abstracts, reviews, etc.

Data extraction and quality assessment

Two reviewers independently screened the literature based on the established study selection and exclusion criteria. Initially identified the article title and abstract, read the full text of the remaining literature, and finally determine the included studies. The other two reviewers extracted the relevant research data of the included articles, including the first author of the article, year, country, sample size, experimental design, age and sex ratio of each group and medical history. Any differences in the above process shall be settled through consultation with a third reviewer. If the article data is incomplete, we will contact the author to obtain relevant experimental data. If the corresponding data is still not available, the article will be included in the systematic review for a qualitative description.

The methodological quality assessment of the included studies was conducted using the Newcastle-Ottawa Quality Assessment Scale (NOS), a bias risk assessment tool recommended by the Cochrane Guidelines. The NOS scale scoring system evaluates the quality of the included literature through the selection of study subjects, comparability between groups, determination of exposure factors and outcome indicators in case-control and cohort studies. Articles with a NOS score of six or more are eligible for meta-analysis, and studies with a score of seven or more are considered high-quality literature. The quality evaluation process was conducted independently by two reviewers. All disputes were settled through discussion with a third reviewer.

Statistic analysis

Meta-analysis was performed using RevMan 5.3 software provided by Cochrane Collaboration Network. Continuous variable data was expressed as mean difference (MD) and its 95% confidence interval (CI), and count data was expressed as Odds Ratio (OR) and its 95% CI. The heterogeneity test between the included studies was analyzed using I^2 statistics. If there was no heterogeneity or the heterogeneity was small ($I^2 \leq 50\%$, $P \geq 0.05$), the fixed-effect model was used to calculate the combined effect. On the contrary, if the heterogeneity is large ($I^2 > 50\%$, $P < 0.05$), analyze the source of heterogeneity. If there is only statistical heterogeneity, the random effect model is used to combine the effect sizes. Otherwise, only descriptive analysis is performed. $P < 0.05$ was considered statistically significant.

Results

Study selection

- According to the search strategy, search electronic databases, and manually search references, a total of 417 articles were initially searched. Through NoteExpress reference management software and manual check, according to the inclusion and exclusion criteria, we finally included ten articles for systematic review. There were 1541 patients, including 635 in the experimental group and 906 in the control group. Seven studies met the meta-analysis criteria. The literature screening process is shown in Table 2.

Characteristics of the include studies

- The basic characteristics of the included studies are shown in Table 3. There are one prospective study and nine retrospective studies involving case-control studies in five countries. Sample sizes ranged from 28 to 398. The average age of the participants ranged from 54.9 to 73.6. And 60.2% of the patients were male.

Table 3
The general characteristic of the included studies

Study	Year	Country	Design	Sample		Age		Gender		(male/ female)	Comorbidity(Medical history)
				SEL	non-SEL	SEL	non-SEL	SEL	Non-SEL		
Abe ¹⁸	2019	Japan	retrospective	30	72	73.1	73.6	24/6	38/34		HTN: 17/26 DM: 11/14 HL: 13/19
Fujita ¹⁷	2019	Japan	retrospective	60	228	73.6	70.1	42/18	146/82		HTN: 27/77 DM: 10/33 HL: 5/18 HD: 7/22
Simon ¹⁹	2019	Germany	prospective	38	51	70.0	72.9	22/16	28/23		HTN: 74% DM: 42% Hypothyroidism: 11%
Ishihara ²⁰	2018	Japan	retrospective	34	17	67.3	68.1	NA	NA		HTN: 20/9 DM: 7/2 HL: 10/4
Morishita ²¹	2018	Japan	retrospective	58	160	68.0	66.6	45/13	88/72		HTN: 26/53 DM: 17/32 HL: 14/30 HD: 7/12
Al-Omari ²²	2016	Jordan	retrospective	14	14	64	65	6/8	7/7		DM: 2/3 Hypothyroidism: 2/2 Smoking: 6/5 Endocrinopathy: 0/0
Yildirim ¹⁴	2016	America	retrospective	199	199	54.9	54.9	133/66	133/66		DM: 72/45 Smoking: 131/104 Endocrine condition: 3/1
Fujita ²³	2016	Japan	retrospective	16	15	71.5	70.3	1/15	14/1		NA
Park ²⁴	2016	korea	retrospective	116	116	65.2	55.8	62/54	65/51		Hypothyroidism: 2.6% Exogenous corticosteroid use: 6.0% Cushing syndrome: 3.5%
Jaimes ²⁵	2014	America	retrospective	70	34	61.7	61.8	43/61	43/61		NA

Note: HTN, hypertension; DM, diabetes mellitus; HL, Hyperlipidemia; HD, Hyperlipidemia; NA, not mentioned

Risk of bias

- The methodological quality scores included in the study are shown in Table 4. There were seven articles of high quality, one article of medium quality and two articles of low quality. Retrospective experiments usually have a higher risk of recall bias.

