Biomarkers of back load. An exploratory study

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Chapter 3

Keratan sulfate as a potential biomarker of loading of the intervertebral disc: a literature study
Abstract

Study design. A review of the literature.

Objectives. To investigate the potential of serum levels of keratan sulfate as a biomarker of the effects of loading of the spine.

Summary of background data. Exposure to mechanical loading of the spine causes changes in metabolism of intervertebral discs, eventually leading to accelerated disc degeneration. This process is characterized by a degradation of proteoglycans, which is reflected by an increase in the blood level of proteoglycan components. The serum level of keratan sulfate, an epitope present on these proteoglycan components, has been suggested as a marker of changes in metabolism of cartilaginous tissues.

Methods. A review of literature on serum keratan sulfate levels in relation to degenerative changes in cartilaginous tissue.

Results. In a number of studies reported keratan sulfate in serum was reported to be related to degeneration of articular cartilage in patients with osteoarthritis. In addition, massive and rapid degradation of intervertebral discs was determined to result in a large rise in serum keratan sulfate levels. Whether degenerative changes of intervertebral discs induced by mechanical stress also cause a detectable increase in serum keratan sulfate should be subjected to further investigation.

Conclusion. Quantification of keratan sulfate in serum offers a promising measure for the early effects of mechanical loading of the spine, but research is needed for validation.

Introduction

Exposure to mechanical stress is considered to be a major risk factor for low back pain.\textsuperscript{33,27} Although extensive research has been done on this topic, there is still little knowledge about the causal correlation between mechanical loading of the back and the pathogenesis of low back pain. Morphologic and biochemical changes in the intervertebral disc are believed to play a crucial role in this correlation.\textsuperscript{22} Intervertebral discs function as shock absorbers and distributors of loads applied to the spine; furthermore, they provide flexibility to the spinal structure.\textsuperscript{25} The intervertebral disc is part of the motion segment of the spine. Damage to the intervertebral disc will subsequently lead to changes of the mechanics of this motion segment, and can eventually affect the whole spine. The relation between exposure and clinical disease can be characterized as a continuum with sequential progression (Figure 1).\textsuperscript{24}

Exposure $\rightarrow$ Internal dose $\rightarrow$ Biologically effective dose $\rightarrow$ Early biologic effect $\rightarrow$ Altered structure/function $\rightarrow$ Clinical disease

Susceptibility

**Figure 1.** Components in the sequel progression between exposure and disease.

Excessive internal stresses and strains due to external mechanical loads on the spine cause structural and biochemical changes in the tissue of the intervertebral disc. It is assumed that these changes can lead either to direct tissue damage and activation of nociceptors leading to pain; or in the presence of small loads delivered cyclically, they can affect metabolism leading to accelerated degeneration of the disc.\textsuperscript{10,53} Knowledge of the changes at tissue level is essential for understanding the relation between exposure to mechanical load and pathogenesis of low back pain.
Unfortunately, the methods for evaluating these changes in vivo are limited. Disc degeneration is fairly advanced before morphological changes can be visualized on radiographs, early biochemical changes and microtrauma resulting from mechanical stresses often cannot be demonstrated in this way. Modern imaging techniques - e.g., magnetic resonance imaging (MRI) - are promising methods for studying changes in biochemical composition and metabolism of the intervertebral disc, but they present the practical problems of limited availability of the necessary equipment and costs. Moreover, the reliability and specificity of MRI for monitoring biochemical alterations associated with disc pathology has been questioned. Another method for studying the early biologic changes at tissue level is to investigate as biomarkers the chemicals that are produced as a result of degenerative processes. A biomarker can be defined as an indicator of biochemical or molecular change occurring in a biologic system such as the human body, which can be measured in biologic media as body fluids. In the causal chain between external exposure and related adverse health effects (Figure 1), a biomarker can reflect an event or a sequel of events. Biomarkers have been used for decades in epidemiologic research in environmental and occupational toxicology. For example the level of lead in blood of workers is a well known example of a biomarker of exposure to lead. During recent years, the concept of biomarkers for studying pathomechanisms of musculoskeletal disorders has gained support. It has been stated that sufficiently defined biomarkers have the potential to detect musculoskeletal disorders at an early, preclinical stage and to monitor the severity in people and populations. If biomarkers are to be useful in epidemiologic research they must be shown to be valid, reliable and practical. Validation of a biomarker should include sensitivity, specificity and predictive value. A reliable biomarker is independent of such confounding factors as diet or other disorders. When this is not possible, the influence of these confounders should be well defined. Also the reliability of the measurement method should be considered. Invasiveness and psychological resistance to assessment of the biomarker determine to a large extent the practical applicability.

