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Risk Factors for Atherothrombotic Disease and Lumbar Spinal Stenosis: Results from the PREFACE Study

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Abstract

Background and aim: Atherothrombotic disease of feeding arteries of lumbar spine could be an underlying mechanism for Lumbar Spinal Stenosis (LSS). We aimed at evaluating the association of a large panel of risk factors for atherothrombotic disease, alone or in combination, with LSS in multivariable models.

Methods: Case-control study: 213 consecutive patients with LSS, eligible for surgery at the Neurosurgery Department of IRCCS Neuromed, were enrolled in the PREFACE study; 426 controls, matched 1: 2 for sex, age (± 6 months) and physical activity, without a history or clinical evidence of LSS were selected from the general population. Odds Ratios (ORs) and their 95% Confidence Intervals (CIs) were calculated using conditional-to-match (for age and sex) logistic regression.

Results: Manual occupation, current smoking, high waist-to-hip ratio, history of hypertension, diabetes and dyslipidemia were independently associated with higher odds of developing LSS in multivariable analysis ($p<0.001$). Only 1.5% of patients with LSS showed absence of risk factors, in comparison with 6.7% in controls ($p<0.001$). The risk of LSS linearly increased with the increased presence of risk factors. The presence of 3 or more risk factors compared with none was associated with 13 times higher risk of LSS (OR: 13.04; 95% CI: 2.87-59.27)

Conclusion: Risk factors for cardiovascular disease and in particular metabolic risk factors are associated with increased risk of LSS. Management of LSS should take into consideration the control of modifiable atherothrombotic risk factors.

Keywords: Risk factors • Central obesity • Lumbar spinal stenosis • Case-control study • Socio-economic status

Introduction

Lumbar Spinal Stenosis (LSS) has become the most common indication for lumbar spine surgery in patients over 65 years [1], in part because of the increasing quality and availability of radiological imaging, in part for the higher need of mobility and flexibility in the aging population. Localized inflammation, triggered by nerve root compression [2] and at least two interdependent vascular mechanisms may contribute to the development of neurogenic claudication in LSS: reduced arterial blood flow resulting in ischemia and venous congestion with compression of the nerves and secondary perfusion deficiency [3]. Since ischemia may cause both pain and degeneration of the involved structures, atherothrombotic disease of the feeding arteries of the lumbar spine has attracted growing attention as one of the possible underlying mechanisms for LSS. Therefore, risk factors for atherothrombotic disease might represent an important target for primary and secondary prevention of the disease. Some studies have already observed an association between risk factors for cardiovascular disease and LSS [4]. Uesugi et al. reported a close association of diabetes and hypertension with LSS in 50 to 69-year-old Japanese patients [5]. Diabetes was also associated with symptomatic LSS in Japanese patients with moderate radiographic stenosis [6]. In a large cohort of Swedish construction workers, obese and overweight persons were at a higher risk of developing LSS [7]. A further analysis of the same cohort showed that tobacco smoking was, in a dose dependent manner, associated with an increased incidence of surgically treated LSS. However, all these studies considered one of few exposures at a time, without taking into consideration the potential presence of multiple risk factors or their interaction and/or possible confounding. The aim of our study was to evaluate the possible association of a large panel of risk factors for atherothrombotic disease, alone or in combination, with LSS in multivariable models.

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Methods

Case patients

Between May 2016 and December 2018, 264 consecutive patients,

aged ≥ 35 years, with symptomatic LSS, confirmed by imaging, eligible for surgery at the Neurosurgery Department of the IRCCS Neuromed, were enrolled in the PREFACE (PREdictive FACtors of risk and surgical outcomEs in lumbar spinal stenosis) study. Subjects with spine instability were excluded. Anthropometric measurements and administration of questionnaires were completed before surgery. The final sample consisted of 213 cases. The study was approved by the Ethical Committee of the IRCCS NEUROMED.

Control subjects

Controls were 426 subjects, without any reported spine degenerative disease or clinical sign of back disease, selected among participants of the Moli-sani Study, a large population-based cohort, of men and women (aged ≥ 35 years) randomly enrolled from the general population of the Molise region, where the IRCCS Neuromed is located [8]. For each case, we selected two controls matched by sex, age (± 6 months) and physical activity (low, moderate, intense).

