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Controversies in Spine Care

Is there an association between lumbosacral epidural lipomatosis and lumbosacral epidural steroid injections? A comprehensive narrative literature review ☆

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ABSTRACT

Background: Exogenous systemic steroid exposure is a well-established risk factor for spinal epidural lipomatosis (SEL), however the association between lumbosacral epidural steroid injections (LESIs) and lumbosacral epidural lipomatosis (LEL) is generally regarded as poorly understood. Our objective was to investigate the rationale and the evidence implicating LESI(s) as a potential cause of LEL as well as the evidence related to use of LESI(s) as a potential pain relieving treatment option for radicular pain in the setting of LEL.

Methods: PubMed, Embase, Google Scholar, OVID were searched from inception until April 2021. Three investigators identified literature that provided original descriptive patient clinical data attributing the development/progression of LEL to LESI(s) or described the use of LESI(s) as a pain relieving modality for radicular pain in the setting of LEL.

Results: Fourteen publications were included for review. Overall, the current level of evidence is of low-quality. There are significant methodological gaps on this subject matter and many studies do not account for confounding variables independently associated with LEL.

Conclusions: This review has identified substantial limitations in the literature regarding that which is truly known regarding LESI(s) and LEL, as well as conservative management overall. To provide a well-rounded perspective, we synthesized literature as it pertains to: 1) current knowledge regarding SEL, notable associations and potential implications for corticosteroid exposure; 2) corticosteroid exposure and lipoatrophy; 3) current management recommendations for SEL and 4) areas for future focus. Although LESI(s) have been associated with LEL in the literature, presently due to a lack of rigorous, high-quality studies, the presence or absence of an independent causal relationship between LESI(s) and LEL cannot be stated with confidence.

Background

Spinal epidural lipomatosis (SEL) is an abnormal, excessive accumulation of normal unencapsulated adipose tissue in the spinal epidural space which results in narrowing of the spinal canal due to hypertrophy of mature adipocytes (Fig. 1a,1b) [1,2]. It is estimated to be prevalent in up to 6.26% of patients presenting with symptomatic spinal stenosis, with an annual incidence of 2.5% [2]. The most commonly affected spinal segments include the thoracic and lumbar spine [1,2]. Lumbosacral epidural lipomatosis (LEL) may occur concomitantly with or independently of osteoligamentous degenerative lumbar spinal stenosis. LEL may present as an incidental finding or can result in symptoms [2–21]. When substantial, LEL may result in non-specific back pain with or without radicular symptoms, neurogenic claudication, or in severe cases, cauda equina syndrome due to direct mechanical compression resulting in indirect vascular compromise, leading to venous engorgement and ischemia [2,3,11].

SEL was first reported in 1975 by Dr. Michael Lee after the administration of corticosteroids to prevent renal transplant rejection [4]. In 2005, Fogel et al., defined four categories of SEL, based on predisposing etiologies which include: 1) exogenous steroid use, 2) obesity, 3) endogenous steroid excess, and 4) idiopathic [7]. There is inconsistency in the usage of the idiopathic categorization, however, this generally refers to the development of SEL in non-obese patients without a known

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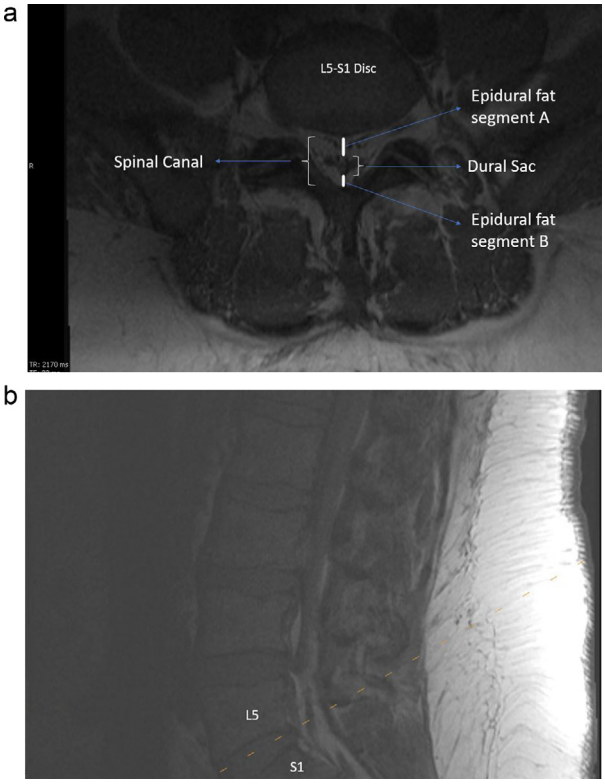

Fig. 1. Representative images of patient (43 year old male, BMI-51.61kg/m^2) presenting with low back pain and bilateral lower extremity neurogenic claudication. **A**: Axial PD weighted sequence showing prominence of the ventral (segment A) and dorsal epidural fat (segment B) at the L5-S1 level, resulting in dural sac compression and characteristic "Y sign" **B**: Midline Saggital T1 weighted sequence again demonstrating prominent ventral and dorsal epidural fat, most notable at the L5-S1 level, compressing the dural sac.

predisposing underlying risk factor or disorder [3,8]. Although the multifactorial pathophysiology of epidural adipose tissue hyperplasia in SEL is not fully understood, recent investigations have focused on the association between the metabolic syndrome and SEL [5,18,22-27].

Most of the literature demonstrating an association between SEL and long-term exogenous steroid use revolves around systemic utilization for purposes such as the prevention or treatment of post-organ transplantation rejection, various autoimmune diseases, chronic obstructive pulmonary disease (COPD), nephritic syndromes, asthma, radiation pneumonitis, in the setting of cancer-related care and even anabolic steroid (without glucocorticoid) use [1-3,6-8,12,24]. Pediatric SEL cases have also been reported [28,29].

Although exogenous systemic steroid use is widely accepted as the most significant risk factor for developing SEL, the literature regarding the association of lumbosacral epidural steroid injections (LESIs) and LEL is less robust and somewhat conflicting [2,7,8,10-21]. For example, after an extensive literature review in 2005, Fogel et al., determined that 55.3% of all reported cases of SEL (104 cases total) were associated with long-term steroid use, however, only 3 of the cases were attributed to multiple epidural steroid injections [7]. Prior to and since this study, literature reports have described the use of LESI(s) as a treatment for LEL-related radicular symptomatology [20,21]. Alternatively, several publications have attributed the development or progression of LEL to LESI(s) [2,9,10-19]. Anecdotally, there is significant heterogeneity in interventional spine practice patterns and associated variance in willingness to perform LESI(s) in patients presenting with radicular pain syndromes in the setting of LEL.

