

The Role of Microelements in Lumbar Disc Degeneration in Patients Undergoing Lumbar Spine Surgery

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Abstract

Background: Lumbar disc degeneration (LDD) is a common musculoskeletal disorder that frequently causes low back pain (LBP). In addition to the discomfort of lower back pain, it can accompany pain in one or both legs. The lumbar spine and sacrum, consisting of five vertebrae and one bone, determine the spine's balance. Microelements are essential in bone metabolism and are associated with preventing osteoporosis and alleviating musculoskeletal pain.

Objectives: To examine the correlation between lumbar spinal surgery and the concentrations of microelements, namely zinc and copper.

Methods: A case-control study was conducted in Ghazi Al-Hariri Hospital in Baghdad, Iraq, during the October 2023 to January 2024. The study included 120 participants ranging in age from 18 to 70 years. Sixty participants underwent lumbar spine surgery and were diagnosed using X-ray or MRI scans. The other 60 were healthy controls. The zinc (Zn) and copper (Cu) levels in the blood were determined using an atomic absorption spectrometer. The body mass index (BMI) was determined using the formula: $BMI (kg/m^2) = \text{weight}/\text{height}^2$.

Results: The patients had a lower mean zinc level ($57.3 \pm 14.56 \text{ Mmol/L}$) and a higher mean copper level ($106.6 \pm 39.41 \text{ Mmol/L}$) in comparison to healthy controls ($96.4 \pm 17.38 \text{ Mmol/L}$) and ($61.0 \pm 9.53 \text{ Mmol/L}$) respectively. There was a weak relationship and a significant correlation between copper and zinc ($r = -0.2$). A very strong relationship and a significant correlation between copper and Cu / Zn ratio ($r = 0.85$) while zinc had a significant very strong correlation relationship with Cu / Zn ratio ($r = -0.7$) in patients.

Conclusion: The present study underscores the noteworthy association between microelements (Cu, Zn) and degenerative lumbar discs underscoring the significance of pre-operative evaluation in achieving the best possible surgical results. The study has demonstrated the utility of measuring serum zinc level and copper level especially their link with lumbar disc degeneration (LDD) as markers of patients undergoing lumbar spinal surgery.

Keywords: Copper; Degeneration; Lower back pain; Lumbar Disc; Spinal surgery; Zinc.

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Introduction:

The lumbar spine, composed of five big vertebrae, and the sacrum, are crucial for spinal equilibrium, with lumbar lordosis influencing sagittal balance, posture, and upright walking, supporting bipedalism (1). Degenerative disc disease (DDD) is a complicated condition that is still poorly understood. Many theories have been put forth to explain the disease such as aging and the interaction of genetic and environmental variables. It has been demonstrated that the disproportion of anabolic and catabolic activity of extracellular matrix (ECM) enzymes including cathepsins, aggrecans and matrix metalloproteinases (MMPs) influences a significant percentage of the degeneration process (2).

Since low back pain is a symptom rather than a diagnosis, it might be caused by a variety of disorders both recognized and undiscovered.

Specific or non-specific low back pain (LBP) is

possible. Specific low back pain (LBP) refers to pain that originates in another area of the body or is brought on by a specific disease or anatomical issue in the spine (3).

A surgical method called lumbar interbody fusion (LIF) is used to treat degenerative lumbar segments, their decompressed neural components and any facet joint problems that may be related (4). Trace elements (TE) were explored in several illnesses such as osteoarthritis (OA), a whole-joint disease characterized by pathological changes in all joint tissues including subchondral bone sclerosis, cartilage loss and synovial inflammation (5). Most of the investigations focus on bone tissue, which is thought to be the storehouse for trace elements and reflects their cycling across the entire organism (6). Aside from that, recent research links TE to bone metabolic failure (7). Additionally, abnormalities in serum TE (Zn and Cu) are linked to cardiac failure and coronary artery disease (8).

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The body contains very small amounts of trace elements, which are vital micronutrients. They are essential to the healthy operation of the immune system and have a significant impact on several physiological functions (9). Trace elements such as copper and zinc, play a part in numerous biological activities as micro sources (10). Zinc (Zn) is a crucial component of bone health and a cofactor in metalloenzymes (11). A significant amount of the body zinc is found in the skeleton, where it is involved in intracellular signaling, endocrine axis modulation and long-bone growth (12). It promotes osteoblast growth and bone production, prevents osteoclastic bone resorption and shields osteoblasts from apoptosis. A zinc deficit affects collagen production, collagenase activity and bone mineralization. It also compromises the integrity of bone tissue (13). Copper (Cu) decreases bone metabolism by inhibiting osteoblasts and osteoclasts. Lysyl oxidase is an enzyme that crosslinks collagen fibers, and Cu is a cofactor for this enzyme (14). Cu deficit raises the risk of osteoporosis and causes bone abnormalities. The element has a strong correlation with bone flexibility and tensile strength, and it is crucial in the lysyl oxidase enzyme production process, which is responsible for the crosslinking of elastin and collagen in the organic matrix of bone (15).

