ORIGINAL RESEARCH PAPER

Orthopaedics

KEYWORD:

STUDY THE FIBROSIS AND HYPERTROPHY OF LIGAMENTUM FLAVUM IN LUMBAR SPINAL CANAL STENOSIS DUE TO LEPTIN INDUCED INFLAMMATION

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ABSTRACT

Lumbar spinal stenosis (LSS) is defined as the narrowing of the spinal canal with cord or nerve root impingement and as consequences the symptoms of radiculopathy or pseudoclaudication are developed. Hypertrophy of the ligamentum flavum (LF) is often involved in the pathogenesis of LSS, resulting in the reduction of diameter of the spinal canal and compression of the dural sac and nerve roots. Leptin's important role in various biological functions further than appetite regulation and energy metabolism. Interestingly collective evidence suggests it has a critical role in the fibrosis process in multiple organ systems, including the liver, kidney, and lung. The aim of this study was to establish a relationship between serum leptin levels and the fibrosis and hypertrophy of ligamentum flavum in lumbar spinal canal stenosis. **METHOD:** Our study include 100 patient with ligamentum flavum hypertrophy with lumbar canal stenosis to evaluate co-relation with increased serum leptin levels. Demographic data, clinical, radiological and laboratory investigation done to find a co-relation between increased serum leptins levels with the fibrosis and hypertrophy of ligamentum flavum in lumbar canal stenosis. **RESULT:** In our study, LF thickness was also measured with a T1 weighted axial MRI. The mean thickness in the high vas scores (> 5) group was signi cantly thicker than that in the low vas (< 5) group. Serum leptin values were positively correlated to LF Thickness at L4-L5 (r=0.228) and L5-S1 (r=0.198) level and the correlation was significant (p>0.05). **CONCLUSION:** Our study has shown strong correlation between serum levels of leptin and hypertrophy of ligamentum flavum. VAS score in low VAS group (< 5) as well as high VAS score group (> 5) are positively correlated with serum levels of leptin.

INTRODUCTION

Lumbar spinal stenosis(LSS) is defined as the narrowing of the spinal canal with cord or nerve root impingement and as consequences the symptoms of radiculopathy or pseudoclaudication are developed [1]. Joints between the vertebrae are protected and supported by various ligaments; one of them is the ligamentum flavum. Ligamentum flavum(LF) are attached to the front of the upper lamina above and to the back of the lower lamina below. As they are connective tissue, they are responsible for the intrinsic stability of the spine, controlling intervertebral movement, and maintaining a smooth surface of the posterior dural sac .

Hypertrophy of the ligamentum flavum is often involved in the pathogenesis of LSS, resulting in the reduction of diameter of the spinal canal and compression of the dural sac and nerve roots. This manifests in symptoms, even in the absence of a bulging annulus fibrosus or herniated nucleus pulposus or osseous spurs [2–4]. Ligamentum flavum (LF) is a well-defined elastic structure that consists of elastic (80%) and collagen (20%) fibers [5]. Hypertrophied LF tissues become disorganized and show decreased levels and degeneration of elastic fibers but increased levels of collagen fibers [6, 7]. During LF hypertrophy, there are increases in the expression and activity of various molecules, including matrix metalloproteases (MMPs) [8–10], tissue inhibitors of matrix metalloproteases (TIMPs) [11], platelet-derived growth factor-BB (PDGF-BB) [12], connective tissue growth factor (CTGF) [13], bone morphogenetic protein (BMP) [14], and inflammatory cytokines [15–17]. The study intended to explore the role of interleukin 6 associated with leptin secreted in hypertrophied ligamentum flavum has indicated that leptin administration elevated IL-6 mRNA and protein [18]

Leptin is a 16kDa peptide hormone product of cytokine family. Since the first identification in 1994 by Zhang [6], the role of leptin has been widely reported by previous studies [19-21]. Interestingly collective evidence suggests it has a critical role in the fibrosis process in multiple organ systems, including the liver, kidney, and lung [21,22,23].