Therefore, the objective of our investigation was to comprehensively review the literature to provide clarity regarding the association between LEL and LESI(s). We provide this synthesis of the data in order to aid clinical decision making regarding the use of LESI(s) in the setting of LEL, as well as to guide future research.

Methods

The present comprehensive literature review was conducted according to methodology described by Grant and Booth [30].

Information Sources and Search Strategy

Studies were identified by searching the electronic databases PubMed, Embase, Google Scholar, OVID and by reviewing the reference lists of retrieved articles. No restrictions were applied regarding publication dates. The search was performed from database inception until April 25, 2021. The aforementioned electronic databases were searched for the following Medical Subject Headings (MeSH) terms and keywords: ("lumbar epidural lipomatosis," "spinal epidural lipomatosis") independently AND with ("lumbar epidural injection," "lumbar epidural steroid injection," "lumbar epidural corticosteroid injection," "epidural injection," "epidural steroid injection," "steroid injection"). The search strategy was not limited to specific study parameters or outcomes. The search was limited to studies written in English.

Study eligibility criteria & quality assessment

The eligibility criteria allowed for inclusion of medical literature that reported original descriptive clinical data describing patient(s) that underwent LESI(s) as a pain-relieving intervention and subsequently developed LEL or demonstrated temporally associated symptomatic progression of pre-procedural LEL. Additionally, studies providing original descriptive clinical data of patients with lumbosacral radicular symptomatology in the setting of LEL and who received LESI(s) as a pain-relieving intervention with benefit were included. Given that there is a relative paucity of literature evaluating the association between LEL and LESI(s) exposure, case reports and case series were eligible for inclusion in addition to any available case-controlled, cross-sectional studies and randomized controlled trials.

Essays, commentaries, editorials, systematic reviews, and publications that did not provide original descriptive patient clinical data demonstrating potential evidence of a relationship between LESI(s) as a causative agent or treatment modality related to LEL were excluded from analysis. However, all pertinent studies related to LEL were reviewed to generate a robust discussion on this subject matter.

The authors reviewed and scored the quality of the available studies utilizing the *Levels of Evidence For Primary Research Question As Adopted by the North American Spine Society January 2005** and graded the recommendations provided utilizing the *Grades of Recommendation for Summaries or Reviews of Studies As Adopted by the North American Spine Society January 2005** [31,32].

Selection process and data extraction

Three of the authors conducted independent literature searches from titles to full text review. Data extraction was performed in duplicate. All reviewers are fellowship-trained practicing spine interventionalists and have completed formal certificate-granting courses in evidence-based medicine. The initial screening was completed by review of title and abstract, and manuscripts that did not meet inclusion criteria were excluded. By simple spreadsheet, each independent reviewer initially categorized the studies as "include," "possibly include," or "do not include." Disagreements for inclusion were resolved by consensus amongst these three authors, or if necessary, consultation with the remainder of the authorship team. If available, the full text of studies determined to be potentially eligible were reviewed.

The included articles were organized into data collection forms which detailed: author, year, digital object identifier, journal, and country of origin. The relevant information evaluated included: study design, number of patients, type and number of epidural spinal interventions, type of corticosteroid and dosage administered, timing between injections, independent predisposing associations/risk factors of LEL, use of a published grading scheme to describe LEL pre-and post-procedure, and the study authors' conclusions.

Results

Characteristics of included studies

The search yielded a total of 321 articles. After assessing titles, abstracts, and bibliographies and after removal of duplicates, 14 publications that met inclusion criteria remained (Tables 1-3) [2,9-21]. Ten publications were either case reports or small patient cohort case series; two were retrospective case control series, and two articles were cross-sectional retrospective chart reviews. Of note, search results yielded no randomized controlled trials or prospective case-controlled studies. Of the 14 articles included, there were 10 publications from the US, 2 publications from Korea, and 1 publication each from Malaysia and France.

General synopsis of studies

Twelve of the 14 articles investigate and/or suggest LESI exposure as a potential cause of LEL [2,9-19]. Two of the 14 articles describe LESI as a potential treatment modality for symptomatic relief of lumbosacral radicular pain and associated disability in the setting of LEL [20,21].

Number of patients/ size of studies

Of the 12 publications examining the relationship between patients receiving LESI(s) and subsequent development or progression of LEL, 7 of the articles were case studies involving a single patient, while 1 study implied an association in two patients [10-16,19]. Of the remaining 4 publications; Jaimes et al., conducted a retrospective chart review of 856 patients. The authors determined that 68 of 70 patients found to have LEL on imaging previously received LESI(s), and the average number of LESI(s) delivered was 1.8 ± 1.5 [17]. In the convenience sample control group of 34 patients without LEL, the average number of LESI(s) performed was 1.00 ± 0.0, and there were no patients who received more than one [17]. The authors determined that the number of LESI(s) provided was a statistically significant independent factor utilizing a logistic regression model (P<0.01). The odds of having epidural lipomatosis equaled 66% after two injections and 98% after three injections, approaching 100% with further injections, independent of BMI [17]. One LESI did not increase the patient's odds of developing LEL [17].

Yildrim et al. performed a retrospective chart review of the 199 patients with LEL [18]. The authors found that of the 199 patients with MRI confirmed LEL, 53 patients previously received LESI(s). Conversely, in their matched control group of 199 patients without LEL, 55 of the 199 patients previously received an LESI(s), indicating no association between LESI(s) and the development of LEL (OR 0.95, 95% confidence interval [CI] 0.60-1.49, P=0.816) [18]. However, Yildrim et al. noted that their study may have been underpowered as the number of LESI(s) were not quantified [18]. Malone et al. performed a retrospective chart review and determined that 17 of the 52 patients with imaging confirmed LEL previously received an LESI(s) and concluded that LESI(s) maybe another associated risk factor for LEL [2]. There was not a matched control group [2]. Theyskens et al. reviewed the MRI records of 28,902 patients (of which 12,621 were lumbosacral studies) and identified SEL in 731 patients (overall prevalence of SEL=2.5%) [9]. The authors determined through multivariate analysis that, amongst other factors epidural steroid injections (ESI(s)) were associated with SEL (OR:3.48, 95% CI:2.82-4.30, P<0.001) [9].

