Systemic alterations in plasma biomarkers levels in patients with chronic pain

Alterações nos níveis plasmáticos de biomarcadores de pacientes com dor crônica

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ABSTRACT

BACKGROUND AND OBJECTIVES: To analyze the scientific evidence on the changes in plasma levels of interleukins, nitric oxide, extracellular matrix metalloproteinases, bradykinins, and cortisol in patients with chronic pain.

CONTENTS: The studies were identified by searching the following electronic databases: Pubmed/Medline, Scopus, LILACS, and Web of Science, published from June of 2016 to December of 2016. The selected articles were presented in a flow chart based on their identification, selection, eligibility and inclusion and exclusion criteria. The content of the articles included in the study was analyzed to identify the biomarkers present in patients with chronic pain. Thirteen articles that addressed the plasma biomarkers levels in humans with chronic pain were selected. Most of the articles presented the cytokines levels, followed by cortisol. Only one article mentioned the nitric oxide, and none mentioned what plasma levels of extracellular matrix metalloproteinases and bradykinins were identified.

CONCLUSION: Changes were observed in inflammatory and anti-inflammatory cytokine plasma levels, and that cortisol is related to anxiety and depression symptoms in patients with chronic pain. However, it was not possible to identify the changes in plasma levels of nitric oxide, bradykinin, and extracellular matrix metalloproteinases due to the absence of scientific evidence.

Keywords: Biomarkers, Chronic pain, Plasma.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Analisar as evidências científicas sobre alterações nos níveis plasmáticos de interleucinas, óxido nítrico, metaloproteinases de matriz extracelular, bradicinina e cortisol em pacientes com dor crônica.

CONTEÚDO: Os estudos foram identificados por meio das bases de dados eletrônicas: Pubmed/Medline, Scopus, LILACS e *Web of Science,* publicados no período de junho a dezembro de 2016. Os artigos selecionados foram classificados em ficha de identificação, seleção dos participantes, elegibilidade, critérios de inclusão e exclusão. Os artigos selecionados foram avaliados por meio de análise de conteúdo, buscando identificar os biomarcadores presentes nos pacientes com dor crônica. Foram selecionados 13 artigos que abordavam a dosagem plasmática de biomarcadores em humanos com dor crônica. A maior parte dos artigos apresentou a dose de citocinas, seguidos pelo cortisol. Apenas um artigo apresentou a dose de óxido nítrico e nenhum artigo identificou a dosagem de níveis plasmáticos de metaloproteinases de matriz extracelular e bradicinina.

CONCLUSÃO: Pôde-se verificar modificações nos níveis plasmáticos de citocinas inflamatórias e anti-inflamatórias, e que os níveis plasmáticos de cortisol estão relacionados com os sintomas de ansiedade e depressão nos pacientes com dor crônica. No entanto, não foi possível verificar as alterações nos níveis de plasma do óxido nítrico, bradicinina e metaloproteinase de matriz extracelular devido à ausência de evidências científicas.

Descritores: Biomarcadores, Dor crônica, Plasma.

INTRODUCTION

Chronic pain is generally defined as persistent pain lasting longer than three months. However, other definitions favor the inclusion of psychosocial factors and the severity of pain in the diagnosis of chronic pain. The severity is graded based on its intensity, suffering, and impacts related to pain and functional impairment[1].

Due to these characteristics, it is considered a complex and multi-factorial affliction, which makes it difficult to evaluate and justify the need for several techniques, such as questionnaires, numeric scales, and non-verbal indices, as well as biochemical and biomechanical parameters[2,3] that although provide for an adequate investigation of the disease, make it difficult for the use at a large scale. Therefore, it is necessary to understand the biological and psychosocial parameters to facilitate the diagnosis of the patient with chronic pain.