Copper influences the equilibrium of humoral and cellular immunity. For growth, development and strong bones, it is necessary (16). Additionally, serum Cu is high in type 2 diabetics (17). Among the three primary disorders in orthopedics are osteoporosis, fractures and arthritis and Cu is crucial to the management of these three conditions (18).

Supplementation with trace metals like copper can help prevent and minimize bone loss (19). A previous study reported that alkaline phosphatase (ALP) activity and osteocalcin concentration were significantly increased with zinc supplementation. This finding demonstrated that zinc positively influences osteoblastogenesis, resulting in increased osteoblast differentiation and proliferation (20).

The aim of this research is to examine the correlation between lumbar spinal surgery and the concentrations of microelements.

Patients and Methods:

The case-control study was conducted on 120 individuals at Ghazi Al-Hariri Hospital in Baghdad, Iraq, during the period from October 2023 to January 2024. The age range of participants was between 18 and 70 years old. The participants were divided into two groups: 60 were patients who underwent lumbar spine surgery, and 60 healthy individuals who served as a group of controls from the same areas of the patients and were randomly selected. Inclusion criteria for both cases and controls were that they did not suffer from kidney or liver disease without known zinc and copper supplementation.

The study questionnaire included a set of questions on demographic and clinical characteristics. X-rays or MRI scans was utilized for imaging the lumbar

spines. Atomic absorption spectroscopy was used to measure the level of zinc and copper. Weight and height were measured to calculate the body mass index (BMI), and to classify the participants according to World Health Organization (WHO) (21).

Statistical Analysis:

The data was managed using SPSS version 25.0 software. Frequency, percentage, mean and standard deviation were used to describe the data. To investigate the association between the qualitative variables, the chi-square test was utilized. The independent t-test was used to evaluate the difference between means and the Pearson correlation coefficient was used to analyze the correlation between two quantitative variables. With values <0.3 signifying no correlation, $0.3 - <0.5$ denoting weak correlation, $0.5 - <0.7$ moderate strength and >0.7 strong correlation. P-values of <0.05 were regarded as significant. Receiver operating characteristic (ROC) analysis was used to determine the ideal threshold for study cases, which had high specificity and sensitivity.

Results:

The mean age of the cases was (50.9 ± 13.76) years compared to (44.5 ± 6.21) years for controls p -value <0.001 .

The mean BMI was $26.2 \pm 3.16 \text{ kg/m}^2$. Patients had a significantly higher BMI mean $(28.1 \pm 3.41 \text{ kg/m}^2)$ in comparison to healthy controls $(24.4 \pm 1.14 \text{ kg/m}^2)$, p -value <0.001 . Regarding BMI groups, 45.4% had a normal BMI; the percentages for overweight were 41.2%, obese 12.6% and severely obese 0.8%, Table 1.

Table 1: Demographic characteristics of the study groups

Demographic	Patients	Controls	Total	p- value
Age (years)	50.9 ± 13.76 (1.77)	44.5 ± 6.21 (0.80)	40.2 ± 15.12	$<0.001^\ddagger$
BMI (kg/m^2)	28.1 ± 3.41 (0.44)	24.4 ± 1.14	26.2 ± 3.16	$<0.001^{*\ddagger}$
Sex	Male (46.7%)	33 (55%)	61 (50.8%)	0.46
	Female (53.3%)	27 (45%)	59 (49.2%)	
	Normal (16.7%)	44 (74.6%)	54 (45.4%)	$<0.001^{*\ddagger}$
	Overweigh (56.7%)	15 (25.4%)	49 (41.2%)	
	Obese (25.0%)	0 (0.0%)	15 (12.6%)	
Morbid ob	1 (1.7%)	0 (0.0%)	1 (0.8%)	

Mean \pm SD (SE), N (%), *p-value is significant, \ddagger independent t-test, \ddagger chi-square test

The patients had a lower mean zinc value $(57.3 \pm 14.56 \text{ Mmol/L})$ compared to the controls $(96.4 \pm 17.38 \text{ Mmol/L})$, p -value = 0.001. The mean copper and Cu/Zn ratios were significantly higher $(106.6 \pm 39.41 \text{ Mmol/L})$ and (2.0 ± 1.06) in cases compared to the control $(61.0 \pm 9.53 \text{ Mmol/L})$ (0.6 ± 0.12) , p -value <0.001 , Table 2.