Although low back pain is a very common health problem, little research has been conducted to identify biomarkers for the potential causes of low back pain - e.g., disc degeneration. However, the possibility of biomarkers for the process of degeneration of articular cartilage in joints like the knee and hip, which to a large extent is similar to intervertebral disc degeneration, has been studied more extensively in the fields of rheumatology and sports medicine. Most of these
investigations have focused on the presence of cartilage components in body fluids, primarily proteoglycans. Among these potential markers of cartilage degeneration, the proteoglycan component keratan sulfate (KS) has received the greatest attention.

The objective of this study was to investigate the potential of the serum level of KS as a biomarker for the early biologic effects of mechanical loading of the spine. This objective was divided into two questions: What are the effects of mechanical loading on the biochemical composition of intervertebral discs, and can serum levels of KS provide a valid, reliable and practically applicable measure for degenerative changes in intervertebral discs?

Methods

A literature search in MEDLINE and EMBASE was conducted for the period from January 1985 to May 1996, using the key words: intervertebral disc, cartilage, biochemical marker, proteoglycan, keratan sulfate and mechanical stress. In addition, the references given in the selected studies and reviews were examined. Attention was focused on human in vivo studies in which KS has been measured in blood.

Results

Biochemical composition of the intervertebral disc
The intervertebral disc consists of an outer portion, the annulus fibrosus, which is characterized by concentrical collagen rings, and a relatively gelatinous central region, the nucleus pulposus. Cartilage endplates form the superior and inferior boundaries and separate the intervertebral disc from the vertebral body. The main chemical components of cartilage endplates are similar to those of the disc itself. The tissue is almost avascular and contains relatively few chondrocytes and an extracellular matrix consisting of a highly hydrated proteoglycan gel which is embedded in a network of collagen fibers. This construction gives the tissue its ability to undergo reversible deformation. The main proteoglycan of the intervertebral disc, aggrecan, consists of a core protein to which two types of very negatively charged glycosaminoglycan (GAG) chains are covalently attached:
chondroitin sulfate, a chain that is prominent in the proteoglycans of most tissues, and KS, a chain found almost exclusively (>95%) in cartilage aggrecan (Figure 2).

**Figure 2. Simplified representation of the structure of aggrecan.**

Because of the negative charges there is a strong attraction of water molecules. Because the disc is largely avascular, transport of nutrients and metabolites depends to a large extend on diffusion through the cartilage endplate. The mechanical function of the intervertebral disc and the cartilage endplates depends on matrix composition, which is maintained by a regular turnover of proteoglycans. Proteoglycan molecules are degraded and replaced by newly synthesized molecules, thereby maintaining a constant proteoglycan content. The synthesis and degradation of proteoglycan molecules are controlled by the chondrocytes, in response to various environmental factors such as enzymes, nutrients and mechanical load.6,8,51