Due to the complex features of chronic pain, it remains a major challenge for clinical management and assessment as it is often

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only examined with one-dimensional scales that do not reflect the diversity of factors that encompass the care and the experience of chronic pain. An aspect that could facilitate the control and treatment of chronic pain could be the use of blood biomarkers. However, the relationships between chronic pain and the continuous presence of nociceptors or inflammatory markers in the plasma of patients with chronic pain are not yet understood. In addition, there is a lack of clinical diagnostic requirements regarding the use of physiological and biochemical biomarkers[4].

Biomarkers are biochemical molecules that aid in the diagnosis and the accompaniment of diseases. In pain, the relationship between proinflammatory biomarkers and pain had been examined in patients with painful inflammation such as a key pathological feature of the disease process[5]. In these cases, high-stress levels may compromise the hypothalamic-pituitary-adrenal axis, interfering with cortisol secretion, and alter cytokine expression and tumor necrosis factor[6,7].

Inflammatory cytokines, as well as nitric oxide (NO), play a key role in the pathogenesis of persistent and exacerbated pain states[8]. Some publications present the relation of these biomarkers with oncologic pain and neuropathic pain[9]. However, the relationships between biomarkers and chronic musculoskeletal pain have not been discussed until now.

Therefore, this scoping review was undertaken to evaluate the scientific evidence on the changes in plasma levels of interleukins, NO, matrix metalloproteinases (MMP), bradykinins, and cortisol in patients with chronic pain.

CONTENTS

Studies were identified by searching the following electronic databases: Pubmed/Medline (via National Library of Medicine) (1990 - present), Scopus (1990 - 2013), ScienceDirect (1990 - present) and Web of Science (1990 - present), indicated in the period from June 2016 to December 2016. The research question was: *"Do patients with chronic pain have changes in the plasma levels of cytokines, nitric oxide, bradykinin, MMP, and cortisol?*

Definition of terms

For that, we selected articles published in the last 10 years, published in English, Portuguese, and Spanish. Keywords were selected by *Mesh Terms* in order to identify the correct nomenclatures. They were: "chronic pain" with the AND search operator "Nitric Oxide", "Hydrocortisone", "Cytokines" "Bradykinin", "Matrix Metalloproteinases", with the OR operator between them. In order to restrict the search for the type of analysis, the word plasma was used as the free term with the AND search operator.

After this initial selection, the titles and abstracts were read and evaluated based on our inclusion and exclusion criteria for relevance. Two reviewers independently reviewed the full texts of all potentially relevant articles, and the eligibility of each was discussed and resolved. If there had been disagreements between two evaluators, a third evaluator was consulted. This review was performed in order to understand changes in biomarkers plasma levels in patients with chronic pain.

Inclusion and exclusion criteria

Studies included in this scoping review: articles describing the plasma levels of biomarkers in patients with chronic musculoskeletal pain; observational and experimental studies that presented plasma levels of biomarkers in this population prior to treatment and only full-text article citations with no restrictions on language. In addition, the following exclusion criteria were used: articles that presented dosages of biomarkers in animals; studies that showed biomarker dosages that were collected in other sample types that are not human plasma. Furthermore, meeting abstracts, unpublished data, review articles, and duplicate articles were excluded from the current study.

The initial search resulted in 193 articles fully assessed in this review, 94 articles were from Pubmed, 40 from the Web of Science, 58 from SCOPUS and one from LILACS. Of these, 62 were duplicates. The remaining 131 articles were evaluated by their abstracts, verifying whether they corresponded to the inclusion criteria. After this stage, 47 articles were included for the complete evaluation of the study. At this stage, 34 articles were excluded, because (although not observed in the summary reading) they did not match the inclusion criteria of this study, since they did not present biomarker plasma evaluation, or these analyses were performed only after some type of treatment.

Regarding the causes of chronic pain, it is possible to observe that four articles referred to patients with fibromyalgia, three articles were related to chronic pelvic pain, one article reported chronic pain caused by sports, one article referred to burning mouth syndrome, and one article mentioned temporomandibular pain. Other articles indicated participants with chronic pain without specifying the cause.