Table 2: Mean ± SD of zinc, copper and Zn/Cu ratio in the study groups

Microelement	Patients	Controls	p-value
Zinc (Mmol/L)	57.3 ± 14.56 (1.89)	96.4 ± 17.38 (2.24)	0.001*
Copper (Mmol/L)	106.6 ± 39.41 (5.08)	61.0 ± 9.53 (1.23)	<0.001*
Copper/Zinc	2.0 ± 1.06 (0.13)	0.6 ± 0.12 (0.01)	<0.001*

Mean ± SD (SE), *p-value is significant

The correlation coefficient was used to determine linear relationships between copper and zinc in patients with lumbar spinal surgery. The results showed that there was a weak relationship and a significant correlation between copper and zinc ($p \leq 0.05$, $r = -0.2$), Figure 1.

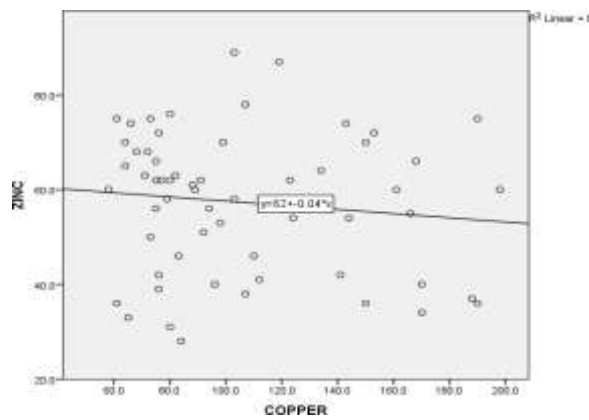


Figure 1: Simple linear regression of Copper and Zinc for lumbar spinal surgery cases.

The results showed a positive relationship and a significant correlation between copper and copper/zinc ($p < 0.001$, $r = 0.85$), Figure 2.

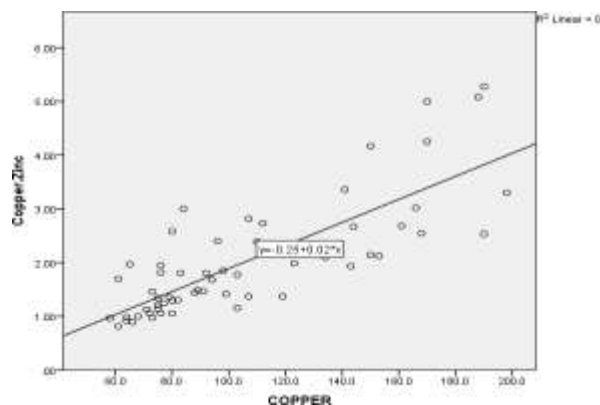


Figure 2: Simple linear regression of Copper and Cu/Zn for lumbar spinal surgery cases.

They also showed a positive relationship and a significant correlation between Cu/Zn and Zn ($p \leq 0.001$, $r = 0.7$), Figure 3.

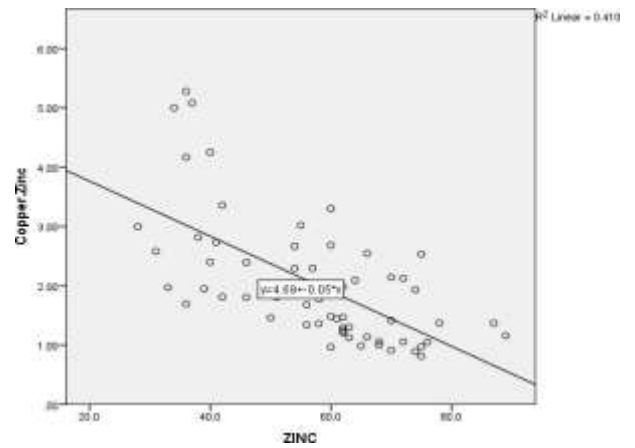


Figure 3: Simple linear regression of Copper/Zinc and Zinc for lumbar spinal surgery cases.