**Effects of mechanical load**

From results of studies on metabolism of articular cartilage, it is known that mechanical load is an important regulator of metabolic activity.14,52 Regular application of mechanical load appears necessary for the cartilage matrix to maintain its composition. Excess loading, however, can damage previously healthy cartilage through changes in cellular activity. Furthermore, accumulation of minor or major insults could lead to accelerated degenerative changes.52 It has been shown that mechanical loading of the intervertebral disc can cause defects of the annulus
fibrosus, leading to dehydration and fraying of the nucleus pulposus. Not only the disc itself can be damaged, the cartilage endplates are affected as well. In fact, it is believed that fractures in the endplates caused by mechanical stress, precede degeneration of the intervertebral disc, as a consequence of increased intradisc pressure and reduced disc nutrition. Changes in biochemical composition in degenerated discs have been studied in experimentally degenerated discs of animals, symptomatic discs from deceased patients and cartilage explants. It can be concluded from these in vitro studies that degeneration of the intervertebral disc is characterized by a loss of proteoglycans and water from the tissue. The proteoglycans and fragments thereof containing KS, that are lost from the matrix, diffuse out of the tissue and appear in the body fluids in which they can be quantified and used as biomarkers to study the process of cartilage degeneration in vivo.

Because the level of KS in serum is supposed to reflect the rate of catabolism of cartilage proteoglycans in vivo, a number of studies have been conducted to investigate the potential of serum KS levels as a biomarker of cartilage degeneration. In the literature 13 relevant studies were found: 2 on disc degradation, 8 on osteoarthritis and 3 on mechanical loading. These studies are presented here, and a summary of the results is given in Table 1.

**Keratan sulfate in serum related to disc degradation**
Degradation of the intervertebral disc has been studied in vivo in patients undergoing chemonucleolysis as treatment for herniated disc syndrome. In both studies KS levels in serum were assessed before and after the injection of the proteolytic enzyme chymopapain into an intervertebral disc. Before the treatment, KS levels did not differ from those of a control population consisting of patients who were surgically treated for disc herniation, and were also comparable with those of healthy control subjects. Keratan sulfate levels rose within a few hours after chemonucleolysis, peak levels were reached in 48 hours and returned to baseline after 2 to 3 weeks. The mean peak KS levels were respectively more than 3- to more than 10-fold higher than the mean baseline levels.

**Keratan sulfate in serum related to cartilage degeneration**
KS levels in serum have been studied relatively often in relation to cartilage degeneration in osteoarthritis patients. Osteoarthritis is characterized by progressive
degradation of components of the extracellular matrix of articular cartilage. The potential of measuring KS levels in serum as a marker for cartilage damage in osteoarthritis was first described by Thonar et al. Their study reported increased KS concentrations in serum samples from 24 patients with osteoarthritis compared with concentrations in healthy control subjects. Subsequently, 4 studies were performed in which findings confirmed those of Thonar et al. In one, results showed that serum KS levels in female osteoarthritis patients were not different from those in a group of women without symptomatic joint disease. In another study, findings showed lower serum KS levels in osteoarthritis patients. In this study, a monoclonal antibody AN9PI, which measures only products with multiple KS chains, was used, whereas in the other studies (except for Sweet et al who used ET-4-A-4), the monoclonal 1/20/5-D-4 antibody, which recognizes single KS chains as well, was used. In the results of all these studies on osteoarthritis, single measurements of KS levels are presented that reflect only differences in the state of the cartilage of osteoarthritis patients and healthy control subjects at that moment. Sharif et al performed a longitudinal study among osteoarthritis patients in which KS levels were measured at baseline and at 1, 2 and 5-year follow-ups. Only the baseline KS levels are given, but the investigators describe that KS levels of the 5-year follow-up correlated well with baseline levels and that the longitudinal analysis showed no differences in the change in KS levels between the patients with and without disease progression.

*Keratan sulfate in serum related to mechanical loading*

Three studies were reviewed in which serum levels of KS as a measure of mechanical loading of the joints were investigated. Roos et al compared serum KS levels before and after the subjects had run on a treadmill for 60 minutes and had played a soccer game (90 minutes). Blood samples before were obtained after 24 hours' rest from running or soccer, and the samples after were obtained 30 to 60 minutes after the exercise. An increase in KS levels was recorded after exercise. Sweet et al measured serum KS levels by well-trained athletes, before and immediately after the athletes had run a marathon and 48 hours later. The investigators noted no differences among results in the three samples. In another study by Sweet et al, the effect of prolonged rest and subsequent mobilization was investigated in previously healthy, young patients who had sustained fractures of the pelvis without involvement of the hips. A significant decrease in the serum KS level was recorded during a period of 5 to 6
Table 1. Summary of study findings on serum KS levels in relation to cartilage degeneration in vivo

