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Clinical Studies

Hyperglycemia and its influence on development of lumbar degenerative disc disease

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ABSTRACT

Study Design: A Retrospective observational study.

Objectives: To determine the influence of hyperglycemia on severity of lumbar degenerative disc disease (LDDD).

Methods: We retrospectively included 199 patients with low back pain (LBP) who visited our tertiary care hospital from June 2016 to December 2018. All patients divided into three groups as per inclusion and exclusion criteria. Group-A had patients without DM (n = 75). Group B had well-controlled DM patients (n = 72) and Group-C had uncontrolled DM patients (n = 52). Group B and C subdivided according to dutation of DM. Group-B1 DM duration was ≤ 10 years (n = 38), Group-B2 DM duration was >10 years (n = 34), Group-C1 DM duration ≤10 years (n = 28), Group-C2 DM duration >10 years (n = 24). Sex, age, BMI, occupation, smoking history, alcohol use and duration of type-II DM were recorded. The severity of LDDD was evaluated using the five-level Pfirrmann grading system. Operated patient's disc material sent for histological examination.

Results: Patients with DM showed more severe disc degeneration compared to patients without DM. The average Pfirrmann scores between Groups A and B1 had no difference; Groups B2, C1, and C2 showed higher average Pfirrmann-scores than Group-A ($p > 0.05$). Group-B2 and Group-C2 showed higher average Pfirrmann-scores than Group-B1 and Group-C1 ($p > 0.05$). Group-C1 and Group-C2 showed higher average Pfirrmann-scores than Group-B1 and B2 ($p > 0.05$). The severity of LDDD was significantly related to DM duration both in groups B & C ($p > 0.05$). DM groups showed increased disc apoptosis and matrix aggrecan fragmentation, Disc glycosaminoglycan content and histological significantly different, the results are similar to Pfirrmann-score results.

Conclusions: There is a positive relationship between diabetes and LDDD. A longer the duration and poor control of hyperglycemia could aggravate disc degeneration.

AGEs	Advanced glycation end products
BMI	Body mass index
DM	Diabetes mellitus
HBP	High blood pressure
LDD	Lumbar disc degeneration;
NP	Nucleus pulposus

Introduction

The most common cause of hyperglycemia is diabetes. Diabetes is associated with high blood glucose levels that result from insulin secretory defects or insulin resistance. There are two main forms of DM, type-I and type-II. Approximately 90% of all cases of DM are type-II DM. According to 2014 data, the estimated prevalence of diabetes mellitus was 11.8% in the adult population of India [1]. Diabetes is a multiorgan disease that affects many types of connective tissues, including bone and cartilage [2]. Diabetes is associated with an increased risk of certain musculoskeletal pathologies. Prolonged and frequent complications of diabetes include diabetic neuropathy, with symptoms such as pain and sensory and motor deficits in the legs [3].

The lumbar degenerative disc disease (LDDD) is caused by vertebral space reduction, which can be due to new bone formation or hypertrophic tissue changes. LDDD is a major contributor to back and radicular pain, resulting imbalance in catabolic and anabolic responses leads

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to the degeneration of intervertebral disc (IVD) tissues, as well as disc herniation and radicular pain. The process usually begins with water loss or reduction in water content, followed by a hard disc protrusion [4].

The changes in the intervertebral disc play a primary role in the pathophysiology of LDDD. Age-related changes in the cartilage matrix in patients with diabetes are different from the changes in healthy subjects [5]. These changes may lead to faster disc 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 disc disease. Additionally, diabetes causes the ossification of the posterior longitudinal ligaments and bone, which leads to spinal stenosis and nerve pressure [6]. 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.[7,8]. Approximately 13% of patients who undergo lumbar disc surgery were diagnosed with diabetes, whereas the prevalence of diabetes in the same population generally was approximately 8% [9].

Diabetic microangiopathy might affect the nutrition of the spine and lead to disc degeneration [10]. 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. However, the relationship between DM and LDDD remains unclear, and different results have been achieved. In this retrospective study, we determined the prevalence and association of DM with LDD using the five-level Pfirrmann scoring system and histopathological evidence.

Methods

This retrospective study was conducted from June 2016 to December 2018 at a single tertiary care institute in India. Total 199 patients with lower back pain included in this study as per inclusion-exclusion criteria. Institution ethics committee approval was taken prior to study.

