Diabetes Mellitus, a New Risk Factor for Lumbar Spinal Stenosis: A Case–Control Study

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ABSTRACT

OBJECTIVES: This study aimed to determine the prevalence of diabetes mellitus in patients with spinal stenosis and lumbar vertebral disk degeneration, and the correlation of diabetes with these diseases.

STUDY DESIGN: This is a cross-sectional study.

METHODS: This case–control study was performed during 2012–2014 with 110 patients suffering from lumbar spinal stenosis and 110 patients with lumbar disk herniation, who were diagnosed using clinical and radiological evidences. Additionally, 110 participants who were referred to the clinic and did not show clinical signs of degenerative diseases of the lumbar spine entered the study as a control group. Demographic data and medical histories of the patients were collected using checklists.

RESULTS: A total of 50 patients (15.2%) were diagnosed with diabetes, which comprised 32 (29.1%) in the stenosis group, 7 (6.4%) in the lumbar disk herniation group, and 11 (10%) in the control group. The prevalence of diabetes in women with spinal stenosis and women with lumbar disk herniation was 35.9% and 10.3%, respectively, whereas prevalence of diabetes in women was 10.9% in the control group. This difference was statistically significant in the spinal stenosis group in comparison with the controls ($P < 0.0001$). Conversely, no significant difference was found in men.

CONCLUSIONS: There is an association between diabetes and lumbar spinal stenosis. Diabetes mellitus may be a predisposing factor for the development of lumbar spinal stenosis.

KEYWORDS: diabetes mellitus, risk factor, lumbar spinal stenosis, lumbar disk herniation

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Introduction

Diabetes is a multiorgan disease that affects many types of connective tissues, including bone and cartilage.[1,2] Furthermore, diabetes causes particular skeletal changes that are more likely in patients with diabetes than in patients without diabetes.[1] Prolonged and frequent complications of diabetes include diabetic neuropathy, with symptoms such as pain and sensory and motor deficits in the legs.[3]

Lumbar stenosis is caused by vertebral space reduction, which can be due to new bone formation or hypertrophic tissue changes. The process usually begins with water loss or reduction in water content, followed by hard disk protrusion into the fiber loop.[4] In other words, changes in the intervertebral disk play a primary role in the pathophysiology of lumbar canal stenosis.[5] Age-related changes in the cartilage matrix in patients with diabetes are different from the changes in healthy subjects.[6] These changes may lead to faster disk degeneration in patients with diabetes. In some studies, significant differences were observed in the incidence of diabetes in patients who have spinal stenosis compared with the degenerative disk disease. For example, in one study, 28% of patients with spinal stenosis had diabetes compared with 12.1% of patients who had degenerative disk disease.[7]

Additionally, diabetes causes the ossification of the posterior longitudinal ligaments and bone, which leads to spinal stenosis and nerve pressure.[8] Therefore, diabetes can be considered a risk factor for spinal stenosis, although the mechanism of the risk for spinal stenosis in patients with diabetes is not well defined. This suggests an association between diabetes mellitus and other spinal disorders and metabolic bone diseases, such as Paget's disease, diffuse idiopathic skeletal hyperostosis, and stenosis.[9] It is also observed that patients without diabetes respond better to stenosis surgery.[2]

On the other hand, studies have shown that diabetes is more prevalent in patients who undergo lumbar disk surgery compared with patients who undergo other surgeries. In fact, approximately 13% of patients who undergo lumbar disk surgery were diagnosed with diabetes, whereas the prevalence of diabetes in the same population generally was approximately

8%.[10] Diabetic microangiopathy might affect the nutrition of the spine and lead to disk degeneration.[11]

With the increasing occurrence of diabetes and the similarity of symptoms of spinal stenosis and diabetic neuropathy, one growing problem in the medical care of these patients is the lack of timely detection of stenosis, which causes several complications. Because adequate studies have not been conducted in this area and information about the status of diabetes in patients with stenosis is not available, this case–control study is the first prospective study to determine the prevalence and association of diabetes in patients with spinal stenosis and lumbar disk herniation and the relationship of diabetes with these diseases in patients who were referred to our clinic during 2012–2014.

