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Association between biological markers and somatic pain

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Abstract. Pain, as one of the major clinical and social problems, still lacks effective objective evaluation indicators. At present, nearly one in five adults suffer from different types and different parts of pain. An important feature of clinical pain is persistent pain, in addition to sensory discrimination processes, it involves a range of brain regions involved in top-down cognitive and emotional processing. However, clinical pain is often affected by multiple factors and is difficult to assess objectively. Recently, blood, urine, cerebrospinal fluid, and biopsy tissue have been identified using novel, sensitive, and specific protein analysis methods in an attempt to detect changes in biological markers associated with different pain types. This paper will summarize the biological markers related to different parts of pain in the latest relevant studies at home and abroad and focus on the application prospect of such biological markers in the diagnosis, treatment, and prognosis evaluation of the pain.

Keywords: Pain, biological markers, application

1. Introduction

Pain seems as a common health problem in primary health care. Around 20% of adults worldwide suffer from pain each year. Pain is an individual subjective experience. Pain can indicate damage, inflammation, and so on. At present, there is still a lack of a measurable laboratory index. Doctors often prescribe and evaluate pain scales based on pain scales. However, pain is subjective, which makes pain scales less reliable. For example, in the case of patients with cognitive or sensory impairments, their subjective judgments of pain levels may be inaccurate. As a result, pain grading scales used in clinical practice may not always be effective. In recent years, with the progress of molecular biology and the human genome project, more and more biological markers have been discovered and applied to the early diagnosis, prevention, and treatment monitoring of diseases.

This study is to collect data on changes in specific serum markers associated with pain in different body parts or diseases. The authors will summarize changes in individual serum markers associated with pain in specific body parts that have been studied. This can help physicians objectively assess pain levels by collecting and screening biological marker values or blood changes, thereby improving medical efficiency [1,2].

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2. The Lower part of the body

2.1. Low back pain(LBP)

Lumbar pain, commonly known as low back pain, is a prevalent condition marked by discomfort or pain in the lower back region. It varies in intensity from mild to severe and can be either acute, lasting for a few days to weeks, or chronic, persisting for over three months. Low back pain can stem from various causes, including muscle strain, ligament sprain, herniated discs, spinal stenosis, osteoarthritis, and sciatica. Factors such as poor posture, improper lifting techniques, and sedentary lifestyles can also play a role in its onset.

A controlled study involving 24 patients with chronic primary LBP and 4 controls found that the concentration of TNF-α in the urine of patients with LBP was increased compared to the control group, and the level of TNF-α was also different in different patients, suggesting the predictive role of TNF-α in urine [3].

Lumbar BMD and BTMs were correlated with lumbar Modic changes in postmenopausal women with chronic LBP. With the increase of BTMs or the decrease of BMD, the incidence of lumbar Modic changes increases, suggesting that the changes of BTMs and lumbar BMD in postmenopausal women with chronic LBP should be monitored early clinically, and anti-osteoporosis therapy should be given early, providing a new idea for the treatment of postmenopausal women with back pain caused by lumbar Modic changes [4].

In a study focusing on treating chronic lower back pain (LBP) and disability in adult patients aged 18 to 65 years using whole-body cryotherapy, the results suggested alterations in serum markers of inflammation. Specifically, there was a reduction in pro-inflammatory markers and an increase in anti-inflammatory markers. The results suggested that for individuals with lower back pain, an increase in the serum marker IL-2 ($p = 0.046$) and a decrease in IL-10 ($p = 0.003$) were indicative of milder lower back pain [5].

Rehabilitation exercise programs are beneficial for improving back pain by strengthening muscles, increasing flexibility, promoting proper posture, and teaching correct body mechanics. This helps reduce strain on the spine and lowers the risk of future injuries. In a study assessing the effects of an 8-week exercise program on BP and C-reactive protein (CRP), interleukin-1β (IL-1β), and interleukin-6 (IL-6) in LBP auto workers, male workers experiencing LBP (n=15) participated in an 8-week multi-component exercise intervention. A control group (CG) consisting of age-matched healthy men without back pain (n=11) was included for comparison. The results indicated that after 8 weeks, the serum CRP level in the exercise group (EG) decreased significantly compared to baseline ($P<0.05$), while the levels of IL-1β/6 showed no significant change. Additionally, back flexibility improved significantly ($P<0.001$), and back pain was reduced ($P<0.05$) in the EG [6].

2.2. Groin pain

Groin pain is a common symptom in pain management, affecting both acute and chronic cases. Groin pain is often associated with an increased risk of various health issues, including musculoskeletal problems, when Body Mass Index (BMI) is higher.". Research suggests that elevated BMI levels can lead to increased pressure on the hip and groin area, potentially contributing to pain and discomfort. Additionally, high BMI levels may also be associated with changes in serum markers of tissue inflammation and damage, which could further contribute to the development or exacerbation of groin pain.