Inclusion criteria:

(a) Age between 20 to 65 years
(b) No previous conservative or surgical treatment history
(c) Spine MRI Scan (No lumbar abnormality other than lumbar degenerative spondylosis)
(d) Non-smoker/ No tobacco chewing
(e) No other Comorbidity

Exclusion criteria

(a) Type-I Diabetes
(b) History of extreme spinal loading occupation
(c) History of spinal trauma or fracture

Total of 199 consecutive patients was included in this study as per criteria. A group-A included patients without DM (n = 75). Patients with DM were divided into two groups: Group B-a well-controlled group (n = 72), and Group C- a poorly controlled group (n = 52). Group B was subdivided into Group B1-DM duration was ≤ 10 years (n = 38), Group B2 -DM duration was >10 years (n = 34). Similarly, Group C was subdivided into Group C1 -DM duration was ≤ 10 years (n = 28), Group C2 -DM duration was >10 years (n = 24). Demographic data, DM duration and clinical-radiological data were recorded. The criteria for a diagnosis of diabetes were fasting plasma glucose ≥ 126 mg/d, or in a patient with classic symptoms of hyperglycaemia or hyperglycemic crisis, random plasma glucose ≥ 200 mg/dL, or HbA1c ≥ 6.5%.

Standing lumbar anteroposterior-AP and lateral radiographs and MRI of the lumbar spine was performed for LDDD Scoring. Grading of the lumbar disc was performed using T2-weighted sagittal images, by a senior radiologist blinded to the patient's demographic information. The five-level Pfirmann grading system was used. Patients with failed conservative management were managed operatively, Various decompression/ spine stabilizing procedure (Laminectomy and decompression, TLIF) performed according to patients clinical finding. The patients who were operated for LDDD their disc material sent for histopathological and quantitative immunofluorescence analysis (Table 1).

Histopathological and quantitative immunofluorescence analysis:

- Histological Analysis: Lumbar Disc material was fixed with 2% paraformaldehyde overnight at 48C^o. (Tissue Tec processors and Leica embedder). 4-mm sections were stained with Safranin-O and fast green dyes (Fisher Scientific, Pittsburgh, PA) by standard procedure and photographed under 40– 200 × magnification.
- Proteoglycan Synthesis
- Quantitative Immunofluorescence
- Apoptosis Assay

Statistical analysis

All statistical analyses were performed using SPSS 19.0 (Inc., Chicago, IL, USA). All data are presented as means ± standard deviation or percentages. The clinical characteristics were compared between patients with and without DM using general linear model analysis for continuous variables and chi- squared tests for categorical data. Multinomial logistic regression analysis was adopted to identify the relationship between the DM and severity of LDDD. Estimated average Pfirrmann scores concerning the presence of DM were calculated by analysis of covariance.

Results

199 adult patients were included with an average age of 56.49 ± 9.81 (20–65). There were no significant differences amongst all groups for sex, BMI, and other comorbidities ($p > 0.05$), except for age ($p < 0.05$).

Average Pfirrmann scores from L1/L2 to L5/S1 of patients with good control of DM and DM duration ≤ 10 years showed no significant difference with patients without DM ($p > 0.05$). Patients with poor control of DM or DM duration >10 years showed higher average Pfirrmann scores than patients without DM ($p < 0.05$). Patients with a longer DM duration showed higher average Pfirrmann scores than patients with a shorter disease course ($p < 0.05$). The average Pfirrmann scores of patients with a poor control of DM were higher than the ones with good control of DM ($p < 0.05$). By utilizing Spearman correlation analysis to investigate the effect of DM duration on LDD, a positive trend was observed between DM duration and severity of disc degeneration ($P < 0.05$) (Table 2).

Result of Histopathological and quantitative immunofluorescence analysis:

- *GAG Content:* The DMMB assay was performed to measure disc GAG content. The GAG amount and level in lumbar discs in all groups was not significantly different after controlling for patient age. This finding was qualitatively confirmed by Safranin-O/fast green histological staining.
- *Proteoglycan Synthesis:* PG synthesis was assessed by measuring 35S-sulfate incorporation into disc tissue using a disc organotypic culture system. A significant reduction of PG synthesis was noted in DM patients.
- Immunoblot Analysis of Aggrecan Fragments: To investigate if disc matrix degradation was caused by increased aggrecan cleavage, Western Blot analysis was performed on disc material of all groups. The amount of disc aggrecan fragments was significantly higher in patients with DM. In particular, the most significant elevation in the number of fragments was noted in patients with a longer duration of diabetes and more poorly controlled diabetes.
- *Quantitative Immunofluorescence:* As ADAMTS seemed to be primarily involved in proteoglycan breakdown within the disc, and thus potentially implicated in LDDD, quantitative immunofluorescence

Table 1
Pfirrmann scores.

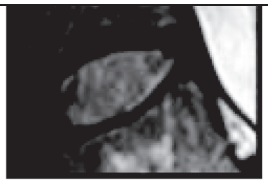
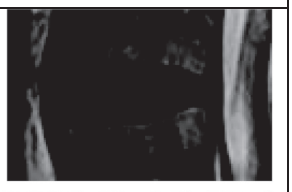
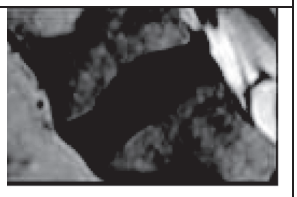
Grade	Structure	Distinction of nucleus and annulus	Signal intensity	Disc height	Sagittal T2 MRI
I	homogeneous with bright white	Clear	Hyperintense	Normal	
II	Inhomogeneous With or Without bright white	Clear	Hyperintense	Normal	
III	Inhomogeneous with a grey	Unclear	Intermittent	Normal to slightly decreased	
IV	Inhomogeneous with a dark grey	Lost	Intermittent to Hypointense	Slightly or moderately decreased	
V	Inhomogeneous with a dark grey	Lost	hypointense	Disc space is collapsed	

Table 2
Demographic data of different groups.