Methods

The study was approved by the local institutional ethics committee (Code:IR.MAZUMS.REC.94.513). Informed consent was obtained from each patient. This research was conducted in accordance with the principles of the Declaration of Helsinki.

This study was performed during 2012–2014, 700 patients attended our clinic with back pain during that time. The selected study population comprised 110 patients suffering from lumbar spinal stenosis and 110 patients with lumbar disk herniation, who were diagnosed using clinical and radiological evidences, as well as 110 participants without clinical signs of degenerative diseases of the lumbar spine, who served as the control group for the study.

For the sake of consistency, rigid criteria were set for the diagnosis of the medical conditions addressed in this study. Two diagnostic criteria were used for spinal stenosis. The first criterion was neurological claudication for at least three months with normal dorsalis pedis and posterior tibial circulation. The second criterion was magnetic resonance imaging (MRI) evidence of a central spinal canal diameter of less than 9 mm. Criteria for the diagnosis of lumbar disk herniation were back pain with radiculopathy that was present for at least three months and MRI evidence of degenerative disk disease. After completing a thorough history and determining demographic characteristics, diagnostic tests were performed. Criteria for diagnosis of diabetes in the subjects were fasting plasma glucose $\geq$ 126 mg/dL (7.0 mmol/L), or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, random plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L), or HbA1c $\geq$ 6.5%. In the absence of unequivocal hyperglycemia, the results were confirmed by repeat testing. HbA1c tests were performed in a laboratory using a method that is NGSP certified and standardized to the diabetes control and complications trial assay. Subjects with previously diagnosed diabetes and instituted treatment were also classified as diabetic for the purpose of this study.

Because of associated complications and the effects of anesthetic drugs, all the patients entered the study before surgery.

Exclusion criteria included age $\geq$ 80 years, body mass index $\geq$ 30, and a history of spinal surgery, diabetogenic drugs (eg, corticosteroid) at least three months before the study, systemic and inflammatory disorder, and smoking.

The control group was selected from 390 lumbar MRI results, reviewed by a radiologist and a neurosurgeon. From these, 110 patients without any evidence of lumbar disk degeneration or lumbar stenosis were selected. This control group was matched with the case groups according to age (±5 years) and sex. Then, they were invited to the clinic for a diabetes follow-up. The control group patients were assessed for risk factors that include genetic factors, occupational exposures, and physical activity; however, the results were incongruous. There was no obvious association with smoking, alcohol, or hormone therapy use.

Statistical analysis. The collected data were subjected to statistical analysis using SPSS version 16. Chi-square and Fisher's exact tests were used, with the significance level set at $P \leq 0.05$. Multinomial logistic regression analysis was performed to determine the prognostic role of diabetes on developing lumbar disk herniation and lumbar spinal stenosis, and this analysis was also used to determine the effect of diabetes status on the likelihood of lumbar disk herniation or lumbar spinal stenosis in each gender.

Results

A total of 330 patients were enrolled; 96 patients (29.1%) were male, and 234 (70.9%) were female. Thirty-two patients in each group were male, and 78 patients were female. The mean ages of the lumbar spinal stenosis, lumbar disk herniation, and control groups were 53 ± 6, 42 ± 5, and 50 ± 3 years, respectively.

Patients were divided into three groups according to age (>60, 50–60, and <50 years). Subgroup analysis showed that the prevalence of diabetes in the three age groups in patients with spinal stenosis was greater than that in the control and lumbar disk herniation groups (Table 1).

A total of 50 patients (15.2%) were diagnosed with diabetes. The number of patients with diabetes were 32 (29.1%) and 7 (6.4%) in the stenosis and lumbar disk herniation groups, respectively. Eleven patients in the control group were diagnosed with diabetes (10%; Table 2). This difference was statistically significant ($P \leq 0.0001$).

Multinomial logistic regression analysis to determine the prognostic role of diabetes for the development of lumbar disk herniation and canal stenosis is shown in Table 3. Diabetes increases the risk of developing canal stenosis to 3.7 times higher than that in the control group (odds ratio: 3.7; confidence interval: 1.8–7.8).

Diabetes is found to be a statistically significant independent risk factor for lumbar spinal stenosis ($P = 0.001$). This analysis also demonstrates that diabetes is not a predictor for lumbar disk herniation ($P = 0.329$).