Table 3 shows the area under the curve and ROC for evaluating serum zinc, copper and their ratio concentrations as potential diagnostic indicators of lumbar disc degeneration in lumbar spine surgery. Serum zinc, copper and their ratio biomarkers exhibited high diagnostic accuracy for predicting lumbar spine surgery.

The copper/zinc ratio produced an AUC of 0.995 (0.988-1.000; $P < 0.001$). The best cut-off value of copper/zinc for the detection of lumbar disc degeneration is 0.9111 with a sensitivity of 96.7%, a specificity of 96.7%, a PPV of 95.1%, an NPN of 96.6% and an accuracy of 95.8%.

The copper produced an AUC of 0.926 (0.883-0.969; $P < 0.001$). The best cut-off value of copper for the early detection of lumbar disc degeneration is 72.5 $\mu\text{g/dL}$ with a sensitivity of 83.3%, a specificity of 88.3%, a PPV 87.7%, an NPN 84.1% and an accuracy of 85.8%. The zinc has an AUC of 0.979 (0.958-1.000; $p < 0.001$). The best cut-off value of zinc for the early detection of lumbar disc degeneration is 75 $\mu\text{g/dL}$ with a sensitivity of 93.3%, a specificity of 95%, PPV of 94%, NPV of 93.4% and accuracy of 94.2%.

Table 3: The ROC curve for the optimal threshold that assesses serum zinc, copper and their ratio for diagnosing lumbar disc degeneration

Test Result Variable(s)	Copper	Zinc	Copper/Zinc
Cut-off points	72.5	75	0.9111
AUC	0.926	0.979	0.995
Sensitivity %	83.3 %	93.3%	96.7%
Specificity %	88.3%	95%	96.7%
PPV	87.7%	94%	95.1%
NPV	84.8%	93.4%	96.6%
Accuracy	85.8%	94.2%	95.8%
CI (95%)	(0.883-0.969)	(0.958-1.000)	(0.988-1.000)
P value	<0.001[S]	<0.001[S]	<0.001[S]

S= Significant, PPV= Positive protective value, NPV= Negative predictive value, AUC= Area under curve, CI= confidence interval

In evaluating the efficacy of copper, zinc and copper/zinc ratio in lumbar disc degeneration

detection, the findings showed that zinc (sensitivity 93.3%) was the most sensitive biomarker for lumbar disc degeneration, followed by copper (sensitivity

83.3%). However, the copper/ zinc ratio (sensitivity 96.7%) reflected a highly specific biomarker for lumbar disc degeneration, Figure 4.

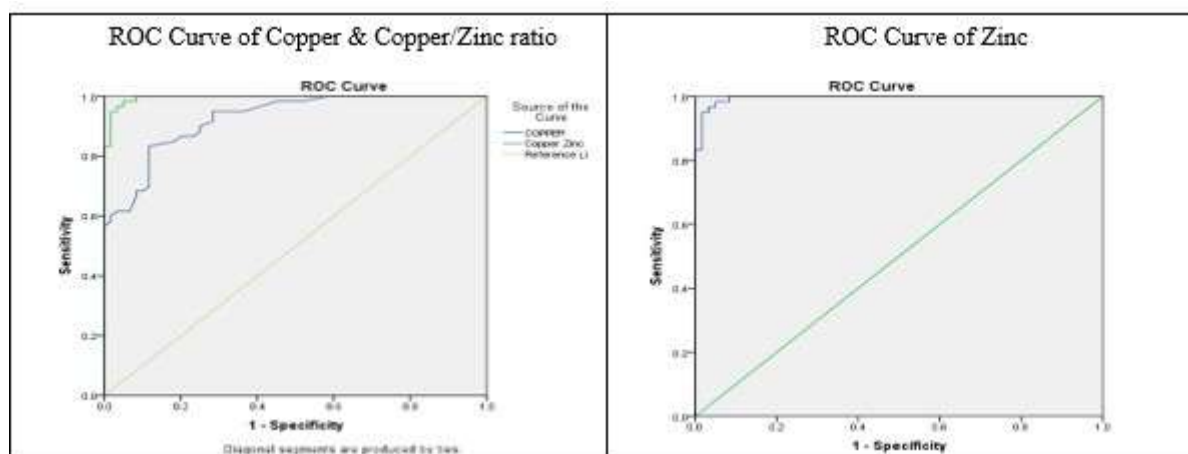


Figure 4: ROC curves for optimal diagnostic point analysis for predicting lumbar disc degeneration in lumbar spine surgery using copper, zinc and their ratio.