Chronic pain after tension-free inguinal hernia repair is common, which seriously affects patients' quality of life. A connection was found between fibrinogen and heightened postoperative pain ($beta= 0.333$, $P< 0.05$), whereas serum LDH concentration exhibited a strong relationship ($beta= 0.606$, $P< 0.001$). The 96 adult male patients (mean 55 years old) from southern Spain underwent inguinal hernioplasty and had their serum markers assessed 8 hours post-surgery. The markers, including fibrinogen, lactate dehydrogenase (LDH), C-reactive protein, cortisol, creatine kinase, glutamate-pyruvate, glutamic oxaloacetate, and γ-glutamyltransferase aminotransferase, were measured using

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standard procedures (β=0.333, $P<0.05$). A strong correlation was found between serum lactate dehydrogenase (LDH) concentration and increased severity of postoperative pain (β=0.606, $P<0.001$). Furthermore, alcohol consumption was linked to higher levels of postoperative pain (β=0.212, $P<0.05$) [7].

2.3. Pelvic pain (sacral pain or symphyseal pain)

71% to 87% of women with the chronic pelvic pain are with endometriosis. Unmanaged pain tends to evolve into complex and intractable chronic pain, pain lasting more than 6 months can be defined as chronic pelvic pain (CPP), chronic pelvic pain is independent of the menstrual cycle, the environment can intermittently continue throughout the menstrual cycle or continuous presentation of dull pain, pain, or sharp pain. Up to now, none of the markers in peripheral blood and endometrium can accurately diagnose endometriosis. The detection of CA125 level is of little significance in the early diagnosis of endometriosis. Increased CA125 levels were more common in patients with severe endometriosis, significant pelvic inflammatory response, endometriosis cyst rupture, or adenomyosis [8].

Late pregnancy pelvic pain is common in pregnant women, typically occurring in the third trimester. It is often caused by the hormone relaxin, which loosens ligaments in preparation for childbirth, leading to instability in the pelvic joints. This pain can be sharp or dull and may worsen with activities like walking or changing positions. While the mechanism remains unclear, certain studies have indicated an association between serum concentrations of type III procollagen propeptide (a marker of collagen turnover) and pelvic pain [9].

3. The upper part of the body

3.1. Neck pain

Neck pain is a very common symptom that can lead to serious health problems; The symptoms persist for a long time in the form of slow primary neck pain. The incidence is as high as 71%, especially in certain occupational groups, such as teachers. Research published in the 《British Medical Journal》 on the analysis of the burden of shoulder and neck pain in the global population shows that the number of patients with shoulder and neck pain worldwide increased by 124.4 million from 1990 to 2017 [10].

Calcium pyrophosphate dihydrate (CPPD) deposition in the transverse ligament of the atlas can lead to various types of damage, primarily due to the formation of CPPD crystals. These crystals can cause inflammation, leading to pain and limited mobility in the neck region. In some cases, the crystals may cause structural damage to the ligament, affecting its integrity and function. This can result in instability of the atlas (C1 vertebra) and potentially lead to serious complications such as spinal cord compression. Early diagnosis and appropriate management are crucial in preventing further damage and ensuring optimal outcomes for patients with CPPD deposition in the transverse ligament of the atlas. An old man (71 years old) presents with severe neck pain. On admission, elevated serum CRP levels are confirmed. Magnetic resonance images showed no obvious abnormalities other than degenerative changes in the spine. Based on computed tomography imaging of the neck, the patient was diagnosed with pseudogout due to dehydration of calcium pyrophosphate, showing linear calcification of the axial transverse ligament. After taking NSAIDs, fever and neck pain disappeared, and CRP levels returned to the normal range. It suggests that the higher the serum CRP level, the higher the neck pain level, and vice versa [11].

3.2. Wrist pain

Wrist injuries are commonly seen in flapping, causing excessive movement of the wrist joint. Or caused by long-term fatigue damage, resulting in wrist pain, swelling, limited activity, and occasionally numbness of the fingers, radiating to the arms and shoulders, seriously affecting the life of patients.