Therefore, the aim of this study was to establish a relationship between serum leptin levels and the fibrosis and hypertrophy of ligamentum flavum in lumbar spinal canal stenosis. We also wanted to study the clinical characteristics of patients with the fibrosis and hypertrophy of ligamentum flavum in lumbar spinal canal stenosis.

This exploratory study is expected to help in understanding the role of leptin in lumbar spinal canal stenosis.

AIMS AND OBJECTIVES

This prospective study was conducted in adult patients of both the genders in patients of lumbar spinal canal stenosis with following objectives.

1. To establish a relationship between serum leptin levels and the fibrosis and hypertrophy of ligamentum flavum in lumbar spinal canal stenosis.
2. To study the clinical characteristics of patients with the fibrosis and hypertrophy of ligamentum flavum in lumbar spinal canal stenosis.
3. To study the demographic data of patients presenting with the fibrosis and hypertrophy of ligamentum flavum in lumbar spinal canal stenosis with serum leptins levels.

METHODOLOGY

A) Inclusion criteria:

1) Patients with the fibrosis and hypertrophy of LF in LSS seen on MRI.
2) Patient with –
a) H/O poor posture at work causing mechanical stress-
b) Neurogenic Claudication

B) Exclusion Criteria:

1) Patients with diagnosed neurological dysfunction such as-

a) Stroke leading to monoparesis /monoplegia /paraparesis /paraplegia /quadriparesis /quadriplegia
b) peripheral neuropathy
c) GB syndrome
d) Ataxia

2) traumatic cervical spine injury.
3) congenital spine deformities
4) fractures in lower limbs.
5) known psychological dysfunction
6) Tuberculosis of spine and other infections of spinal cord

C) Study design: Cross-sectional observational study
D)Study setting: In hospital,

SAMPLE SIZE- Based upon the hospital based prevalence of LSS in100 patients fulfilling the inclusion criteria in 2 years span of study will be included

D) Source : Patients attending either in orthopedic opd or admitting in orthopedic ward in all 3 units of orthopedics of this teaching hospital shall be included in the study.

E) Study period: 2 years
F) Risk involved: The additional risk involved in this study is minimal.

G) Expected results: study will show the relationship between severity of fibrosis and hypertrophy of LF in LSS with increased levels of serum leptins.

H) Institutional Ethics Committee Approval:
Institutional Ethics Committee approval was obtained prior to the start of the study. A synopsis was presented along with complete protocol

I) Duration: It was planned in the duration 2017-2019.
J) Design: prospective study with above mentioned selection criteria.

Patients with a history of previous lumbar surgery or radiotherapy, patients with congenital anomalies, scoliosis, spondylolisthesis and patients with cardiac pacemakers, aneurysms, clips and metallic implants plants and joint replacements were excluded from MRI procedures.

MRIs of the whole spine of the included patients were performed on a (1.5T) capacity machine. In each patient, the MRI was performed in the sagittal and axial plane. The mobi view was used to count the number of vertebrae. Cases with lumbarization or sacralization were marked separately.

T2-weighted sagittal images were used to locate the spinal level of intervertebral spaces and after confirmation, measurements of the LF thickness were made on the T2-weighted axial images at the L3–L4, L4–L5, and L5– S1 spinal levels. The measurements were done with the help of Dicom works software installed on the computer.

STATISTICAL ANALYSIS METHOD

Primary data was collected in paper based proforma and the data was then entered in Microsoft Excel spreadsheets. Statistical analysis was done on IBM SPSS STATISTICS VERSION 20.

Categorical variables were taken in the form of frequencies and proportions and were compared using chi square test.

Means were compared using independent sample T test.

Categorical data was plotted using bar charts, column charts and pie diagrams.