Assessment of covariates

Physical activity level was assessed through the question "How was your leisure-time physical activity in the last six months?" with three possible answers (sedentary lifestyle, low active lifestyle or physically active lifestyle). Evaluation of covariates was conducted with identical procedures both in cases and in controls. Education was based on the highest qualification attained and was categorized as up to secondary (≤ 8), upper secondary (>8 ≤ 13), and post-secondary (>13). Present occupation was described through 5 groups: non-manual or manual occupation, retired, housewife and unemployed/unclassified. Former employment considered the previous occupation for retired; as a result subjects were classified as non-manual, manual, housewife and unclassified. Subjects were classified as never-smokers, current smokers or ex-smokers (having quitted for at least 1 year). Height and weight were measured, and Body Mass Index (BMI) was calculated as kg/m^2 and then grouped into 3 categories as normal (≤ 25), overweight (>25 to <30), or obese (≥ 30).

Moreover, waist circumference, in cm, was measured in the middle between the twelfth rib and the iliac crest and hip circumference, in cm, was measured around the buttocks. The waist-to-hip ratio was then calculated. Abdominal obesity was defined as waist-to-hip ratio ≥ 0.90 for men and ≥ 0.85 for women [9]. Hypertension, hypercholesterolemia and diabetes were defined by current pharmacological treatment. History of cardiovascular (angina, stroke and myocardial infarction) and peripheral artery disease included self-reported diagnosis. The study sample was also stratified as living in an urban or rural environment on the basis of the urbanization level as defined by the European Institute of Statistics (EUROSTAT definition) and obtained by the tool "Atlante Statistico dei Comuni" provided by the Italian National Institute of Statistics (www.istat.it) [10].

Statistical analysis

The main characteristics of cases and controls were reported as frequency and percentages or mean values and Standard Deviation (SD). Differences between cases and controls for categorical or continuous variables were evaluated by general linear models (PROC GENMOD and PROC GLM in SAS for categorical and continuous variables, respectively), taking into account the match for age, sex and physical activity. Multivariable conditional logistic regression analysis was used to quantify the association of potential risk factors or their combination with LSS status. Odds Ratios (ORs) and their 95% Confidence Intervals (CIs) were calculated using conditional-to-match (for age, sex and physical activity) logistic regression. Multivariable model included occupation, income, urban or rural residence, smoking habits, waist-to-hip ratio, physical activity, history of hypertension, diabetes or dyslipidaemia and peripheral artery disease as potential risk factors (Table 1). The multivariable model incorporated potential risk factors that had resulted associated with LSS status with p-value <0.20 in matched analysis.

An Atherothrombotic (AT) risk score was calculated, allocating 1 point for each risk factor: current smoking, abdominal obesity, hypertension, diabetes, dyslipidaemia. All the five risk factors contributed equally to the AT risk score which potentially ranged from 0 to 5. Three multivariable models were fitted. Model 1 included age, sex and physical activity; model 2 was additionally adjusted for occupation; model 3: as model 2 plus all the risk factors included into the score. Appropriate multiplicative terms for testing interaction between pair of risk factors were included in the model 2. The data analysis was generated using SAS/STAT software, Version 9.4 of the SAS System for Windows©2009. SAS Institute Inc. and SAS are registered trademarks of SAS Institute Inc., Cary, NC, USA.

Results

The baseline characteristics of cases and controls are shown in Table 1. In both cases and controls the mean age was 66.5 years (SD=9.3), 34.3% were women and 69.1% were subjects with a sedentary lifestyle. There was no difference between cases and controls regarding educational level, BMI distribution, or history of cardiovascular disease (Table 1). In univariable analysis, patients with LSS, matched for age, sex and physical activity with controls, were more likely to have manual occupation, lower income, to live in an urban area and to be smokers, along with a higher prevalence of hypertension, diabetes, dyslipidaemia and history of peripheral artery disease (Table 1). When all these conditions were included in a multivariable analysis, present manual occupation, current smoking, high waist-to-hip ratio and history of hypertension, diabetes and dyslipidaemia remained independently associated with higher odds of suffering of LSS (Model 2, Table 1). Table 2 reports AT risk score, its distribution in cases and controls and odds ratio for LSS.