In regards to the 2 publications describing LESI(s) as a treatment option for radicular pain in the setting of LEL, a total of 5 patients received LESI(s) with reported benefit [20,21].

LESI Approach, number of LESI(s), corticosteroid type and dosage

Eight of the 12 publications that assess and/or indicate LESI(s) as a potential cause of LEL do not clearly describe the injection approach utilized [2,9-12,13,16,18]. Of the remaining 4 studies, 3 utilized an interlaminar epidural steroid injection (ILESI) approach and the remaining study utilized a caudal approach [14,15,17,19]. Three of the 12 publications did not provide details regarding the number of LESI(s) that each individual patients received [2,9,18]. In the remaining 9 publications, the number LESI(s) any single patient received ranged from 1 to 103 LESI(s) [10-17,19]. Four of the 12 publications do not describe the type or dose of corticosteroid utilized[2,9,18,19] Of the remaining 8 publications, all utilized particulate corticosteroid, either methylprednisolone acetate (Depo-Medrol) or triamcinolone acetate (Kenalog), with dosages ranging from 40 mg to 120 mg per injection [10–17]. Notably in the Jaimes et al. study that determined the odds of having LEL were 66% and 98% after two and three LESI(s) respectively, a particularly high dose of 120 mg of methylprednisolone per LESI was utilized [17].

In the 2 publications describing LESI as a treatment modality for radicular pain in the setting of LEL, a transforaminal epidural steroid injection (TFESI) approach was utilized in both publications on a total of 5 patients [20,21]. The number of injections received ranged from 1 to 3 TFESI(s). Botwin et al. performed the injections with triamcinolone 80 mg per injection and McCormick et al. used dexamethasone 16 mg per injection [20,21].

Timing between LESI(s)

In the publications suggesting LESI(s) as a possible cause of LEL in patients that received multiple injections, the timing between each individual injection was clearly delineated in only 1 case report [12]. However, 4 publications describe the timeframe from initial injection to the last of multiple injections received, which ranged from a few weeks to 12 years [10,11,13,19]. In the remaining studies, the timing between injections as well as the overall time frame from initial to last injection when more than two injections were performed was not described [2,9,16-18]. Some reports have suggested LESI(s) as a cause of LEL after only one injection [14–16].

Of the 2 publications referencing LESI(s) as a treatment modality for radicular pain in the setting of LEL, only 1 of the 2 reports included multiple injections performed in their cohort [21]. The timing between injections ranged from 2 to 3 weeks and the highest number of LESI(s) performed in any single patient was three [21].

Possible confounding patient risk factors

In the publications suggesting LESI as cause of LEL, several confounding risk factors that have been independently associated with LEL were identified. Many of the publications did not fully take this into consideration. Overall, the majority of the patients determined to have LEL were male, which has been described an as independent risk factor for developing LEL [1-3,5,8-10]. Additionally, many of the patients had additional metabolic risk factors that have independently been associated with LEL, including obesity, diabetes mellitus and elevated triglycerides [2,10,12,14,15-17,18].

As an example,Yildrim et al. determined that 66.8% of those found to have LEL on imaging were men and when compared to matched controls without LEL on imaging, LEL patients were more likely to have a history of smoking (OR 1.90, 95% CI 1.23-2.94, P=0.004], diabetes mellitus type 2 (OR 2.17, 95% CI 1.33-3.56, P=0.002) and a significantly

Table 1
Summary of Studies-Lumbosacral Epidural Steroid Injections (LESIs) as Potential Cause of Lumbosacral Epidural Lipomatosis (LEL)

Reference	Design	# of Patients Total	# of Patients that Received ESI (s)	Approach technique and # of Epidural Steroid Injections (ESIs)	Type of Corticosteroid Used & Dosage per injection	Timing Between LESI(s)	Possible Confounding LEL Associations Described?	Pre-Procedure MRI Grade of EL? Use of published grading system?	Post-Procedure MRI Grade of EL? Use of published grading system?	Conclusion & Level of Evidence
Roy-Camile et al. (1991) [10]	Case Series	2 patients	1 patient: 64 yo F	Approach: ND # of ESIs: 103 for MS misdiagnosed 13 years prior.	Methylprednisolone acetate (40mg)	ND *Received for 12 years.*	hyperglyceridemia	No grade.	No grade. "irregular compression of the dura from T10 to L2"	"Rare steroid complication must be known" **Level V**
McCullen et al. (1999) [11]	Case Report	1 patient	1 patient: 61 yo F	Approach: ND # of ESIs: 13	Depo-Medrol 1200mg total over 4 years	8 ESIs between 1991-1993 5 ESIs in 1995	ND	No grade. "Small accumulation of epidural fat ventral and caudal to L5-S1 without nerve compression"	No grade. "A significant increase in epidural fat was observed circumferentially at L5-S1, L4-L5, and to a lesser extent at L3-L4"	"One must consider the diagnosis of SEL in a patient with neurologic symptoms during or after a period of steroid treatment." **Level V**
Sandberg et al. (1999) [12]	Case Report	1 patient	1 patient: 68 yo M	Approach: Inj(s) 1,2 ND. Inj(s) 3-5 performed at the "L2-L3 interspace." # of ESIs:5	Inj #1,2: Depomedrol (120 mg) per inj. Inj# 3-5: (80 mg Kenalog) per inj.	1 month between inj. 1 &2. 3 years between 2nd & 3rd inj. 1 month in between inj(s) 3-5.	Male Sex "Denied any significant medical history or any previous systemic glucocorticoid treatments."	No grade. "An MRI scan revealed lumbar stenosis from L4 to L5."	No grade. After inj #2 underwent repeat MRI Scan 3 years later, unchanged degenerative finding from initial study, but now with mild LEL. MRI performed 3 months after 5th injection, "substantial interval increase in epidural lipomatosis from L2 to L5."	Possible complication of not only systemic glucorticorticoid therapy but also local epidural corticosteroid injections. Mechanism not yet established. **Level V**
Kim et al. (2009) *Abstract only available** [13]	Case Report	1 patient	1 patient: 59 yo F	Approach: ND # of ESIs: 19	Triamcinolone	ND *Received for 3 years*	ND	No grade	No grade. "Extensive epidural fat deposition compressing cauda equina from L3 to S1."	"Therefore, we concluded that multiple ESIs caused iatrogenic Cushing's syndrome and SEL." **Level V**

(*continued on next page*)

Table 1 (*continued*)