Accordingly, among female subjects, diabetes was found to be a statistically significant independent risk factor for lumbar spinal stenosis ($P < 0.0001$). This analysis

Table 1. Prevalence of diabetes in three groups of study according to age.

AGE GROUP	GROUP			TOTAL
	LSS	LUMBAR DISK HERNIATION	CONTROL	
<50				
Non diabetic				
Count	28	79	30	137
% within group	87.5%	92.9%	88.2%	90.7%
Diabetic				
Count	4	6	4	14
% within group	**12.5%**	**7.1%**	**11.8%**	**9.3%**
Total				
Count	32	85	34	151
50–60				
Non diabetic				
Count	28	15	37	80
% within group	66.7%	100.0%	92.5%	82.5%
Diabetic				
Count	14	0	3	17
% within group	**33.3%**	**00.00%**	**7.5%**	**17.5%**
Total				
Count	42	15	40	97
>60				
Non diabetic				
Count	22	9	32	63
% within group	61.1%	90.0%	88.9%	76.8%
Diabetic				
Count	14	1	4	19
% within group	**38.9%**	**10.0%**	**11.1%**	**23.2%**
Total				
Count	36	10	36	82

Abbreviation: LSS, lumbar spinal stenosis.

Table 2. Prevalence of diabetes in three groups of study.

GROUP	PATIENTS		TOTAL
	NON DIABETES	DIABETES	
Control			
Count	99	11	110
% within group	**90.0%**	**10.0%**	100.0%
LSS			
Count	78	32	110
% within group	**70.9%**	**29.1%**	100.0%
Lumbar disk herniation			
Count	103	7	110
% within group	**93.6%**	**6.4%**	100.0%
Total			
Count	280	50	330
% within group	84.8%	15.2%	100.0%

also demonstrated that in the female group, diabetes is not a predictor for lumbar disk herniation ($P = 0.57$). Diabetes was not a significant factor for lumbar spinal stenosis or lumbar disk herniation in the male group (Table 4).

Discussion

Diabetes is a multiorgan disease that affects many types of connective tissues, including bone and cartilage.[1,2] In this cross-sectional study, we determined that diabetes in patients with symptomatic spinal stenosis is more common than in those with lumbar disk herniation or in a control group.

Sakellaridis[10] reported that patients operated on for lumbar disk disease have a statistically significant increased incidence of diabetes mellitus compared with similar patients operated on for other reasons. They showed that the incidence of diabetes mellitus was 32% in the patients who underwent surgery and 13% in those who did not, and the authors stated: "Diabetes mellitus seems to be a predisposing factor for the development of significant lumbar disc disease that needs to be operated." In our study, prevalence of diabetes in the lumbar disk herniation group (6.4%) compared with the control group (10%) did not show a statistically significant difference ($P \leq 0.325$). This difference can be explained because our patients were assessed before any procedure for lumbar disk disease and were not affected by surgical complications and related medications.

Our comparison of the prevalence of diabetes between the stenosis group and the control group found a statistically significant difference (29.1% vs. 10%, $P \leq 0.0001$). Patients were divided into three groups according to age (>60, 50–60, and <50 years). Subgroup analysis showed that in all the three age groups, the prevalence of diabetes in patients with spinal stenosis was greater than in the control and lumbar disk herniation groups (Table 1).

Impacts on the prognosis of patients with diabetes mellitus who undergo spinal fusion procedures, spinal canal stenosis surgery, and disk herniation surgery are frequently studied. In addition to an increased risk of postoperative infection and related medical complications, the poorer prognosis with respect to symptoms in patients with diabetes compared with patients without diabetes has been shown to improve after surgery. Additionally, patients with diabetes have reported a greater pain score visual analog scale (VAS) than patients without diabetes who previously had surgery.[11]

In a study on the effect of diabetes on lumbar spine surgery with 173 patients who underwent lumbar disk herniation or spinal stenosis, Takahashi et al found that postoperative pain in patients with diabetes was more than in patients without diabetes ($P = 0.013$); complications after fusion surgery were similar in patients with and without diabetes ($P = 0.095$).[12]

Previously, in another study by Lotan et al, the relationship between stenosis and systemic disease was investigated using records from 537 patients with spinal stenosis. The results showed that 13.6% of the patients had diabetes, 23.2%

Table 3. Multinomial logistic regression analysis to determine the prognostic role of diabetes on developing lumbar disk herniation and lumbar spinal stenosis.