Serum hyaluronic acid (HA) is a form of hyaluronic acid found in the blood, playing a role in lubricating joints and protecting soft tissues. Interleukin-6 (IL-6), a cytokine involved in immune responses and inflammation, is implicated in conditions such as rheumatoid arthritis. Seventy-one

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chronic hemodialysis patients, with or without carpal tunnel syndrome (CTS) and shoulder discomfort, underwent evaluation of their serum levels of hyaluronic acid (HA), interleukin-1-β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). The patients were then split into two groups: The control group was represented by group 1 (n = 40), and group 2 (n = 31). Groups 1 and 2 had serum HA concentrations of 106.0 and 442.6 ng/dl(mean), respectively. There was a significant difference between the two groups (p=0.01). Group 1's serum IL-6 concentration was substantially lower than Group 2's (p=0.05). Thus, every piece of information suggests that there is a positive correlation between the amount of serum HA and IL-6 and the degree of pain connected to carpal tunnel syndrome [12].

3.3. Chest pain

Angina pectoris is caused by myocardial ischemia, mainly manifested as pain in the chest or adjacent parts, mostly caused by fatigue, and related to myocardial dysfunction. Typical angina lasts a few minutes and gradually worsens. Relief within minutes of resting, sitting down, stopping walking, or using medication is typical for angina patients. Unstable pectoris is a cardiovascular condition characterized by chest pain or discomfort that typically occurs at rest or with minimal exertion, unlike stable angina. The presence of unstable angina could be a sign of impending acute coronary syndrome (ACS), a critical condition necessitating immediate intervention. Treatment includes medication management and possibly interventional procedures.

Serum deoxyribonuclease I (DNase I) activity is a crucial indicator of the enzyme's activity in the bloodstream. DNase I, an endonuclease enzyme, is responsible for DNA cleavage and plays vital roles in processes like apoptosis and inflammation. The activity of serum DNase I can serve as an essential marker for assessing the severity and prognosis of various autoimmune and inflammatory diseases. In a recent study, thirty patients with chest pain syndrome (CPS) and thirty-three patients with non-ST elevation myocardial infarction (NSTEMI) measured the serum DNase I activity levels. The assessments were conducted three hours after the onset of chest pain and again three hours after admission. The findings revealed significantly higher absolute median DNase I activity levels in NSTEMI patients compared to those with CPS. In patients with UAPNSTEMI who tested positive for DNase I activity, evaluate DNase activity within 6 hours of chest pain if the serum level or percentage difference surpassed the relevant cutoff value. Consequently, a reference serum marker for chest discomfort can be the serum DNase I activity level [13].

Acute myocardial infarction (AMI) may cause the heart muscle to become damaged or die. Persistent precardiac pain is the most common symptom of AMI. In a study involving 50 patients with acute myocardial infarction (AMI) who reported chest pain within 6 hours of onset and 50 healthy controls matched for age and sex, spectrophotometry was used to measure serum levels of ischemia-modified albumin (IMA), creatine kinase (CK), mast cell tryptase (MAST), and lactate dehydrogenase (LDH). Serum cardiac troponin I (cTnI) was measured using LumaxCLIA. The mean duration from chest pain onset to venipuncture was 4.35 hours. When comparing patients with AMI to healthy controls, the mean concentrations of all parameters were significantly higher. Serum IMA demonstrated the highest sensitivities-specific positive and negative predictive values compared to the other parameters. Therefore, compared to other traditional cardiac biomarkers, serum iso-modified albumin is a more sensitive sign in the diagnosis of acute myocardial infarction [14].

Fatal chest pain refers to chest pain that results in death and can occur in severe medical conditions such as aortic dissection, pulmonary embolism, or severe pneumonia. Immediate medical attention is crucial if experiencing chest pain, as it could indicate a life-threatening condition.

A study involving 150 patients with chest pain lasting over a year in the emergency department found that 90 individuals (group 1) had acute myocardial infarction (MI), aortic dissection, or pulmonary thromboembolism, which can lead to life-threatening chest discomfort. The control group consisted of 30 healthy individuals with normal blood thrombin levels, while group 2 comprised 60 patients with non-specific, non-life-threatening causes of chest discomfort. The study found that serum copeptin levels can be useful in distinguishing potentially life-threatening chest discomfort [15].

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4. Conclusion

Pain is not only a protective response necessary for the survival of species, but also a global health problem affecting human life and health and social development. Although this article has discussed biomarkers for pain in various fields, it is worth noting that the main issue is still that each marker has its own advantages and disadvantages. In addition, due to the overall small sample size of each study, the results lack specificity, there is no uniform standard for quantifying pain, and whether there is a linear relationship between pain degree and biomarkers is not conclusive. It is still necessary to carry out further research to verify this proposition. Meanwhile, with the development of molecular biology technology and the further development of clinical research, the mechanism of pain will be further revealed. The discussion of different sites or different types of pain markers can also help in pain prevention and treatment. To sum up, the occurrence and development mechanism of pain should be revealed from multiple levels, multi-levels and multi-targets in the future, so as to provide theoretical basis and solutions for in-depth research on the pain prevention and treatment.

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