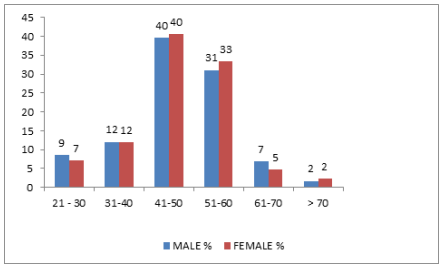
Mean values represented by column charts are added with error columns representing actual standard deviation in plus and minus values. Correlations between values were done using Pearson's coefficient of correlation.

P value less than 0.05 was taken significant. P values less than 0.01 shall be considered highly significant.

OBSERVATIONS AND RESULTS

Table 1: Frequency Distribution Of Patient Age Groups Stratified By Gender

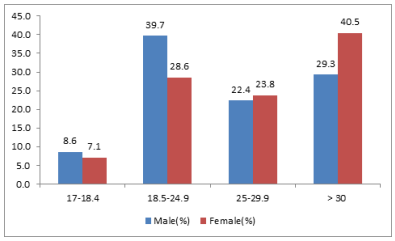
Frequency Distribution of Patient Age groups stratified by Gender						p
RANGE	**FREQUENCY**	**MALE**		**FEMALE**		
	N=100	**Number**	**%**	**Number**	**%**	
21 - 30	8	5	9	3	7	>0.05
31-40	12	7	12	5	12	>0.05
41-50	40	23	40	17	40	>0.05
51-60	32	18	31	14	33	>0.05
61-70	6	4	7	2	5	>0.05
> 70	2	1	2	1	2	>0.05
Total	**100**	**58**	**100**	**42**	**100**	



- 52 males and 48 females in the study population
- > 70 % cases in both the genders were in the age group 41-60.
- Age distribution among patients was comparable in both the genders. (p>0.05)

Table 2: Frequency Distribution Of Patient Bmi Groups Stratified By Gender

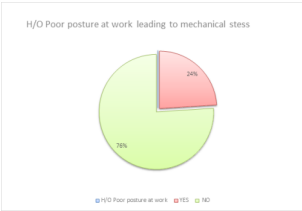
Frequency Distribution of Patient Age groups stratified by Gender						p
RANGE	**FREQUENCY**	**MALE**		**FEMALE**		
	N=100	**Number**	**%**	**Number**	**%**	
17-184	8	5	9	3	7	>0.05
18.5-24.9	35	23	40	12	29	>0.05
25-29.9	23	13	22	10	24	>0.05
>30	34	17	29	17	40	>0.05
Total	**100**	**58**	**100**	**42**	**100**	



- 23 % of the patients were overweight while 34 % were obese.
- More males (40 %) than females (29%) were in the normal BMI range.
- The BMI distribution between genders was comparable (p >0.05)

Table3:h/o Poor Posture At Work Causing Mechanical Stress

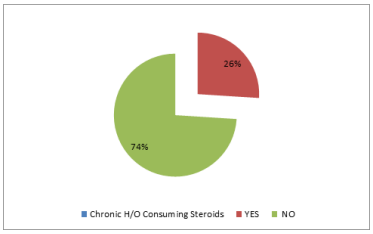
	H/O Poor posture at work
YES	24%
NO	76%



- 24 % cases have poor posture at work.

Table 5: History Of Chronic Consumption Of Nsaids Or Opoids

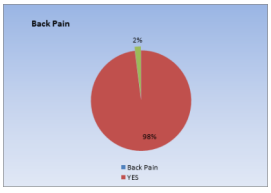
History of Chronic Consumption of NSAIDS or Opoids	
YES	26%
NO	74%



26% of the patients had been consuming NSAIDs or opoids > 6 months.

Table 6: Back Pain Percentage

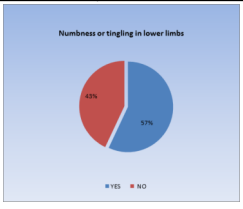
Back Pain	
YES	98%
NO	2%



Majority (98%) of the cases reported that they hadcomplaint of back ache.