<table>
<thead>
<tr>
<th>Study</th>
<th>Independent var.</th>
<th>Epitope</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>mean serum level ng/ml⁷¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>before</td>
</tr>
<tr>
<td><strong>Intervertebral discs</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Block et al., 1989¹¹</td>
<td>chemonucleolysis</td>
<td>KS (5-D-4)</td>
<td>254 ± 148</td>
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<td>Muralikuttan et al., 1991²¹</td>
<td>chemonucleolysis</td>
<td>KS (5-D-4)</td>
<td>191 ± 21</td>
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<tr>
<td></td>
<td></td>
<td>female</td>
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<td></td>
<td></td>
<td></td>
<td>233 ± 32</td>
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<td><strong>Articular cartilage</strong></td>
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<tr>
<td>Thonar et al., 1985⁴⁷</td>
<td>OA</td>
<td>KS (5-D-4)</td>
<td>356 ± 73</td>
</tr>
<tr>
<td>Sweet et al., 1988⁴⁹</td>
<td>OA</td>
<td>KS (ET-4-A-4)</td>
<td>475 ± 178</td>
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<tr>
<td>Campion et al., 1991¹⁵</td>
<td>OA (knee)</td>
<td>KS (5-D-4)</td>
<td>393 ± 124</td>
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<td>Mehraban et al., 1991¹⁹</td>
<td>OA</td>
<td>KS (5-D-4)</td>
<td>1852 ± 1236</td>
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<td>Spector et al., 1992²⁰</td>
<td>OA (knee)</td>
<td>KS (5-D-4)</td>
<td>388 ± 108</td>
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<td>322 ± 88</td>
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<td>Poole et al., 1994³¹</td>
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<td>KS (AN9PI)IgG</td>
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<td>KS (AN9PI)Fab</td>
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<td>Sharif et al., 1995⁹⁹</td>
<td>OA</td>
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<td><strong>Longitudinal OA</strong></td>
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<tr>
<td>Sweet et al., 1990⁴⁴</td>
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<td>KS (ET-4-A-4)</td>
<td>108 ± 61</td>
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<tr>
<td>Mechanical loading</td>
<td>bedrest</td>
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<tr>
<td>Sweet et al., 1992²⁵</td>
<td>physical exercise</td>
<td>KS (ET-4-A-4)</td>
<td>224 ± 69</td>
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<tr>
<td>Roos et al., 1995³⁶</td>
<td>physical exercise</td>
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</table>

KS = keratan sulfate; OA = osteoarthritis
Practical applicability, validity and reliability of keratan sulfate in serum

As marker of biochemical changes in intervertebral discs KS, can be assessed either in urine or in blood. Urine is easy to obtain, but KS concentrations are too low to measure. Obtaining blood samples is more invasive but is still not a problem for most people. Only a small blood sample is needed, because quantification of the KS epitope requires less than 50 μl of serum for analysis in duplicate. The KS epitope in serum is not denatured by repeated freezing and thawing and is stable at room temperature for several days.

Interpretation of KS in serum is difficult, because KS present in serum is derived from all cartilaginous structures in the body, and a slight change in the rate of aggrecan catabolism in a small structure is unlikely to give rise to a measurable increase in the level of KS in serum. However, it has been shown that a massive and rapid degradation of proteoglycans in the intervertebral disc causes a large transient rise in the level of serum KS. In general, large variations in serum KS levels exist between subjects; in contrast, within subjects the level is very constant with time, showing no diurnal variation and fluctuating little from day to day. Thus, a single determination of KS under normal circumstances is supposed to be a reliable measure of each person’s baseline serum level, with 10% variation expected. Serial measurements of KS levels may provide a sensitive marker of perturbations in cartilage metabolism. The movement of the KS fragments from cartilage to blood is relatively slow. However, once they arrive in the blood, the fragments are eliminated relatively rapidly (half-life < 60 min).