Reference	Design	# of Patients Total	# of Patients that Received ESI (s)	Approach technique and # of Epidural Steroid Injections (ESIs)	Type of Corticosteroid Used & Dosage per injection	Timing Between LESI(s)	Possible Confounding LEL Associations Described?	Pre-Procedure MRI Grade of EL? Use of published grading system?	Post-Procedure MRI Grade of EL? Use of published grading system?	Conclusion & Level of Evidence
Tok et al. (2011) [14]	Case Report	1 patient	1 patient: 45 yo M	Approach: Interlaminar # of ESIs: 1 * *Multilevel facet joint corticosteroid injections performed 2 weeks prior. Also underwent bilateral multilevel RFA 3 weeks post LESI. Does not mention if steroid utilized post ablation.*	Triamcinolone Acetate (40mg)	NA	Male Sex, DM, Obese (BMI 32 kg/m2), Hypertension	No grade provided but does mention absence of excessive fat deposition. Does not mention how far in advance of procedure MRI was completed.	No grade provided. 3 months post ESI Y- shaped configuration of thecal sac with excess epidural fat noted.	"SEL is a recognized complication due to the administration of ESI injection even after a single injection." **Level V**
Danielson et al. (2011) [15]	Case Report	1 patient	1 patient: 56 yo M	Approach: Caudal # of ESIs: 1	80 mg Triamcinolone Acetate (40mg/mL)	NA	Male Sex, Overweight (BMI 29 kg/m2),No prior systemic steroid use	No grade. Performed 8 months prior to ESI. Showed L5-S1 central to left paracentral disk protrusion with slight left S1 nerve root displacement	No grade. Performed 3 months post ESI. New focal area of increased posterior epidural adipose tissue causing thecal compressin at the L5-S1 level.	"Further research is needed to better clarify the true effect of an ESI on spinal epidural adipose and how to treat SEL. Questions of whether preexisting SEL should be a contraindication to ESIs also needs to be further studied, especially in setting of a prior study that showed patients benefiting from ESIs for symptomatic SEL." **Level V**

(*continued on next page*)

Table 1 (*continued*)

Reference	Design	# of Patients Total	# of Patients that Received ESI (s)	Approach technique and # of Epidural Steroid Injections (ESIs)	Type of Corticosteroid Used & Dosage per injection	Timing Between LESI(s)	Possible Confounding LEL Associations Described?	Pre-Procedure MRI Grade of EL? Use of published grading system?	Post-Procedure MRI Grade of EL? Use of published grading system?	Conclusion & Level of Evidence
Choi et al. (2012) [16]	Case Series	2 patients	2 patients: Patient 1:(67 yo M) Patient 2: (64 yo M)	Patient 1: Approach: ND # of ESIs: 2 Patient 2: Approach: ND #of ESIs: 1	40 mg Triamcinolone Acetate per injection.	Patient 1: ND Patient 2: NA	Patient 1: Male Sex, Hypertension, Prior lumbar surgery, No history of steroid intake, Not obese Patient 2: Male Sex, No history of steroid intake, Not obese	Patients 1,2 No grade provided, although does mention minimal LEL present	Patient 1, 2 No grade provided. Reports extensive epidural lipomatosis in both cases. 6&5 months respectively after ESI(s), LEL progressed rapidly.	"These cases of the SEL caused by epidural steroid injection progressed exceptionally rapid and compromised neural structure." "The pathogenesis of SEL with epidural steroid injection is unknown." **Level V**
Jaimes et al. (2014) [17]	Retrospective Case Control	856 patients referred to clinic for lower back pain, 70 of which found to have LEL on MR imaging review. Control group w/o LEL included 34 patients based on convenience sampling.	"There were two patients in EL group who did not receive any ESI." 68 patients received ESI based on this statement. Average Age 61.8 ± 2.8 yo	Approach: 2 person loss of resistance interlaminar technique. # of ESIs: The average number of ESI delivered in the patients with no EL was 1.0 ± 0.0, and there were no patients who received more than one. The average number of ESI delivered was 1.8 ± 1.5 to the EL group	120 mg Depomedrol per injection	ND	Obesity (*Average BMI for patients with EL 36 ±0.9* kg/m2) Elevated Triglycerides (*Average Triglycerides patients with EL 250 ± 30*)	No grade	Grade performed on a "visual basis" of mild, moderate or severe. Does not use published grading system. Out of 70 EL patients: 46: mild 16: moderate 8: Severe. Does not specify further in terms of number of ESIs per patient or on average # of ESIs in each subcategory.	"Absence of ESI deliveries or 1 ESI delivery did not increase the patient's odds of developing EL. After 2 ESIs the odds of developing EL was 66%. After 3 ESIs the odds of developing EL was 98%. 4 or more ESIs increased odds approaching 100%." The incidence was not studied. **Level IV**

*F- female; *M- male, *yo- years old, *MRI- Magnetic Resonance Imaging, *Tx- treatment. * ESI(s)- epidural steroid injection(s), Inj(s)- injections(s), *ND-not described. * NA- not applicable. *BMI- body mass index.* DM- Diabetes Mellitus, *W/o- without.

Table 2
Summary of Studies-Lumbosacral Epidural Steroid Injections (LESIs) as Potential Cause of Lumbosacral Epidural Lipomatosis (LEL) continued.