Table 7: Numbness or tingling in a foot or leg

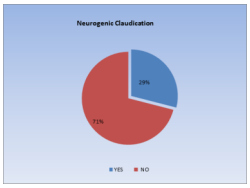
Numbness or tingling in a lower limbs	
YES	57%
NO	43%



57 % cases have numbness or tingling in the foot or leg.

Table 8: Neurogenic Claudication

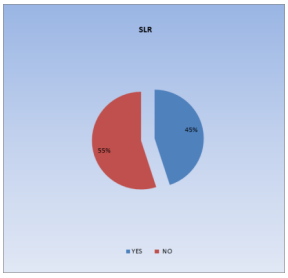
Neurogenic Claudication	
YES	29%
NO	71%



29 % of the cases have neurogenic claudication.

Table 9: SLR Test among patients.

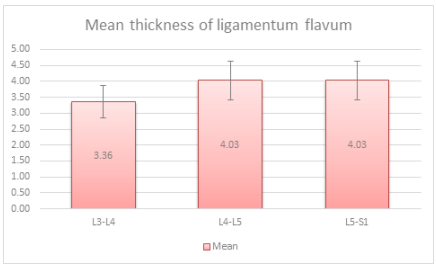
SLR POSITIVE TEST	
YES	45%
NO	55%



45 % of the patient have positive SLR.

Table 10: Comparison Of Average Thickness Of Lf In The Complete Study Population.

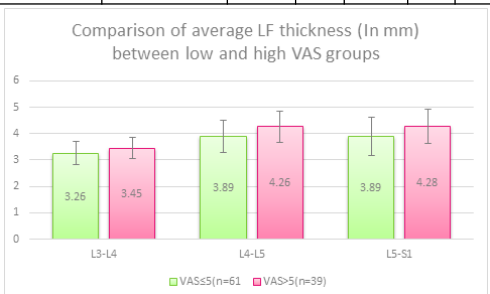
Thickness of Ligamentum Flavum in mm.	Level of Intervertebral disc space	L3-L4	L4-L5	100 L5-S1	P
	Mean	3.36	4.028	4.03	<0.00001
	SD	0.45	0.63	0.73	



Average thickness of LF at L3-L4 level was 3.36 mm, at L4-L5 was 4.028 mm and at L5-S1 was 4.03 mm.The mean difference was found statistically significant by one way ANOVA.

Table 11: Comparison Of Average Lf Thickness (in Mm) Between Low And High Vas Groups

Ligamentum Flavum Thickness in mm	Intervertebral Disc level	VAS≤5 (n=61)		VAS>5 (n=39)		
		Mean	SD	Mean	SD	P
	L3-L4	3.26	0.44	3.45	0.4	0.030*
	L4-L5	3.89	0.6	4.26	0.6	0.003**
	L5-S1	3.89	0.73	4.28	0.66	0.008**



Average LF thickness in high VAS (>5)

- at L3-L4 level was 3.45 mm which was significantly higher than low VAS (≤5) cohort at where the average thickness was 3.26 mm. ($p<0.05$)
- at L4-L5 level was 4.26 mm which was significantly higher than low VAS (≤5) cohort at where the average thickness was 3.89 mm. ($p<0.01$)
- at L5-S1 level was 4.28 mm which was significantly higher than low VAS (≤5) cohort at where the average thickness was 3.89 mm. ($p<0.01$)

Table 12: Correlations Of Age with LF Thickness at different levels

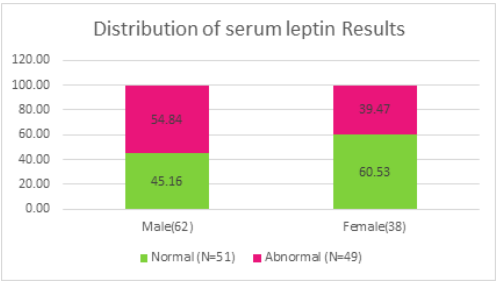
Correlations Of Age with LF Thickness at different levels				
		LF Thickness at L3-L4	LF Thickness at L4-l5	LF Thickness at l5-S1
AGE	Pearson Correlation	.360**	.297**	.342**
	P value	.000	.003	.001
	N	100	100	100
**. Correlation is significant at the 0.01 level (2-tailed).				