AT risk score was higher in cases than in controls and was associated with an increased odd of LSS (OR: 2.22; CI 95%: 1.72-2.86, Table 2, Model 2). Further adjustment of BMI did not modify the association between AT risk score and LSS (OR: 2.32; CI 95%: 1.78-3.02). Absence or one metabolic risk factors was observed in 38.7% of cases and 17.4% of controls, while 41.1% of cases showed three or more risk factor as compared to 22.7% of controls (Table 2). Risk of LSS increased progressively with increasing number of risk factors, with the highest category (> 3 components) associated with the greater LSS risk in comparison with individuals with zero components (OR: 13.04; 95% CI: 2.87-59.27; Table 2, Model 2 and Figure 1). Multiplicative terms of interaction included in Model 2 were all largely not statistically significant. In Model 3, we further adjusted for each component included into the score, and as a consequence the AT risk score completely abolished its association with LSS (Table 2, Model 3).

Discussion

A number of risk factors for LSS were evaluated in the context of a

Table 1. Characteristics of cases and controls, and odds ratios for lumbar spinal stenosis.

Variables	Cases N=213	Controls N=426	Odds ratio (95%CI)Model 1	Odds ratio (95%CI) Model 2
Sex, (Male, %)	65.7	65.7	Matching variable	Matching variable
Age (years)	66.5 (9.5)	66.5 (9.5)	Matching variable	Matching variable
Physical activity level (%)				
Sedentary lifestyle	69.1	69.1	Matching variable	Matching variable
Low active lifestyle	26.8	30.0		
Physically active lifestyle	4.2	0.8		
Educational level (%)				
Upper secondary	67.6	63.1	-1-	Not included
Post-secondary	32.4	36.8	0.79 (0.54-1.16)	
Occupation (%)				
Non-manual	11.8	14.1	-1-	-1-
Manual	18.3	6.6	4.31 (1.98-9.41)	4.54 (1.96-10.56)
Retired	51.6	61.7	0.62 (0.32-1.19)	0.57 (0.28-1.17)
Other	18.3	17.6	1.00 (0.51-1.97)	0.85 (0.41-1.79)
Former occupation (%)				
Non-manual	32.4	56.4	-1-	Not included
Manual	56.8	27.9	3.82 (2.55-5.71)	
Other	10.8	15.7	1.22 (0.69-2.17)	
Place of residence (%)				
Rural	34.3	39.0	-1-	Not included
Urban	65.7	61.0	1.23 (0.87-1.73)	
Smoking habit (%)				
No	38.5	41.6	-1-	-1-
Yes	27.7	18.5	1.72 (1.07-2.75)	1.96 (1.15-3.34)
Ex	33.8	39.9	0.93 (0.60-1.42)	0.94 (0.58-1.52)
Body mass index (kg/m^2; %)				
Normal (≤25)	20.2	17.4	-1-	Not included
Overweight (>25 <30)	39.9	44.8	0.76 (0.48-1.21)	--
Obese (≥30)	39.9	37.8	0.90 (0.56-1.43)	--
Waist circumference (cm)	106.1 (11.0)	99.6 (12.2)	1.05 (1.03-1.07)	Not included
Waist-to-hip ratio (%)*				
Normal	4.2	14.1	-1-	-1-
High	95.8	85.9	3.87 (1.82-8.22)	3.09 (1.40-6.81)
History of hypertension (%)				
No	37.6	51.6	-1-	-1-
Yes	62.4	48.4	1.89 (1.32-2.71)	1.87 (1.25-2.82)
History of diabetes (%)				
No	79.8	88.7	-1-	-1-
Yes	20.2	11.3	1.95 (1.25-3.04)	1.89 (1.16-3.07)
History of dyslipidemia (%)				
No	73.7	84.0	-1-	-1-
Yes	26.3	16.0	2.08 (1.34-3.25)	1.87 (1.13-3.08)
History of cardiovascular disease (%)				
No	85.4	84.5	-1-	Not included
Yes	14.6	15.5	0.92 (0.56-1.50)	
History of peripheral artery disease (%)				
No	96.7	98.6	-1-	Not included
Yes	3.3	1.4	2.33 (0.78-6.94)	