Reference	Design	# of Patients Total	# of Patients that Received ESI	Approach technique and # of Epidural Steroid Injections (ESIs)	Type of Corticosteroid Used & Dosage per injection	Timing Between LESI(s)	Possible Confounding LEL Associations Described?	Pre-Procedure MRI Grade of EL? Use of published grading system?	Post-Procedure MRI Grade of EL? Use of published grading system?	Conclusion & Level of Evidence
Yildrim et al. (2016) [18]	Retrospective Case Control	199 patients total with LEL. Control group w/o LEL included 199 patients based on convenience sampling.	LEL group: 53 patients. Control group w/o LEL: 55 patients. Average age of patients in LEL group: 54.9 yo, 66.8% men	Approach: ND # of ESIs per patient or average # of ESIs per patient: ND	ND	ND	DM, Previous Oral Steroid Use, Obesity (median BMI 36.7 kg/m2), Smoking, Male Sex Predominance	No grade	No grade provided. Any evidence of EL within at least 1 level of the lumbosacral spine. Used exact terminology from radiologist note.	" We were unable to quantify the number of epidural spine injections, which may have limited our conclusions as we found no association between epidural spine injections and development of EL" **Level IV**
Theyskens et al. (2017) [9]	Cross-Sectional Retrospective Chart Review	731 out of 28,902 patients found to SEL on MRI (2.5%). 12,621 (44%) were lumbosacral MRIs.	Incidental SEL (N=168) ESI Mean (95%CI)=16(10) SEL with symptoms(N=526) ESI Mean (95% CI)=97(18) Symptomatic SEL(N=37) ESI Mean (95% CI)=4(11) p Value .014	Approach: ND # of ESIs per patient or average # of ESIs per patient: ND	ND	ND	Other factors associated SEL with Symptoms Male Sex, Systemic Steroids, BMI>30 kg/m2, Older Age, Higher Charlson Comorbidity Index, Cushing Syndrome or Disease Only factor associated with Symptomatic SEL Cushing 's Syndrome or Disease	No grade	No grade. "We did not correlate the extent of SEL with clinical symptoms."	Factors associated with overall SEL (asymptomatic and symptomatic) in multivariate analysis: Older Age (OR 1.01) Higher Modified Charlson Comorbidity Index (OR:1.10) Male Sex (OR:2.01) BMI>30 (OR:2.59) African American Race(OR:1.66) Systemic Corticosteroid Use (OR: 2.59) Epidural Corticosteroid Injections (OR:3.48, p<.001) **Level IV**
Malone et al. (2017) [2]	Cross-Sectional Retrospective Chart Review	52 patients (21 Females) (31 Males)	17 patients	Approach: ND # of ESIs per patient or average # of ESIs per patient: ND	ND	ND	Obesity, Systemic Steroids, DM, Prior lumbar surgeries, Male sex predominance	No grade	Borré et al. grade 31 % of Grade 2 LEL pts had ESI 35% of Grade 3 LEL pts had ESI	"ESI(s) maybe another associated risk factor for SEL, but further research is needed." **Level IV**
Silcox et al. (2018) [19]	Case Series	2 patients	1 patient: 51 yo M	Approach: Interlaminar #of ESIs: 3	ND	3 injections over a 5 week period.	Obesity (BMI-34 kg/m2), Male Sex, No history of anabolic or corticosteroid use	Borré et al. grade Grade 0	Borré et al. grade Grade I (borderline Grade II). Performed 3 months after final ESI and 5 months after initial MRI.	"Demonstrates a possible association between steroid injections and spinal epidural lipomatosis. An association of this kind has not been established; further research is needed to determine the significance." **Level V**

*F- female; *M- male, *yo- years old, *MRI- Magnetic Resonance Imaging, *Tx- treatment. * ESI(s)- epidural steroid injection(s), Inj(s)- injections(s), *ND-not described. * NA- not applicable. *BMI- body mass index.* DM- Diabetes Mellitus, *W/o-without.

Table 3
Summary of Studies- Describing Lumbosacral Epidural Steroid Injections (LESIs) as a Potential Treatment Modality for Radicular Pain in Setting of Lumbosacral Epidural Lipomatosis (LEL)

Reference	Design	# of Patients Total	# of Patients that Received ESI	Approach technique and # of Epidural Steroid Injections	Type of Corticosteroid Used & Dosage per injection	Timing Between LESI(s)	Possible Confounding LEL Associations?	Pre-Procedure MRI Grade of EL? Use of published grading system?	Post-Procedure MRI Grade of EL? Use of published grading system?	Conclusion & Level of Evidence
Botwin et al. (2004) [20]	Case Report	2 patients	2 patients: Patient 1 (78 yo F) Patient 2 (68 yo M)	Patient 1 Approach: TFESI # of ESIs: 1 Patient 2 Approach: TFESI # of Inj: 1	Kenalog 80 mg per injection	NA	Patient 1: Overweight, BMI (28.2 kg/m2), Hypothyroidism, Hypertension Patient 2: Obesity (34.2kg/m2), Male Sex, Hypertension	No grade	No post procedure MRI documented.	ESI can be beneficial for temporary relief of radicular pain secondary to LSS associated with epidural lipomatosis. More research is needed to establish causal relationship between SEL and ESI. **Level V**
McCormick et al (2013) [21]	Case Series	3 patients	3 patients Patient 1 (79 yo M) Patient 2 (47 yo M) Patient 3 (50 yo M)	Patient 1 Approach: TFESI # of ESIs: 2 Patient 2 Approach: TFESI # of ESIs: 3 Patient 3 Approach: TFESI # of ESIs: 1 * *This patient also underwent 2 level facet joint steroid injection prior to ESI with transient relief.*	Dexamethasone 1.6 mL (10 mg/mL) per injection for all patients.	Patient 1: 2 weeks apart Patient 2: 2 weeks apart for 1st 2 injections. 3rd injection 3 weeks post 2nd injection. Patient 3: Not applicable	Patient 1 Hypercholesterolemia, Hypertension, Obesity (BMI-42.1 kg/m2), Type 2 DM, **Prior right L4-L5 facet injection 1 year prior,* Male Sex Patient 2: Hyperlipidemia, Hypertension, Obesity (BMI-32.5 kg/m2), Male Sex Patient 3: Type 2 DM, Hypertension, Obesity (BMI-48 kg/m2), Male Sex	Borré et al. grade Patient1: Grade III Patient 2: Grade II Patient 3: Grade II	No post procedure MRI documented.	TFESI can provide modest short–term symptom relief of lumbosacral radicular pain and improvement in disability caused by SEL. Further study is warranted. **Level V**

*F- female; *M- male, *yo- years old, *MRI- Magnetic Resonance Imaging, *Tx- treatment, *TFESI- transforaminal epidural steroid injection, * ESI(s)- epidural steroid injection(s), Inj(s)- injections(s), *ND-not described.
* NA- not applicable. *BMI- body mass index.* DM- Diabetes Mellitus.