Age of the patients was positively correlated to the LF thickness

1. at L3-L4 level with coefficient of correlation (r) = 0.36 (p<0.0001).
2. at L4-L5 level with coefficient of correlation (r) = 0.297 (p<0.01).
3. at L5-S1 level with coefficient of correlation (r) = 0.342 (p<0.01).

Table 13: Distribution Of Serum Leptin Levels

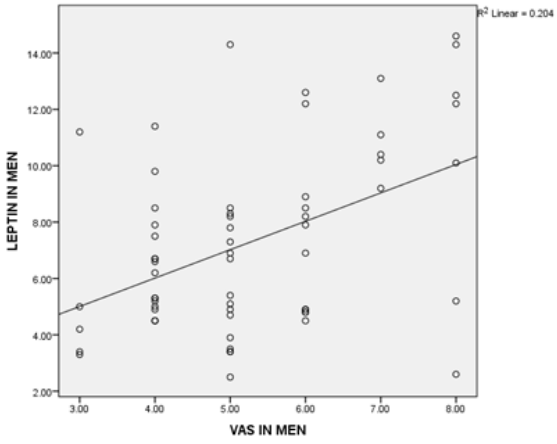
	Male(62)		Female(38)		
	Frequency	%	Frequency	%	P
Normal (N=51)	28	45.2	23	60.5	0.139
Abnormal (N=49)	34	54.8	15	39.5	



- Serum leptin levels normal in male in the ranges 3.63-5.63 ng/ml
- Serum leptin levels normal in female in the ranges 2.05-11.09 ng/ml
- 60.5 % of the males had serum leptins increased than normal level compare to 39.5 % females.

Table 14: Correlations Between Vas And Leptin Levels In Men

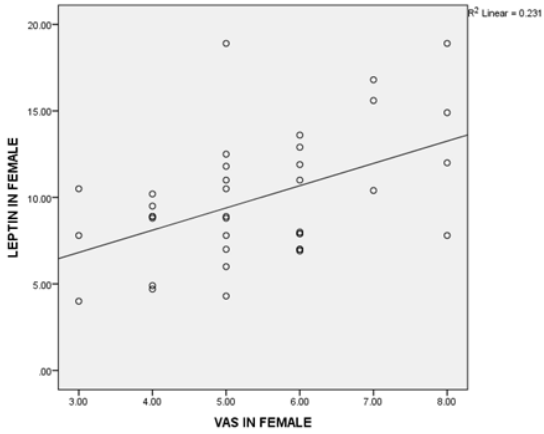
Correlations			
		VAS IN MEN	LEPTIN IN MEN
VAS IN MEN	Pearson Correlation	1	.452**
	Sig. (2-tailed)		.000
	N	62	62
**. Correlation is significant at the 0.01 level (2-tailed).			



VAS values in men were correlated positively (r=0.452) with serum Leptin values. The correlation was found highly significant. (p<0.01)

Table 15 : Correlations Between Vas And Leptin Levels In Female

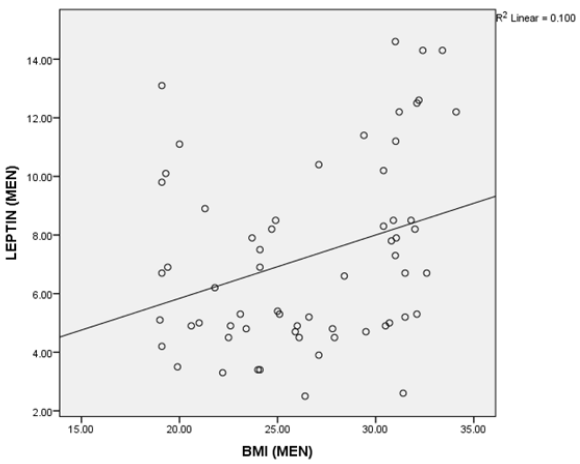
Correlations			
		VAS IN FEMALE	LEPTIN IN FEMALE
VAS IN FEMALE	Pearson Correlation	1	.481**
	Sig. (2-tailed)		.002
	N	38	38
**. Correlation is significant at the 0.01 level (2-tailed).			