	COEFFICIENTS	ODDS RATIO	95.0% CI FOR ODDS		*P*-VALUE
			LOWER	UPPER	
Diabetes in the LSS group	1.306	3.69	1.75	7.79	0.001
Diabetes in the lumbar disk herniation group	−0.228	0.612	0.228	1.64	0.329

Abbreviation: LSS, lumbar spinal stenosis.

had hypertension, 11.9% had ischemic heart disease, and 4.4% had hyperlipidemia. The prevalence of diabetes in the general population is approximately 5.9% and hypertension is approximately 7.8%. In the studied stenosis patients, the rates of these diseases were significantly greater than that in the general population.[13]

Uesugi et al investigated the relationship between stenosis and comorbidities present in 526 patients with stenosis. The results showed that there were significant associations between diabetes and high blood pressure with spinal stenosis ($P < 0.05$).[14] However, we prospectively studied patients using the same design (110 patients with stenosis and 110 patients with disk degeneration). Moreover, in this study, we used an equal number of patients in the control group (without diabetes and with no stenosis or lumbar disk), which adds value to the study. Diabetes incidence was 29.1% in the spinal stenosis group, 10.0% in the control group, and 6.4% in the lumbar disk herniation group, and this difference was statistically significant ($P < 0.0001$).

Anekstein et al found that 28% of patients with stenosis had diabetes ($P < 0.001$). We used HbA1c for the diagnosis of diabetes to decrease mistaken diagnoses, and this is a point of strength of our study, which may have caused the difference between results (28% vs. 29.1%). In the study by Anekstein et al, the prevalence of diabetes increased with age, such that 18.2% of those under age 50 years, 16.7% of those between 50 and 60 years, and 33.3% of those older than 60 years had diabetes.[7] In our study, subgroup analysis showed that the prevalence of diabetes in patients with spinal stenosis for all the three age groups was greater than in the other two groups (control and lumbar disk herniation). However, the view that both diabetes and degenerative stenosis also occur later in life is justified.

Diabetic neuropathy is one of the differential diagnoses to rule out spinal stenosis symptoms and may be, in some cases, an improper diagnosis of spinal stenosis. This misdiagnosis can be improved by electrodiagnostic studies that differentiate these conditions. However, in this study, patients with neurogenic claudication symptoms were evaluated based on accurate clinical findings and confirmed by precise imaging. We did not use electrodiagnostic findings to prove the spinal stenosis diagnosis.

Limitations

It is a limitation of this study that the discopathy group was younger than the other two groups, with too few participants in the >60 age group, which might bias the diabetes prevalence assessment. Spinal stenosis, compared with lumbar disk herniation, occurred in older patients. Therefore, it is possible that the length of time needed for the effect of diabetes as a causative factor for spinal stenosis increases with age. If this is the case, we can evaluate the effects on the spine in high-risk patients at the time of diabetes diagnosis.

Another limitation of this study was poor correlation of the control group. We investigated 390 people to find 110 volunteers for the control group. We did not investigate the duration of diabetes and the type of diabetes treatment.

Accordingly, among female subjects, diabetes was found to be a statistically significant independent risk factor for lumbar spinal stenosis ($P < 0.0001$). This may be due to

Table 4. Multinomial logistic regression analysis to determine the prognostic role of diabetes grouped by sex.

	COEFFICIENTS	ODDS RATIO	95.0% CI FOR ODDS		*P*-VALUE
			LOWER	UPPER	
Male					
Diabetes in the LSS group	0.323	1.381	0.283	6.734	**0.690**
Diabetes in the lumbar disk herniation group	−1.165	0.312	0.031	3.179	0.325
Female					
Diabetes in the LSS group	1.589	4.9	2.1	11.6	**<0.0001**
Diabetes in the lumbar disk herniation group	−0.316	0.729	0.241	2.2	0.577

Note: Statistical significance was set at a likelihood value less than 0.05.

our selected bias that the number of our female subjects was greater than the number of male subjects.