Table 4
Borré et al. Epidural Lipomatosis Grading Scheme [3]

Borré MRI Grade	Ratio of epidural fat (A +B in Fig. 1a.) to the spinal canal width	Ratio of dural sac to the epidural fat (A + B in Fig. 1a.) width	Meaning
Grade 0	≤40%	≥150%	Normal amount of epidural fat
Grade 1	41-50%	149-100%	Mild overgrowth of epidural fat
Grade 2	51-74%	99-34%	Moderate overgrowth of epidural fat
Grade 3	≥75%	≤33%	Severe overgrowth of epidural fat

increased BMI (36.7 vs. 29.4 kg/m^2, P<0.001) [18]. Similarly, although Jaimes et al. found that LESI(s) were statistically associated with LEL, when compared to study control group, he also found that the average BMI (36.0 ± 0.9 vs. 29.2± 0.9, p<0.01) and triglyceride levels (250± 30 vs. 186± 21 mg/dL p<0.01) of the LEL cohort were statistically greater [17]. Some of the authors detailed prior patient exposure to steroids either systemically or through other injections prior to receiving LESI(s) [14,18]. It is also important to note that in some of the publications implicating LESI(s) as a potential causative agent for LEL limited historical information was provided regarding potential independent confounding risk factors or whether any attempt was made to identify confounding independent risk factors [10,11].

Pre- and post-LESI(s) LEL grade

In 11 of the 12 that assess and/or indicate LESI as potential cause of LEL, no specific published grading system was provided to describe the presence or absence of LEL prior to LESI [2,9,10-18]. Commonly cited grading systems have been published in studies by Borré et al. in 2003 (Table 4) and Ishikawa et al. in 2006 (which popularized the grading system proposed by Naka) [3,33]. Post-injection, 2 of the 12 publications describing a relationship between LESI and LEL utilized the Borré et al. classification to grade the severity of LEL, while the remaining studies utilized descriptive terms to illustrate the extent of LEL [2,19].

With respect to the two publications describing LESI(s) as a treatment modality, only 1 utilized a published grading system, specifically the Borré et al. grading, to describe the severity of pre- LESI(s) LEL [21]. There was no description of post-injection LEL characteristics in either report [20,21].

Study conclusions and level of evidence

In the publications suggesting LESI(s) as a potential cause of LEL, the authors indicate that there is a potential association between LESI(s) and LEL. However, most emphasize that further research is needed to establish causation [2,9,10-19]. Likewise, the reports illustrating that LESI(s) can provide symptomatic benefit for radicular pain in the setting of LEL also indicate that further study is warranted [20,21]. The present literature represents low-quality evidence of an association between LESI(s) and LEL, and thus there is insufficient evidence to determine causation. Limitations of the current body of evidence include retrospective design, small sample sizes, and lack of consistent assessment of confounding variables independently associated with SEL. Furthermore, many publications failed to clearly describe one or more aspects related to the (1) temporal association between LESI and LEL diagnosis, (2) frequency of LESI(s), (3) epidural access approaches, and (4) corticosteroid dosage. Most reports also often failed to describe LEL severity pre and/or post procedure based on an established grading system. Thus, the level of evidence for the referenced studies is “low”, generally Level IV or V, and the grade of recommendation is classified as Grade C *(Grades of Recommendation for Summaries or Reviews of Studies As Adopted by the North American Spine Society January 2005*)*, due to overall "poor-quality evidence" insufficient to allow for a recommendation for or against the intervention with confidence [32].

Discussion

LEL is classically described as a rare condition, which may present as an asymptomatic, incidental finding or can result in high-grade compression of the central canal neural structures, resulting in substantial pain and compromised quality of life and functionality [1]. Awareness of this condition is particularly pertinent to outpatient musculoskeletal practitioners and especially so for those focused on spinal care. Clarity regarding recommended nonoperative treatment protocols in this patient population are needed, particularly as it pertains to interventional spine care. Bayerl et al. indicated that thus far there is no prospective evidence for conservative medical therapy and prior to their study in 2019, there were no prospective studies of outcomes of LEL patients after surgery [1]. Likewise, there are no comparative clinical trials evaluating outcomes of conservative treatment versus surgical intervention or any prospective study evaluating the long-term course of LEL patients with conservative management [1,8,22,28,34].

Given the lack of high-quality outcome studies, patients with symptomatic SEL often undergo protracted, poorly-formatted courses of conservative management despite debilitating refractory symptoms due to limitations in or lack of evidence-based nonoperative clinical practice guidelines. Although there are several retrospective studies, case reports and/or series describing positive surgical outcomes, the stigma of poor surgical candidacy remains due to limited high-level evidence [1,7,10,12,14-16,35-39]. Some authors advocate that LEL should be considered an absolute contraindication for steroid exposure including interventional pain procedures with steroids due to the potential to enhance adipose deposition, worsening the patient’s condition [2,10,11,28,40]. Other authors have suggested a sequential approach of an LESI as a one-time injection option in LEL patients with radicular symptomatology and thereafter if truly necessary, any repeat epidural injections should be performed with local anesthetic only [41]. This ambiguity is further compounded by publications demonstrating potential pain-relieving benefits of LESI(s) in the setting of LEL, overall resulting in a clinical quandary for many spine interventionalists [20,21]. Notably, although trends from 2000 to 2018 demonstrate a decline in utilization of epidural injections in Medicare population, overall use is still classified as high [42,43]. Additionally, authors have expressed concern that epidural injections are potentially over-scrutinized, leading to reduced access to these procedures despite numerous favorable systematic reviews, randomized controlled trials and cost utility analysis studies demonstrating benefit [43–51].

Thus, the purpose of this comprehensive narrative review was to evaluate the quality of the literature directly implicating LESI(s) as a potential causative agent of LEL or treatment for radicular pain in the setting of LEL in a thorough, comprehensive and nuanced manner. The present review identified the available literature regarding LESI(s) and LEL, which is generally comprised of retrospective case control studies, cross-sectional retrospective chart reviews, small case series (Level IV) or expert-opinion case reports (Level V), which lack critical data and/or do not account for confounding risk factors that are independently asso-

Table. 5
Reported Associations with SEL

Excessive endogenous cortisol production (Cushing syndrome/disease or other endocrinopathies) [9]
Older Age [3,9]
African American [9]
Diabetes Mellitus [1,2,26]
Systemic Steroid Use [1,2,3,9]
Epidural Steroid Injections [2,9,10-19]
Obesity (particularly visceral fat) [2,3,5,9,22,24,25,27,33]
Alcohol Abuse [17]
Smoking History [18]
Increased Levels of Stress [17]
Genetic Predisposition [17]
Elevated serum insulin levels [5]
Elevated serum uric acid levels [5]
Elevated serum ferritin levels [5]
Hyperlipidemia [1,25]
Metabolic Syndrome [1,5,22]
Male Sex [1-3,5,8,9,10]
Prior Spine Surgeries [2,8]
Highly Active Antiretroviral Therapy [8,9,21]
Carcinoid Tumor[8]
Androgen Antagonist Therapy[8]
Hypertension [1,22]
Higher Modified Charlson Comorbidity Index [9]

ciated with the condition, many of which are characteristics of metabolic syndrome [2,10-21]. Nonetheless, it is important to be keenly aware of this proposed relationship.