Table 4 Quality evaluation according to the Newcastle-Ottawa Quality Assessment Scale

Study	Selection ⁴	Comparability ²	Exposure ³	Total score ⁹
Abe ¹⁸	4	2	2	8
Fujita ¹⁷	4	1	2	7
Simon ¹⁹	2	1	3	6
Ishihara ²⁰	4	2	2	8
Morishita ²¹	3	2	2	7
Al-Omari ²²	2	1	2	5
Yildirim ¹⁴	3	2	2	7
Fujita ²³	4	2	2	8
Park ²⁴	3	1	2	6
Jaimes ²⁵	4	1	2	7

Meta-analysis

Seven literature met the meta-analysis criteria. The statistical results show that the heterogeneity between the initial studies is significant, the source of heterogeneity may be that there is no uniform standard for the diagnosis of SEL in various studies. Four studies [17–20] defined SEL as an EF/SpiC index greater than 0.4 or 0.6, four reviews [21–24] diagnosed as SEL based on MRI showing enlarged fat tissue compressing the dura sac, two studies [14, 25] obtained the diagnosis basis based on clinical symptoms and signs and MRI imaging but did not clearly explain. After excluding articles by the one-by-one elimination method, the heterogeneity between studies was significantly reduced ($I^2 = 17\%$). The results suggest a positive correlation between SEL and BMI (Fig. 1: Mean difference of BMI between the SEL group and the non-SEL group. SD standard deviation, CI confidence interval, IV inverse variance). Under the fixed-effect model, the MD given by the meta-analysis is 1.37, 95% CI [0.81, 1.92], indicating that there is a positive correlation between the observed variable and the outcome variable. Still the strength of the correlation is weak.

Discussion

- With the aging of the population, the improvement of social and economic level, and the increase of the number of people who are overweight, obesity-related issues have become a research hotspot. SEL is one of the representative diseases of fat ectopic deposition. Because the morbidity of the disease is relatively low, clinical studies of large samples are almost rare. Asymptomatic SEL is generally only found during a health examination. At a same time, symptomatic SEL affects the quality of life of patients with varying degrees of low back pain or cauda equina syndrome. The diagnosis of SEL is most sensitive to MRI, which shows adipose tissue in high signal strength. Kuhn et al [26] proposed a "Y" sign as a characteristic image manifestation of SEL on MRI, which means that the fat tissue oppresses the dura mater and presents a "Y" shape. But generally, only severe cases have this kind of imaging performance. Treatment strategies were selected according to different etiologies, for example, reducing or stopping the injection of epidural steroid hormones, treating Cushing's disease to reduce endogenous steroids, reducing fat and weight. When conservative treatment fails, surgical decompression treatment is also an option, and patients can generally get better symptom relief.
- Obesity has been reported to be one of the most risk factors for a range of metabolic disorders such as coronary heart disease, hypertension, type 2 diabetes, cancer, respiratory disease and osteoarthritis [27]. It can be seen that obesity affects the occurrence and development of many diseases. Yildirim's [14] research indicates that spinal lipomatosis is related to visceral fat accumulation (metabolic syndrome). Al-Khawaja [28] also suggested that 70% of SEL patients are obese. Among non-exogenous steroid-related diseases, obesity is considered to be the most common cause of SEL. Whether there is a correlation between obesity and epidural lipoma disease, no research has been concluded yet.