KS in serum is assumed to have predictive value with respect to development of osteoarthritis. It has been stated that people with high a serum level of KS are turning over aggrecan in cartilage more rapidly and that this places them at increased risk of developing osteoarthritis. Disease progression in osteoarthritis patients cannot be predicted, however, because the serum level of KS is not believed to fluctuate markedly as the severity of the disease progresses.

Assessment of KS levels is usually performed by quantification of a highly sulfated epitope present on KS by a competitive indirect ELISA (Enzyme-linked immunosorbent assay) that uses the 1/20/5-D-4 anti-KS monoclonal antibody. According to Thonar et al this assay provides a reliable measure of KS present in aggrecan from adult cartilage. The specificity of this assay has been questioned, because the 5-D-4 antibody probably also recognizes KS or KS-like structures in different tissues. However, since most of the KS in the body is present in cartilage,
the amount of KS from other structures is considered to contribute little to the entry of KS-bearing molecules in the blood circulation.

**Discussion**

If well defined, biomarkers for degeneration of the intervertebral disc can provide a measure for early, preclinical effects of mechanical loading of the spine. In this literature study, the potential of KS levels in blood as such a biomarker was investigated, because this component had already received a lot of attention as a biomarker of cartilage degeneration in osteoarthritis patients. Although in general the biochemical structure of proteoglycans in the intervertebral disc can be considered similar to that of proteoglycans in articular cartilage, some differences do exist. The most important difference is thought to be the size of the proteoglycan core protein, which is smaller in the intervertebral disc. Furthermore, the chondroitin sulfate chains are shorter and the KS chains longer in the intervertebral disc, and disc proteoglycans contain more KS and less chondroitin sulfate. However, the impact of these differences is not considered a serious hindrance to a useful comparison. In addition, it is assumed that the process of degradation is also comparable. This is partly substantiated by Liu et al. who found that (in vitro) the human intervertebral disc, similar to articular cartilage, is capable of secreting proteinases that participate in matrix turnover.

From *in vitro* studies, it was concluded that mechanical load is necessary for maintaining cartilage integrity, but that excess loading could cause damage and disturbed metabolism, leading eventually to accelerated degeneration. These effects are characterized by a loss of proteoglycans and fragments thereof from the cartilage. Fragments containing KS received the most attention as biomarker of cartilage degeneration, mostly because the majority of KS present in the human body is found in cartilaginous tissue. Other fragments of aggregan and components involved in regulating metabolism (e.g., enzymes) have also been studied as potential biomarkers for cartilage degradation. The disadvantage of most of these components is that they occur only in low amounts in serum or that they are also found in significant amounts in other tissues, and therefore their serum concentrations do not necessarily reflect cartilage proteoglycan metabolism. However, when assessed in synovial fluid
of an articular joint, levels of components like chondroitin sulfate, hyaluronate, link protein and proteinases proved to be related to degradation of the particular joint under study.\textsuperscript{32,36} Likewise, KS levels in synovial fluid were shown to be related to osteoarthritis of the particular joint.\textsuperscript{e.g. 5,31} It has been stated that when measured in serum, KS levels represent an integrated measure for cartilage degenerative activities in all joints\textsuperscript{5,47} and that the level is correlated to the number of joints involved.\textsuperscript{46} In contrast to this, some investigators found serum levels of KS not to be related to synovial fluid levels,\textsuperscript{5,9} a plausible observation in that levels in serum reflect the average of the metabolic activities in many joints and the extent of joint effusion varies with time and from patient to patient.