	GROUP A (No DM)	Group B (Controlled DM)		Group C (Uncontrolled DM)	
		B1 (≤ 10 years)	**B2** (>10 years)	**C1** (≤ 10 years)	**C2** (>10 years)
N	75	38	34	28	24
Age (years)	55.2 ± 7	58.8 ± 6	61.2 ± 7	59.1 ± 7	61.8 ± 7
BMI (kg/m^2)	18.9 ± 2.2	6.6 ± 0.4	6.7 ± 0.4	7.5 ± 0.6	7.7 ± 0.5
HbA1c (%)	5.6 ± 0.2	6.6 ± 0.4	6.7 ± 0.4	7.5 ± 0.6	7.7 ± 0.5

with anti- ADAMTS antibodies was performed to identify which isoform could be mainly responsible for aggrecan degradation. More specifically, ADAMTS4 and ADAMTS5 protein expression were investigated in disc sections. These proteins were significantly higher in DM patients, and were noted to be most significantly elevated in patients with longer duration of diabetes and poorly controlled diabetes.

Discussion

The most common cause of hyperglycemia is diabetes. Diabetes is one of the common condition that causes metabolic disturbances in many organs. Degenerative disc disease is a serious healthcare problem. It can be a cause of moderate to severe pain, affecting the patient's quality of life as well as increasing healthcare costs [9]. It is important to clarify the risk factors of LDDD to prevent or delay its onset or progression. This study was the first to use the Pfirrmann grading system to evaluate the association between DM and LDDD with histopathological evidence. In this study, we included patients without DM and patients with different durations and different control effects of DM for comparisons. After removing the effect of age, our study demonstrated that patients with DM tended to develop more severe LDDD than those without DM. The length of DM duration had a positive relationship with severity of LDDD, which meant that the longer DM duration was, the

more severe disc degeneration would be. Patients with poor control of DM seemed to show more severe disc degeneration than patients with good control. All these demonstrated that DM was a risk factor for LDD, and such effect was time and control effect dependent.

Frymoyer et al. [11] reported that degenerative spondylolisthesis is more prevalent in diabetic patients, while a community-based study by Vogt et al. [12] did not find any correlation between a history of DM and the prevalence of L4-5 degenerative spondylolisthesis. In previous studies, one reported that the DM patients had a poorer outcome following lumbar discectomy than controls, and the rates of reoperation and prolonged hospitalization were also significantly higher in DM patients [13]. Sakellaridis et al. [14] and Machino et al. [15] both reported that high preoperative glycated haemoglobin levels and long-term DM were risk factors for poor cervical laminoplasty outcomes in patients with DM and cervical spondylotic myelopathy. Now, we can understand the underlying mechanisms of it and conclude that there is a positive relationship between DM and LDDD. Several studies assumed that hyperglycemia enhances the formation of advanced glycation end products (AGEs) in the NP which leads to the progression of disc degeneration [16,17]. Chen et al. found that DM accelerated the degeneration process of the disc by microangiopathy [18]. Autophagy of the nucleus pulposus and annulus fibrosis cells also appears to play an important role in LDDD. Park et al. [19] and Kong et al. [20] demonstrated that high glucose-induced oxidative stress accelerates premature stress-induced senescence in young rat AF cells in a dose and time dependent manner rather than replicative senescence. However, no conclusion has been made. Some studies have investigated methods to slow down the process of LDDD caused by DM. Kong et al. suggested that strict blood glucose control is important in preventing or delaying LDDD in older patients with DM [20].

In our study, we also found that the average pfirrmann scores of patients with good control of DM and DM duration ≤10 years showed no difference with patients without DM after the removal of the age effect. To the best of our knowledge, this was the first study to investigate the relationship between DM and LDDD using the five-level Pfirrmann grading system with Histopathological evidence. A HbA1c was used to detect diabetes that increases the accuracy of our study.

Drawbacks of this study are the short follow-up and smaller data size. Another limitation is the fact that degenerative disk disease, spinal stenosis and vertebral osteoporotic fractures, may simultaneously exist in the same patient. Future prospective comparative studies with the larger patient number and longer follow-up are required for confirmation of our results.

Conclusion

There is a positive relationship between hyperglycemia / diabetes and LDDD. A longer the duration and poor control of DM could aggravate disc degeneration.

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Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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