Against these limitations, our study is the first prospective study in this area, and the use of HbA1c for the detection of diabetes increases the accuracy of our study. Although this small group of patients confirms an already well-noted relationship between diabetes mellitus and lumbar spinal stenosis, perhaps some further patients and pathological collections could help elucidate the pathophysiology of this association.

Conclusions

There is an association between diabetes and lumbar spinal stenosis. Diabetes mellitus may be a predisposing factor for the development of lumbar spinal stenosis.

Diabetes type (1 or 2), hereditary factors, drug and insulin medication, the quality of treatment, and HbA1c from the time of diabetes diagnosis are all factors that could be considered a guide for future studies to seek a more scientific basis for understanding how diabetes possibly affects the structure of the spine, results in stenosis, and causes clinical symptoms. This information can aid in preventing this debilitating process. It is necessary to investigate the molecular effects of diabetes on spinal column structure (ligamentum flavum, facet joint, disk, etc.) in patients with spinal stenosis.

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Author Contributions

Conceived and designed the experiments: KH. Analyzed the data: MA. Wrote the first draft of the manuscript: LA. Contributed to the writing of the manuscript: LA. Agree with manuscript results and conclusions: KH. Jointly developed the structure and arguments for the paper: AZ. Made critical revisions and approved final version: KH. All authors reviewed and approved of the final manuscript.

REFERENCES

1. Silberberg R. The skeleton in diabetes mellitus: a review of the literature. *Diabetes Res*. 1986;3:329–338.
2. Sternberg M, Cohen-Forterre L, Peyroux J. Connective tissue in diabetes mellitus: biochemical alterations of the intercellular matrix with special reference to proteoglycans, collagens and basement membranes. *Diabete Metab*. 1985;11(1):27–50.
3. Cinotti G, Postacchini F, Weinstein JN. Lumbar spinal stenosis and diabetes. Outcome of surgical decompression. *J Bone Joint Surg Br*. 1994;76(2):215–219.
4. Hilibrand AS, Rand N. Degenerative lumbar stenosis: diagnosis and management. *J Am Acad Orthop Surg*. 1999;7(4):239–249.
5. Rohrbach DH, Hassell JR, Kleinman HK, Martin GR. Alterations in the basement membrane (heparan sulfate) proteoglycan in diabetic mice. *Diabetes*. 1982;31(2):185–188.
6. Robinson D, Mirovsky Y, Halperin N, Evron Z, Nevo Z. Changes in proteoglycans of intervertebral disc in diabetic patients. A possible cause of increased back pain. *Spine*. 1998;23(8):849–855. Discussion 856.
7. Anekstein Y, Smorgick Y, Lotan R, et al. Diabetes mellitus as a risk factor for the development of lumbar spinal stenosis. *Isr Med Assoc J*. 2010;12:16–20.
8. Inamasu J, Guiot BH, Sachs DC. Ossification of the posterior longitudinal ligament: an update on its biology, epidemiology, and natural history. *Neurosurgery*. 2006;58(4):1027–1039.
9. Devogelaer JP, Maldague B. Lumbar spinal stenosis in metabolic bone disease. In: Gunzburg R, Szpalski M, eds. *Lumbar Spinal Stenosis*. Philadelphia, PA: Lippincott Williams & Wilkins; 1999:279–301.
10. Sakellaridis N. The influence of diabetes mellitus on lumbar intervertebral disk herniation. *Surg Neurol*. 2006;66(2):152–154.
11. Moskowitz RW, Ziv I, Denko CW, Boja B, Jones PK, Adler JH. Spondylosis in sand rats: a model of intervertebral disc degeneration and hyperostosis. *J Orthop Res*. 1990;8(3):401–411.
12. Takahashi S, Suzuki A, Toyoda H, et al. Characteristics of diabetes associated with poor improvements in clinical outcomes after lumbar spine surgery. *Spine*. 2013;38(2):516–522.
13. Lotan R, Oron A, Anekstein Y, Shalmon E, Mirovsky Y. Lumbar stenosis and systemic diseases: is there any relevance? *J Spinal Disord Tech*. 2008;21(4):247–251.
14. Uesugi K, Sekiguchi M, Kikuchi S, Konno S. Relationship between lumbar spinal stenosis and lifestyle-related disorders: a cross-sectional multicenter observational study. *Spine*. 2013;38(9):E540–E545.