VAS values in females were correlated positively (r=0.481) with serum Leptin values. The correlation was found highly significant. (p<0.01). The coefficient of correlation was stronger in case of females compared to male counterparts.

Table 16: Correlations Between Bmi And Leptin In Men

Correlations			
		BMI (MEN)	LEPTIN (MEN)
BMI (MEN)	Pearson Correlation	1	.316*
	Sig. (2-tailed)		.012
	N	62	62
*. Correlation is significant at the 0.05 level (2-tailed).			

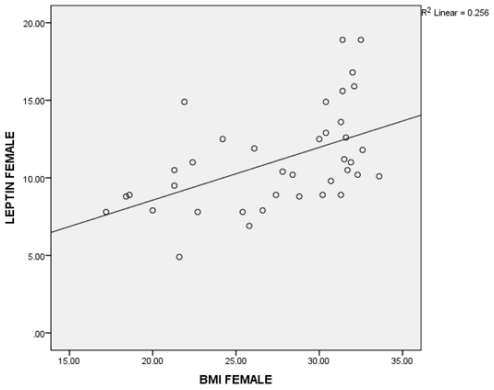


BMI in male patients was positively correlated to serum leptins. (r=0.3160 ,p<0.05)

Table 17: Correlation Between Bmi And Serum Leptins In Females.

		BMI FEMALE	LEPTIN FEMALE
BMI FEMALE	Pearson Correlation	1	.506**
	Sig. (2-tailed)		.001
	N	38	38

*. Correlation is significant at the 0.01 level (2-tailed).



BMI in female patients was positively correlated to serum leptins. (r=0.506 ,p<0.01). Coefficient of correlation was strongly positive and compared to male counterparts.

Table 18: Serum Leptin Levels With Thickness Of Lf At Various Levels.

Correlations				
		LF Thickness at L3-L4	LF Thickness at L4-L5	LF Thickness at l5-S1
serum leptin	Pearson Correlation	.175	.228*	.198*
	Sig. (2-tailed)	.082	.022	.048
	N	100	100	100
*. Correlation is significant at the 0.05 level (2-tailed).				

Serum leptin values were positively correlated to LF Thickness

- at L3-L4 (r=0.175) however the correlation was not significant (p>0.05)
- at L4-L5 (r=0.228) the correlation was significant (p>0.05)
- at L5-S1 (r=0.198) the correlation was significant (p>0.05)

DISCUSSION

In our study, LF thickness was also measured with a T1weighted axial MRI. The mean thickness in the high vas scores (> 5) group was signi cantly thicker than that in the low vas (< 5)l group.

At all of the levels investigated, LF thickness was significantly greater in patients with greater pain compared with the patients with lower pain (P < 0.05).

American College of Physicians and the American Pain Society recommended that for patients who do not improve with self-care options, clinicians should consider the addition of nonpharmacologic therapy with proven benefits-for acute low back pain, spinal manipulation; for chronic or subacute low back pain, intensive interdisciplinary rehabilitation, exercise therapy, acupuncture, massage therapy, spinal manipulation, yoga, cognitive-behavioral therapy, or progressive relaxation (weak recommendation, moderate-quality evidence) [27]. In our study a detailed history of physiotherapy was obtained and the cohorts were compared for their current pain by VAS.