Model 1= Univariable (but matched for age, sex and physical activity)
Model 2 = Including occupation, smoking habits, waist–hip ratio, history of hypertension, diabetes or dyslipidaemia (matched for age, sex and physical activity).
*Abdominal obesity was defined as waist to hip ratio ≥ 0.90 for men and ≥ 0.85 for women

case-control design including 213 cases and 426 controls. Patients with LSS were more likely to report manual occupations and lower income, to live in an urban area, and to be smokers. This is in line with previous evidence indicating that severe LSS, assessed by MRI scanning, was associated with heavy manual work particularly in the factory/construction industries [11] and tobacco smoking was associated with increased incidence of surgically treated LSS [7]. Among metabolic risk factors, diabetes was a major risk factor for LSS, as already seen by Asadian in Iranian subjects from a case-control study, where diabetes increased the risk of developing canal stenosis by 3.7 times [4]. BMI has been shown as an independent risk factor for symptomatic spinal stenosis in previous studies [12,13]. Our results found that central

obesity rather than BMI was a powerful predictor of LSS. BMI has traditionally been used to measure obesity in epidemiological studies; however, waist-to-hip ratio more accurately describes the distribution of body fat and is more closely associated with morbidity and mortality [14]. Our results point out that visceral obesity, with its metabolic implications, rather than the simple increase in body weight, could play a role in the pathogenesis of LSS.

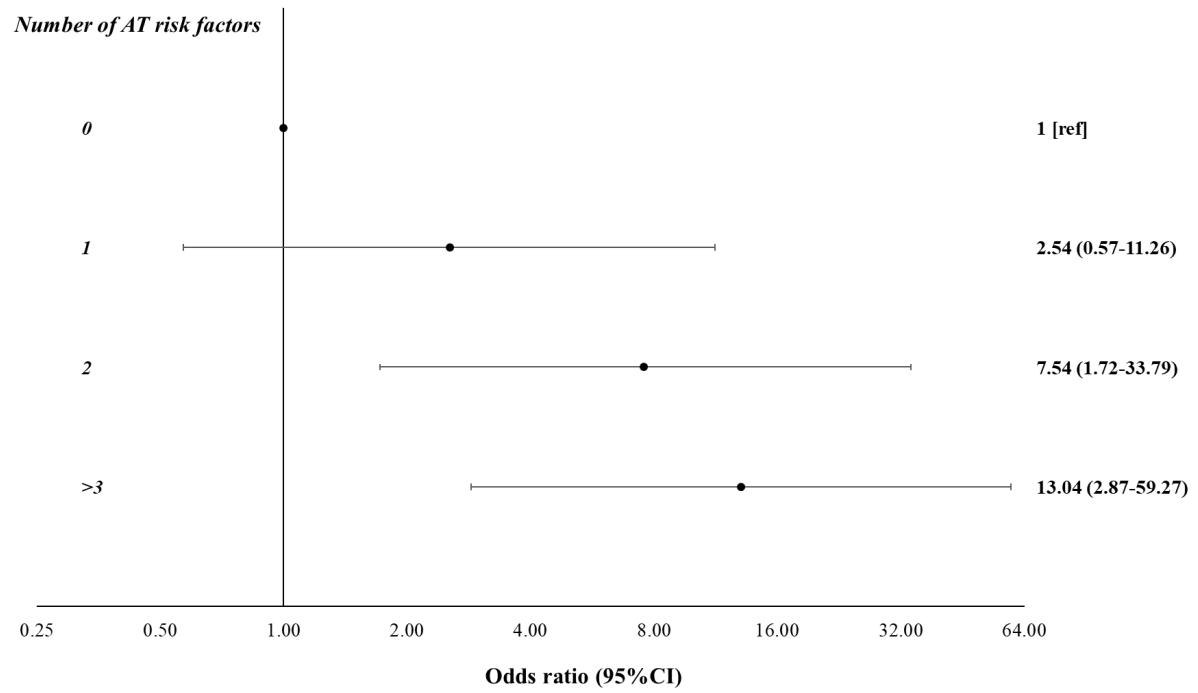
Taken altogether, the majority of previous studies took only into consideration one or few factors at a time, with limited power to control for possible confounding. Indeed, risk factors for atherosclerosis are often simultaneously present and multivariable models are necessary to dissect their independent effect on the disease. When a multivariable model was performed, including all the risk factors associated with LSS, manual occupation, waist-to-hip ratio, current smoking, and history of hypertension, diabetes and dyslipidaemia remained all associated with LSS, suggesting that they all contributed independently to the risk of LSS. This implies that the simultaneous presence of different risk factors can additively contribute to the risk or multiply their effect. To better explore this hypothesis, we elaborated a score of risk factors assessing the association of their combination on the risk of LSS in our study population. To date, very limited evidence was available on the association between combined factors and risk of LSS, with the exception of one study by Memtsoudis et al. indicating that patients with metabolic syndrome (actually a combination of risk factors) were more likely to undergo surgery for spinal stenosis [15].