Discussion:

The significantly higher mean age in the patients than the controls found in the current study is consistent with the findings of Lee *et al.* who combined information from other studies that considered advanced age to be a risk factor for lumbar kyphosis and lumbar disc degeneration (22). Rajasekaran *et al.*, also found that aging causes changes in the lumbar vertebrae and intervertebral discs (23).

The higher mean BMI in patients than controls is consistent with the findings of Flippin *et al.*, based on a community-based spine registry that covers a range of diseases. An increase in BMI was associated with a statistically significant increase in operating time (24), that due to a combination of intervertebral disc degeneration, fatty infiltration of paraspinal muscles and medical changes such as bone marrow lesions visible on magnetic resonance imaging and suggestive of low back pain. Obesity is also linked to degenerative spinal pathology in the lumbar spine (25).

The significantly lower zinc levels in patients than controls in the current study is consistent with the results of Akoniuk *et al* (26). According to Molenda *et al.*, individuals with osteoporotic illness have lower zinc levels in their bones compared to healthy individuals, Zinc is an essential co-factor for alkaline phosphatase, a protein that is involved in the synthesis of many components of the bone matrix and is especially crucial for appropriate collagen synthesis and bone mineralization (27).

The finding of the current study that patients had significantly higher copper levels than controls supports that of Mahmood where patients' serum copper concentrations were much higher than controls (28). Elevated serum copper ions are an indicator of osteoporosis, fractures and joints. Copper ions are released from ceruloplasmin during the stage of an inflammatory reaction, which is a crucial component of the immune response and results in elevated serum copper (29).

Conversely, copper acts as a co-factor for lysyl oxidase an enzyme that initiates and controls the production of collagen and elastin. Copper deficiency results in a significant decrease in the activity of this enzyme in areas of bone, which is thought to lead to a decrease in collagen crosslinking. This can affect the stability and structure of collagen in bones, as well as cause abnormalities in skeletal growth and osteoporosis (30).

The finding of the current study of a significantly higher Cu/Zn ratio in patients compared to controls is consistent with those of Jakoneiuk *et al.* According to this evidence, a high serum Cu/Zn ratio could indicate an inflammation if it results from a drop in serum Zn or a rise in serum Cu (26). It is also consistent with another study which found that the Cu/Zn ratio was favorably correlated with mineral content and bone density, indicating that the ratio may be a significant predictor of bone health. The high serum Cu/Zn ratio may be connected with a decreased ability to maintain or reestablish homeostasis following a disruptive event (31).

The weak but significant correlation between copper and zinc found in the current study agrees with the results of another study which found a positive correlation between Zn and lumbar vertebrae bone mineral density. According to this finding, osteoporosis is caused by zinc deficiency. In the same way, it has long been known that Cu deficit causes pathological alterations that are indicative of osteoporosis and limits bone formation (32). Gaier *et al.*, discovered several significant associations between serum Cu and Zn and clinically important markers of bone and physical function (33). The degenerative process affects human intervertebral discs, affecting trace elements like copper and zinc. The concentration in bone tissue reflects body changes and periodic reactions, reflecting the accumulation of these elements (34).

The significant positive correlation between copper and the Cu/Zn ratio in the current study matches a previous study that found significant relationships between high Cu/Zn ratios and high serum Cu with lower bone mineral density (BMD), lean mass, strength and power and lower extremity function. The results support the use of the Cu/Zn ratio as a functional and predictive biomarker for overall health. Those with elevated serum Cu and a high Cu/Zn ratio had low BMD (33). It is also consistent with the number of studies that discovered positive relationships between Cu concentrations and the Cu/Zn ratio (35, 36). Our patient had a very strong relationship and a significant correlation between the copper/zinc ratio and zinc. Unfortunately, not all previous studies have measured markers of the correlation between copper/zinc ratio and zinc, which may be one reason for the observed difference in early healing response among patients who underwent lumbar spine surgery.

The current study revealed that measuring serum copper/zinc (at a cut-off value of $> 0.9111 \text{ ug/dL}$ and zinc (at a cut-off value of $> 75 \text{ ug/dL}$, while copper (at a cut-off value of $> 72.5 \text{ ug/dL}$ were the best biomarkers for distinguishing lumbar disc degeneration with lumbar spine surgery from healthy groups. These biomarkers have a higher AUC for serum copper/zinc, followed by zinc and then copper. The results contribute to the theory of delayed lumbar disc healing as a major mechanism involved in lumbar disc degeneration in patients undergoing lumbar spine surgery.

Limitation: The current study's limitation was its limited sample size; a larger number is needed to generalize the existing findings on the Iraqi population.