In our study 39 % of the patient reported that they had received physiotherapy while 61 % reported that they never took physiotherapy. Also Mean VAS score in patients receiving physiotherapy was significantly lower than patients who never took physiotherapy (p<0.05)

LF thickness is an age dependent phenomenon. In the Indian study by Vrushali et al [25] significant Changes in LF thickness were witnessed at the L4–L5 and L5–S1spinal levels as age increased. These findings were matching to our study where we noted that age of the patients was positively correlated to the LF thickness at L3-L4 level with coefficient of correlation (r) = 0.36 (p<0.0001) at L4-L5 level with coefficient of correlation (r) = 0.297 (p<0.01) and at L5-S1 level with coefficient of correlation (r) = 0.342 (p<0.01).

In most of these studies (Abbas et al. [3] and Altinkaya et al. [24] the thickness of the LF varied at different Spinal levels, attaining a Maximum thickness At the L4–L5 level, followed by the L3–L4, and then the L5–S1levels.However our findings were consistent with studies conducted by Fu-kuyama et al. [15] and Safak et al. [2] who reported the maximum thickness to be at levelL5–S1.

Sun et al [26] concluded that leptin was detected in the hypertrophied LF and its expression was substantially increased in LSCS group and positively correlated with LF thickness and fibrosis score(P<0.05).

Serum leptin values were positively correlated to LF Thickness at L4-L5 (r=0.228) and L5-S1 (r=0.198) level and the correlation was significant (p>0.05).

Our findings of LF thickness and serum leptins were reestablishing the findings of Sun etal [26] however the leptin detected in their study was found in hypertrophied LF while we measured leptin values in the serum.

The present study too is in close agreement with Sakamakiet al. [11] and Abbas et al. [3], where the thicknes of the LF at the L3/L4, L4/5 and L5/S1 spinal levels significantly increased with age. We noted that age of the patients was positively correlated to the LF thickness at L3-L4 level with coefficient of correlation (r) = 0.36 (p<0.0001).(r=0.297 L4/L5,R=0.342, L5/S1)

We tried to correlate clinical outcomes of the lumbar stenosis patients with serum leptin values. We noted that as VAS scores increased the values of serum leptins also increased .The VAS values in females were correlated positively (r=0.481) with serum Leptin values and the correlation was found highly significant. (p<0.01). The coefficient of correlation was stronger in case of females compared to male counterparts suggesting higher sensitivity of serum leptins in females.

Binvu et al [28] showed that the intervertebral disc disorder and chronic LBP are linked with obese and overweight bodyweight status. We recorded 23 % of the patients were overweight while 34 % were obese and BMI in female patients was positively correlated to serum leptins. (r=0.506 ,p<0.01). Coefficient of correlation was strongly positive and compared to male counterparts.

SUMMARY AND CONCLUSION

A cohort of 100 Patients with the fibrosis and hypertrophy of LF in LSS seen on MRI were selected from the orthopaedic department. The primary objective of the study was to establish a relationship between serum leptin levels and the fibrosis and hypertrophy of LF in LSS.

The outcomes of this prospective cross sectional study are summarized as follows

1. Total 100 cases were studies 52 males and 48 females in the study population
2. More than 70 % cases in both the genders were in the age group 41-60.
3. 23 % of the patients were overweight while 34 % were obese.
4. 24 % cases reported that their posture during their work was not proper and led to mechanical stress .
5. 26 % of the patients reported that they had been consuming NSAIDs or opoids medications for duration more than 6 months.
6. 57 % cases were found to have numbness or tingling in the

foot or leg.

7. 29 % of the cases were found to have neurogenic claudication.
8. Average thickness of LF at L3-L4 level was 3.36 mm, at L4-L5 was 4.028 mm and at L5-S1 was 4.03 mm. The mean difference was found statistically significant by one way ANOVA.
9. Average LF thickness in high VAS (>5) at all levels was significantly more than the average LF thickness in low VAS (≤5)
10. VAS values in Males and females were correlated positively (r=0.452 for males and r=0.481 for females) with serum Leptin values. The correlation was found highly significant. ($p<0.01$).
11. Serum leptin values were positively correlated to LF Thickness at all levels.

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