In an academic effort to foster further understanding of this potential relationship beyond the current limitations in the interventional spine literature, the discussion will synthesize literature as it pertains to: 1) current knowledge regarding SEL, notable associations and potential implications for corticosteroid exposure; 2) corticosteroid exposure and lipoatrophy; 3) current management recommendations for SEL and 4) areas for future focus.

Epidural Lipomatosis, Associations and Potential Implications for Corticosteroid Exposure

There are several conditions that have been associated with SEL (Table 5). This intersectionality is often not fully accounted for in the studies implicating LESI(s) as a cause of LEL. The full clinical picture of the patient should be taken into consideration. Many of the referenced studies implicating LESI(s) predate literature focused on the interrelatedness of conditions associated with LEL, and thus, it is imperative that the full clinical picture of this patient population is taken into account to further our understanding of these nuances and formulate best-practice recommendations.

Metabolic syndrome

Precision and refinement of future research is required to better understand the possible relationship between LESI(s) and LEL through high-quality, methodologically-sound study. It is apparent that there are coexisting, interwoven, collective and likely compounding factors that predispose to SEL. This has been a focus of recent studies and metabolic syndrome is postulated to be the connecting link [1,5,18,22-27]. Based on the National Health and Nutritional Examination Survey (NHANES) data, it has been estimated that at least 68 million U.S. adults meet the criteria for the metabolic syndrome and the trend only seems to be increasing [52].

It has been observed that the clinical findings associated with metabolic syndrome exist more frequently in SEL patients than would be expected by chance alone and that this accretion is of clinical importance. In many of the publications linking LESI(s) to LEL, the authors' commentary described underlying features of metabolic syndrome in their patient cohorts that are independently associated with SEL (Table 1-3).

In 2009, a consensus definition for metabolic syndrome was formulated by representatives from the International Diabetes Federation, American Heart Association, National Institutes of Health, International Atherosclerosis Society, World Heart Federation and International Association for the Study of Obesity [53]. This working group described five key components, of which three are necessary to qualify for the diagnosis of metabolic syndrome including: elevated waist circumference (central obesity), elevated triglycerides, reduced HDL cholesterol, hypertension, and elevated fasting plasma glucose [22,53-55]. Although the pathophysiological origin for the metabolic syndrome remains uncertain, several contributing factors have been proposed including genetics, insulin resistance, obesity, sleep disturbance, disturbed circadian rhythm bodily functions, lifestyle and/or an inflammatory state [55]. Adipose tissue is considered an important endocrine organ which secretes substances involved in the pathogenesis of the metabolic syndrome [55]. Ischihara et al. noted that metabolic syndrome is associated with systemic fat deposition and hence proposed that SEL is not an independent pathological entity but one of the manifestations of metabolic syndrome and should be treated as such [22].

Most prior studies associating LESI(s) with LEL, have not fully considered the conceptual framework of the metabolic syndrome and its association with SEL, as this association is a more recent area of focus. The variance seen in the literature and in clinical practice regarding LEL development maybe explained by the difference in tissue sensitivity to glucocorticoids of each individual patient based on their metabolic profile [24]. It is imperative that further investigation into this correlation is considered to provide further clarity regarding best-practice recommendations.

Gender

SEL demonstrates a male predilection [1-3,5,8 -10]. It has been established that men in comparison to women of similar age and BMI classification have a significantly higher degree of visceral fat, which is characteristic of the metabolic syndrome [1,5,22,53-56]. This is consistent with our review demonstrating the overall majority of patients were male in both the studies implicating LESI(s) as a potential cause of LEL or as a potential pain-relieving treatment modality in the setting of LEL [2,9–21].

Corticosteroids and SEL

Generally, systemic exogenous corticosteroid exposure is considered the strongest associated risk factor for SEL and believed to predispose to

hypertrophy of adipose tissue already present in the spinal canal [1,2,7]. It has been determined that steroid hormones employ their effect at the cellular level by first binding to certain cytoplasmic receptors [57,58]. Feldman and Loose first determined that there are glucocorticoid receptors in adipose tissue by demonstrating the ability of dexamethasone to bind to various adipose tissues of adrenalectomized rats. Additionally, it was determined that although aldosterone (mineralocorticoid) bound to these receptors, dexamethasone demonstrated an increased competitive capacity, demonstrating that the receptors were glucocorticoid rather mineralocorticoid receptors which allows glucocorticoids to exert their effects on adipose tissue [58].

Further work by Lundholm and colleagues, determined that human adipose tissue (subcutaneous and omental) binds triamcinolone and that binding is saturable [57]. Interestingly, Lundholm et al. evaluated the competitive inhibition of triamcinolone binding by other steroid hormones, including dexamethasone. Equal amounts of dexamethasone or even 10-fold excess did not compete with triamcinolone's ability to bind to human adipose tissue. They determined that 100-fold excess dexamethasone was required to compete with triamcinolone for human adipose receptors [57]. Thus, triamcinolone demonstrated a substantial competitive advantage over dexamethasone for human adipose tissue binding despite both being glucocorticoids [57]. It is notable that when information pertaining to corticosteroid type was provided in the studies directly implicating LESI exposure as a cause for the development or progression of LEL, particulate steroid, including either triamcinolone or methylprednisolone, was utilized. Whether or not the particulate nature of the steroid utilized is of any true relevance as it pertains to the possibility or likelihood of development of LEL after LESI is not known and may benefit from further investigation.

It has been previously demonstrated that SEL associated with systemic corticosteroid usage accumulates in the thoracic region twice as frequently as in the lumbar region [7,10,11,15,17,21]. In contrast, SEL occurs three times more frequently in the lumbar region than in the thoracic region in obese patients [7,17,21]. Interestingly, there has only been one case of isolated SEL accumulation in the cervical spine [28]. Further evaluation of epidural versus systemic route of steroid administration and location of SEL accumulation is warranted. Based on our literature review, patients predominantly developed LEL after LESI(s), which contrast studies demonstrating thoracic proclivity with systemic corticosteroid exposure [10–19]. Further investigation into corticosteroid administration route (systemic versus LESI) as well as epidural administration route (TFESI, ILESI, Caudal) would be useful to further characterize epidural lipomatosis presentation, as this may be of relevance to clinical practice and provide clues regarding risk mitigation. Our review of the literature demonstrates that the corticosteroid dose, frequency, treatment duration and number of LESI(s) varied substantially before LEL development and/or progression. This is concordant with the variability in prior studies associating SEL with systemic corticosteroid exposure [10,11,14,24].