In almost all studies of the relation between serum KS and cartilage degeneration in osteoarthritis patients, results show that osteoarthritis patients have higher KS levels than healthy control subjects. The lower levels reported in one study can probably be explained by the type of antibody used, which is supposed to detect fewer fragments in serum than the antibody that is mostly used. The absence of differences in KS levels between women with osteoarthritis and healthy women, found by Spector et al,\textsuperscript{40} might be partially explained by a less pronounced loss of KS in women, as suggested by Campion et al,\textsuperscript{5} who found higher serum KS levels in male osteoarthritis patients than in female osteoarthritis patients, whereas no such sex-related differences were found in people without osteoarthritis. In general, differences in KS levels between osteoarthritis patients can be explained, among others, by the fact that osteoarthritis is heterogeneous with regard to etiology,\textsuperscript{48} and also the number of joints involved and the level of inflammatory joint changes can differ between patients. The diagnosis of osteoarthritis in these studies is based on clinical and radiological findings, but osteoarthritis has begun long before this diagnosis can be made. Therefore, these studies cannot provide information about the validity of KS as biomarker of preclinical signs of osteoarthritis. Based on a dog model of posttraumatic osteoarthritis, Thonar et al\textsuperscript{50} suggested that the rise in serum level of KS in osteoarthritis patients probably develops before the appearance of clinical signs. This could mean that people without clinical signs of joint disease but with an abnormally high serum level of KS are at risk of developing osteoarthritis - i.e., that osteoarthritis follows and is a consequence of metabolic changes in cartilage. In the only longitudinal study included in this review,\textsuperscript{39} the subjects had osteoarthritis at the beginning of the study. Serum levels of KS were not found to be predictive of disease progression, which was explained by the hypothesis that serum
levels of KS are not thought to fluctuate very much as disease progresses. More longitudinal studies are needed to support solid conclusions about KS levels in relation to development of osteoarthritis.

The literature thus provides considerable evidence that serum levels of KS reflect cartilage degeneration in osteoarthritis patients and disc degradation induced by chemonucleolysis. However, whether serum levels of KS will be sensitive enough to detect tissue changes and degenerative activities caused by mechanical stresses on the intervertebral disc cannot be inferred from these data. Regarding the effects of mechanical loading of articular joints, the results of the two studies on physical exercise were inconsistent. The effects of long term unloading on serum KS, as presented in the study on the effects of prolonged bedrest, were more pronounced. This suggests that serum levels of KS could provide a marker for long-term changes in loading, whereas they are not sensitive enough to reflect short-term changes. However, the relation between mechanical loading and serum KS levels has to be subjected to further investigation to verify this assumption.

Because a biomarker of processes involving the intervertebral disc must be assessed in blood or urine, aspects of sensitivity and specificity have to be considered carefully. Results in the 2 studies evaluating the effects of chemonucleolysis supported the idea that degradation of an intervertebral disc leads to a measurable increase in the level of KS in serum. However, this degradation is so much more massive and rapid than degenerative changes caused by mechanical loading that these findings cannot be indiscriminately generalized. Because changes in serum levels of KS can originate from articular cartilage as well as the intervertebral disc, identification of the tissue source of KS is essential. This means that anti-KS antibodies need to be developed that shows a difference in reactivity with KS chains from discs and articular cartilage. Until such an antibody is available, other ways of identifying the tissue source must to be considered. This can be done, for instance, by making sure that there are no joint disorders or excessive loading of articular joints. Another way is to search for a biomarker more unique for intervertebral disc degeneration by designing in vivo studies to identify possible differences in the degradation processes or biochemical properties of the components involved. Also, the assessment of a combination of epitopes can be considered in order to obtain a more complete and probably more specific measure.

In conclusion, the serum level of KS has the potential to be a biomarker of degeneration of intervertebral discs. However, at present there is still little
knowledge about the relation between serum levels of KS and disc degeneration caused by mechanical stress. This relation can be studied, for example, by relating KS levels after mechanical loading of the back to other effect measures, such as MRI or spinal shrinkage. In longitudinal studies among workers with a heavy physical workload on the back, the predictive value of KS levels in serum should be investigated. As long as no anti-KS antibody that makes it possible to distinguish between KS from discs and articular cartilage is found, other potential causes of changes in serum KS - i.e., osteoarthritis - must be eliminated as much as possible, so that KS levels in serum can be used as a biomarker of the effects of excessive mechanical stress on the intervertebral disc.

References