Our results show that the AT risk score was higher in LSS patients than in the control group and was associated with LSS risk after adjustment for social status confounders. Each additional metabolic component doubled the odds of LSS risk in comparison with individuals with zero components. We also tested the possibility of interaction between risk factors by adjusting the multivariable model for the individual components of the AT risk score and by formally testing for interaction pairs of risk factors. In both cases, the hypothesis of additively was not rejected. To the best of our knowledge, this is the first study that has associated combination of AT risk factors to LSS. Although individual metabolic risk factors, such as abdominal obesity, hypertension or diabetes have been previously associated with LSS, very seldom the global effect of such disorders was distinguished from that of the increased body weight. Indeed, the effect of metabolic components could be merely attributed to an abnormal and altered load on the spine by BMI or body weight and to a relative reduction in muscle mass, which further increases strain on the lumbar spine [16-18].

Table 2. Combination of Atherothrombotic (AT) risk factors in cases and controls.

Variables	Cases (N= 213)	Controls (N=426)	Odds ratio (95%CI) Model 1	Odds ratio (95%CI) Model 2	Odds ratio (95%CI) Model 3
		Number of AT risk factors			
0	3 (1.5)	28 (6.7)	-1-	-1-	-1-
1	34 (16.3)	137 (32.8)	3.51 (0.81-15.24)	2.54 (0.57-11.26)	1.05 (0.17-6.48)
2	86 (41.1)	158 (37.8)	9.11 (2.07-40.16)	7.54 (1.68-33.79)	1.66 (0.17-15.77)
≥3	86 (41.1)	95 (22.7)	16.13 (3.61-72.14)	13.04 (2.87-59.27)	1.35 (0.08-22.92)
Score AT risk factors	-	-	2.17 (1.69-2.77)	2.22 (1.72-2.86)	1.15 (0.51-2.61)

Model = Univariable (but matched for age, sex and physical activity)
Model 2= Including occupation (matched for age, sex and physical activity).
Model 3= Model 2 plus current smoking, abdominal obesity, hypertension, diabetes, dyslipidemia



Note: Model 2: Including occupation (matched for age, sex and physical activity).

Figure 1. Increase in LSS risk as a function of the increase in number of Atherothrombotic (AT) risk factors.

Our study points out that besides direct biomechanical effect on cartilage and skeleton, central obesity acts through altered metabolism that induces changes in insulin sensitivity, levels of fatty acids, cytokines and growth factors. All these factors have the potential to alter the properties of bone matrix, ligament, synovia, and cartilage, and promote the development of spine and disc degeneration [19-26]. Furthermore, ischemic change of neural structures by these risk factors might contribute to the development of the cauda equina syndrome, a hypothesis supported by previous evidence [27]. Decreased muscle mass is indeed associated with insulin resistance, which further impairs the skeletal muscles and promotes systemic inflammation [28]. Adiponectin and leptin, hormones secreted by adipocytes function, determine low-grade inflammation that has been related to the progression of spondylosis [29,30]. In addition, a high serum concentration of free fatty acids increases systemic inflammation and induces development of osteoarthritis [31-33]. Finally, hyperlipidemia-induced atherosclerosis is proposed as a cause of disc degeneration and ischemic pain [34,35]. We tried to dissociate the effect of obesity-related load from that of obesity associated-metabolic disorder by adjusting for BMI the association between AT risk score and LSS, but no change was observed. Additionally, in our sample, BMI was not associated with LSS in multivariable analysis taking into account metabolic features.

Conclusion

Risk factors for atherothrombosis are independently and additively associated with LSS. Central obesity reduction, control of metabolic factors and smoking cessation should be prominent measures in prevention and management strategies of LSS.

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Strengths and Limitations

The novelty of our study is the simultaneous evaluation of several risk factors for LSS and the possibility to account for confounding and interactions. There are however some limitations to this study: it is possible that risk factors, occurring infrequently, may not have been identified. Moreover, the retrospective nature of a case-control study and the potential for recall bias might limit its clinical relevance.

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