It is known that glucocorticoids affect the triglyceride storage function of adipose tissue, predisposing to redistribution from peripheral to central deposition as seen in metabolic syndrome [59,60]. Additionally, any exogenous steroid use, including epidural injections are known to have potential systemic side effects, including but not limited to hypothalamic-pituitary-adrenal axis suppression, increased glucose levels, hypertension and dyslipidemia, all of which are features of the metabolic syndrome [59,60]. Thus, it is important to carefully consider the complete metabolic profile of the patient prior to steroid exposure.

Lipoatrophy and corticosteroid exposure

It is worthy of mention that subcutaneous soft tissue atrophy (along with skin hypopigmentation) is a known rare complication of superficial corticosteroid injections with an estimated incidence up to 5.8% [61–63]. Although the exact mechanism is unknown, studies have demonstrated through subcutaneous tissue sampling from regions of localized post-corticosteroid injection lipoatrophy, that there is a decrease in number and size of adipocytes, potentially attributed to the infiltration of "lipophage-like" activated macrophages [61,63-65]. However, despite the presence of activated macrophages in close proximity to altered adipocytes, it has been demonstrated other inflammatory cells are lacking, suggesting that the macrophages are possibly activated through non-immunologic means such as trauma [61,63-65]. These side effects tend to manifest 2 to 4 months post-injection, but have been reported to occur even 10 months post-injection [61]. Soft tissue atrophy and hypopigmentation often resolve spontaneously by 9 to 12 months post-injection and, occasionally, are permanent [61]. It has been shown that these side effects are more common in women and tend to occur more frequently with superficial and concentrated injections involving less soluble (longer-acting) preparations such as methylprednisolone and triamcinolone acetonide [61,65]. Furthermore, clinical lipoatrophy has also previously been recognized after administration of vasopressin, human growth hormone, insulin and antibiotics [65–69]. Translatability of literature regarding the uncommon complication of lipoatrophy with superficial corticosteroid injections as a rationale for LESI(s) in the setting of LEL requires further substantiation. In addition, this hypothesis has questionable justification based on our evolving understanding of SEL and metabolic syndrome.

Management of SEL

As it currently stands, conservative management of SEL generally revolves around abstaining from or marked reduction in steroid use, increasing physical activity, dietary modifications, weight loss and/or treating any underlying predisposing endocrinopathies dependent on applicability and symptom management with physical therapy and medications [8,28]. Many small studies have demonstrated the benefit of this conservative treatment model [7,11,21,24,28,33,70]. However, prospective studies evaluating outcomes with conservative treatment recommendations are needed [1]. A comprehensive multidisciplinary healthy lifestyle approach should be considered with an appreciation and planning for any adverse, detrimental social determinants of health that could potentially detract from the patient's ability to participate in the care plan [55].

For patients with radicular pain without LEL and a clinical picture consistent with metabolic syndrome, consider inquiring for concomitant exogenous steroid exposure via other routes. As generally advised in any clinical scenario, consider utilizing the lowest possible effective LESI corticosteroid dose if LESI is to be performed. In the referenced studies higher dose corticosteroids were commonly utilized and many predate literature focused on determining optimal dosing. It has been previously demonstrated by Ahadian et al. that lumbar transforaminal epidural steroid injections with doses as low as 4 mg of dexamethasone provide clinically meaningful benefit and that efficacy did not differ when compared to 8mg or 12 mg [71]. Likewise, numerous studies have demonstrated no statistically significant difference in pain reduction or functional improvement between non-particulate (dexamethasone) and particulate corticosteroid epidural injections [72]. Consider educating the patient about the theoretical risks and current limitations in our understanding.

There are no specific guidelines regarding threshold for surgical intervention, however refractory pain despite attempts at maximizing conservative treatment and/or significant or progressive neurologic compromise warrants surgical evaluation [1]. Fogel et al. previously noted that Borré et al. grade I patients often improve with conservative management and that Borré et al. grade III patients may be more likely to require surgical intervention [7,15]. However, LEL patients often have multiple comorbidities that increase their surgical risk given the association with metabolic syndrome and thus risk-benefit assessment is necessary along with clear communication with the patient regarding risks and expectations based on current evidence.

Overview of literature limitations and areas for future investigation

This review has identified substantial limitations in the literature regarding that which is truly known regarding LESI(s) and LEL, as well as conservative management overall. These include but are not limited to the following: *(a)* there are no prospective clinical trials evaluating the outcome of patients with conservative treatment; *(b)* there are no randomized controlled trials comparing conservative versus surgical intervention in patients with LEL; *(c)* there are only a few, mostly small studies attributing LEL to LESI which lack consistent nuanced evaluation of: the role of other independent associations/risk factors; corticosteroid type, dose, timing between and overall time frame of exposures; concomitant peripheral injection or systemic exposure; epidural injection approach and location/morphology of LEL accumulation; *(d)* evaluation of variance in SEL accumulation with systemic exposure versus LESI(s) and clinical pertinence *(e)* lack of use of reproducible, published SEL grading schematics to describe LEL characteristics and disease progression*;(f)* evaluation of cumulative corticosteroid exposure regardless of route and LEL onset; *(g)* evaluation of LESI in the context of the metabolic profile of the patient and the associated risk of LEL development *(h)* clinical practice guidelines for the threshold for surgical evaluation and patient optimization. Future studies should consider addressing these grey areas to clarify the association between LESI (s) and LEL and conservative management recommendations for this patient population with a greater level of confidence than the currently published literature allows.

Conclusion

The association between systemic corticosteroid exposure and SEL is well established. However, the association between LESI(s) and LEL has generally been depicted as poorly understood. The literature regarding this association has significant gaps. The present comprehensive literature review identified the available literature regarding the association between LESI(s) and LEL, which is generally comprised of low-quality evidence, which lack critical data and/or do not account for confounding variables. As such, although LESI(s) have been associated with LEL in the literature, presently due to lack of rigorous, high-quality studies, neither the presence nor absence of an independent causal relationship between LESI(s) and LEL can be stated with confidence. Further research is needed with an awareness of the methodological gaps described in this review.

Declarations of Competing Interests

None of the authors have any relevant conflict of interest.

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