- The results of this study showed that SEL was positively correlated with BMI, although the correlation was weak. We believe that the pathological mechanism of obesity leading to epidural fat deposition may be the disorder of glucose and lipid metabolism firstly. Based on the close relationship between visceral fat accumulation and abnormal lipid metabolism [29–31], it is speculated that SEL may be another site of systemic fat accumulation caused by abnormal lipid metabolism; Secondly, high BMI and obesity are considered as a chronic inflammatory state, which may be one of the causes of excessive growth of adipose tissue in the spinal canal. Hypertrophic adipocytes continued to express pro-inflammatory cytokines, tumor necrosis factor TNF- α , interleukin-1 β , etc. High levels of adipocytokines (such as adiponectin and leptin), are involved in energy metabolism and inflammation regulation. These factors are also expressed in the adipose tissue of SEL patients with hyperplasia [32]. Fujita [20] also confirmed the increased expression levels of inflammatory cytokines such as tumor necrosis factor- α and interleukin-1 β in the adipose tissue of patients with SEL hyperplasia. Besides, we hypothesized that ectopic lipid deposition is also regulated by genes or molecules: Khan et al [33] reported that mice lacking collagen VI (mainly expressed in adipose tissue) might experience unrestricted expansion of adipose tissue and a significant increase in insulin sensitivity under a high-fat diet. It shows that when the fat stored in adipose tissue is reduced, it will cause the lipid to be stored in non-adipose tissue (e.g., liver, skeletal muscle, pancreas, etc.), and affect the metabolic function of these organs. Leptin is synthesized and secreted by white adipose tissue. Its physiological role is to bind to the leptin receptor in the hypothalamic appetite center, which plays a role in inhibiting food intake, increasing energy consumption, and inhibiting fat synthesis. Therefore, the leptin regulatory system is considered to be one of the endocrine mechanisms that play a central role in body weight, body fat distribution, and metabolic diseases; Leptin expression is reduced, and the expression of the cellular inflammatory factor adiponectin is reduced, resulting in abnormal body fat distribution [34]; In addition to obesity, other factors may also lead to abnormal fat distribution and cause the occurrence of SEL, such as deformed osteoarthritis, congenital spinal stenosis, and the use of lipase inhibitors, there is insufficient evidence-based evidence [35–39].
- So is the development or postoperative relapse of SEL related to the progression or status of obesity? Some scholars pointed out that the number of involved vertebral levels and obesity are strongly correlated, and weight loss may reduce the number of vertebral segments of SEL lesions [40, 41]. It can be seen that the persistent state of obesity should also be considered as an influencing factor of SEL.
- However, there are limitations in our study: the first is that most of the included studies are retrospective observational studies. Inevitably, the results of comprehensive analysis of various studies can only provide weak clinical evidence to prove the relationship between variables; In addition, we have not collected information about the percentage of body fat, these can make up for BMI indicators can only provide simple evidence of obesity. In addition to BMI being used to define obesity, internationally, there are also body fat ratio, waist-to-hip ratio, and visceral fat ratio. In a given BMI category, differences in the average percentage of body fat among ethnic groups may also contribute to some of the differences observed. For example, Asians generally have higher levels of fat compared to Caucasians for the same BMI [42]. Therefore, their independence and potential confounding effects remain unknown. Besides, there are few relevant case-control studies published at domestic and overseas, our analysis may have a higher risk of mixed bias. However, the results of this study still have particular reference value. In the future, more high-quality randomized controlled trials are still needed to determine the clear correlation between BMI and SEL.

Conclusions

- The exact mechanism of SEL development is difficult to determine, suggesting that large demographic studies with appropriately selected control groups are needed to establish pathogenic factors. Our results are only a reference for the etiology of SEL or provide a new perspective to study ectopic lipid deposition. We suggest that surgeons should consider obesity as a possible factor leading to SEL and take active control of BMI as the preferred treatment strategy before considering surgical intervention, to reduce the mental and economic burden of patients.

Abbreviations

BMI, body mass index; SEL, spinal epidural lipomatosis; MRI, Magnetic Resonance Imaging; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; NOS, Newcastle-Ottawa Quality Assessment Scale; MD, mean difference; CI, confidence interval.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Both HY and BZ were responsible for the content and organization of the manuscript, LH and MS were take charge of the search parameters of this systematic review of reviews. BZ did the majority of the writing of the manuscript, with HY, LH and MS contributing significantly to the discussion and recommendations. All authors take full responsibility for the content of this manuscript.

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Figures

Figure 1

Mean difference of BMI between the SEL group and the non-SEL group. SD standard deviation, CI confidence interval, IV inverse variance