Conclusion: The low serum zinc level is a predictor of lumbar disc degeneration in patients undergoing lumbar spine surgery, particularly its association with lumbar disc degeneration, and the patient had a weak correlation and a high correlation between copper and zinc. The serum level of copper in the patient has a very strong relationship and significant correlation between copper/zinc, and a very strong relationship and significant correlation between copper/zinc and zinc.

Authors' declaration:

We confirm that all the Figures and Tables in the manuscript belong to the current study. Besides, the Figures and images, which do not belong to the current study, have been given permission for republication attached to the manuscript. Authors sign on ethical consideration Approval-Ethical Clearance: The project was approved by the local ethical committee in Ghazi AL-Hariri Hospital in Baghdad, Iraq. according to the code number (40681) on (15 /10/ 2023).

Conflict of Interest: None

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Authors' contributions:

The manuscript should mention the contribution of each author to the research done:

Study conception & design: (Manal K Rasheed & Ali T. Abdul Wahid). Literature search: (Sadiq R. Karkush). Data acquisition: (Sadiq Rahim Karkush). Data analysis & interpretation: (All Authors). Manuscript preparation: (Sadiq R. Karkush). Manuscript editing & review: (Sadiq Rahim Karkush).

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دور العناصر الدقيقة في إنحطاط القرص القطني في المرضى الذين يخضعون لجراحة العمود الفقري القطني

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الخلاصة

الخلفية: إنحطاط القرص القطني هو اضطراب عضلي هيكلي شائع يتسبب في كثير من الأحيان في ألم أسفل الظهر. بالإضافة إلى عدم الارتياح الناتج عن ألم أسفل الظهر قد يصاحبهما ألم في إحدى الساقين أو كليهما. العمود الفقري القطني والعجز الذي يتكون من خمس فقرات وعظم واحد يحدد توازن العمود الفقري. العناصر الدقيقة ضرورية في إسقلاب العظام وترتبط مع الوقاية من هشاشة العظام وتخفيف من ألم العضلات والعظام. **الاهداف:** فحص العلاقة بين جراحة العمود الفقري القطني وتركيزات النحاس والزنك.

المواد والمنهجية: أجريت دراسة حالة وضبط في مستشفى غازي الحريري في بغداد، العراق، خلال الفترة من تشرين الأول ٢٠٢٣ إلى كانون الثاني ٢٠٢٤. شملت الدراسة ١٢٠ مشاركاً تتراوح أعمارهم بين ٧٠-١٨ سنة. خضع ستون منهم لعملية جراحية في العمود الفقري القطني وتم تشخيصهم بالأشعة السينية أو التصوير بالرنين المغناطيسي وكان ستون منهم يمتعون بصحة جيدة وكانوا بمثابة مجموعة مراقبة. تم قياس مستويات النحاس والزنك في المصل بواسطة جهاز قياس الامتصاص الذري. تم تحديد مؤشر كتلة الجسم (كجم / م²) = الوزن / الطول².

النتائج: كشفت النتائج أن المرضى لديهم متوسط أقل للزنك (3.57 ± 0.14) ملليمول / لتر مقارنة مع الأصحاء (41.96 ± 38.17) ملليمول / لتر، القيمة الاحتمالية $(P < 0.001)$. أظهرت النتائج وجود علاقة ضعيفة وارتباط معنوي بين النحاس والزنك $(r = -0.2)$. ومع ذلك، هناك علاقة قوية جداً وارتباط معنوي بين النحاس ونسبة

النحاس/الزنك $(r = 0.85, p < 0.001)$ ، بينما كان للزنك علاقة ارتباط معنوية قوية جداً بين الزنك مع نسبة النحاس/الزنك $(r = -0.7)$ في المرضى. **الاستنتاجات:** تؤكد الدراسة الحالية على الارتباط الجدير بالملاحظة بين العناصر الدقيقة (النحاس والزنك) وإنحطاط الأقراص القطنية مما يؤكد أهمية التقييم قبل الجراحة في تحقيق أفضل النتائج الجراحية الممكنة. أظهرت الدراسة فائدة قياس مستوى الزنك ومستوى النحاس في الدم وخاصة ارتباطهما بتحطم القرص القطني كعلامات على إنحطاط القرص القطني في المرضى الذين يخضعون لجراحة العمود الفقري القطني.

مفتاح الكلمات: إنحطاط القرص القطني؛ النحاس؛ الزنك؛ جراحة العمود الفقري القطني؛ ألم أسفل الظهر.