Selected articles were published between 2007 and 2016. There were two articles published in each of the following years: 2007, 2012, 2014, 2015 and 2016 with only one article published each year in 2008, 2009 and 2013.

Regarding biomarkers analyses (Table 1), it is possible to observe that with a total of thirteen articles, nine studies presented cytokine analyses, one study showed NO analyses and four articles described cortisol analyses, all in plasma samples. Among the most common cytokines were interleukins 6, 2, and 10 (IL-6, IL-2, IL-10), tumor necrosis factor alpha (TNF-α) and interferon gamma (INF-γ).

In summary, six articles identified an increase in interleukins correlated to chronic pain. The biomarker with the highest number of alterations was IL-6 with three articles reporting increases in patients. One study reported decreased levels of IL-6, IL-4, IL-1, IL-2, IL-8, and TNF-α, was also indicated to increase in serum levels in the chronic pain group. Anti-inflammatory cytokines, IL-4, IL-5, and IL-13 are reported to have decreased in these studies. Finally, one study reported a direct correlation between increased NO plasma concentration and disease severity. Moreover, in relation to cortisol, it was observed that despite being related to depression and other emotional aspects, such as the response to stress, there is no difference in plasma concentrations between the patient and control group.

In this scoping review, no study was found evaluated plasma bradykinin and MMP in patients with chronic musculoskeletal pain.

Table 1. Biomarker analysis of selected articles

	Autors	Sample	Biomarkers	Result / comparison
1	Koch et al.[8]	Chronic pain (94) Healthy controls (6)	Cytokines (TNF-α, GM-CSF, IL-1β, IL-6, IL-8, INF-γ, IL-2, IL-4, IL-5, IL-10); nitric oxide (NO).	Patients with mild pain x control: increased IL-6 Patient with severe pain x control: significant increase of IL-6 and NO. Non-significant increase IL-1b, TNF-a, IL-2, and IL-4
2	Vaisberg et al.[10]	Handball athletes with pain (14) Handball athletes without pain (41)	Plasma cortisol; adrenaline; prolactin; growing hormone; dopamine; L-dopa; epinephrine, norepinephrine, cytokines (IL-1, IL-2, IL-4, IL-6, TNF-α, IFN-γ, PGE2).	There was no difference between the groups in the hormones; IL-1, IL-2, TNF-α, IFN, and PGE2 were significantly higher in the chronic pain group.
3	Wingenfeld et al.[11]	Chronic pelvic pain (18) Fibromyalgia (17) Healthy control (24)	Plasma cortisol; salivary cortisol; hormone adrenocorticotrophic (ACTH); inhibition of the hypothalamic-pituitary-adrenal (HPA) axis by dexamethasone.	Plasma cortisol: there was no difference between groups, but with a significant increase after stress. Fibromyalgia group has a higher concentration than the chronic pelvic pain and control. In the others, there was no statistical difference.
4	Anderson et al.[12]	Chronic pelvic pain (60) Healthy controls (30)	Plasma cortisol; ACTH; salivar cortisol.	Decrease in ACTH hormonal response, with an average response of 30% less to control. Regarding cortisol, there was no difference between groups.
5	Behm et al.[13]	Fibromyalgia (110) Healthy controls (91)	Cytokines (IFN-y, IL-5, IL-6, IL-8, IL-10, MCP-1 e MIP1-α).	The concentrations of most cytokines were lower in stimulated patient samples than in controls. IL-6 was the one with the greatest decrease.
6	Malhotra et al.[14]	Fibromyalgia (26) Healthy controls (26)	Cytokines (IFN-y, IL-2, IL-4, IL-6, IL-10).	IL-6: Mean increase of 242.8% in the patient group when compared to healthy controls. The level of IL-6 correlates directly with the severity of pain. IL-4: Mean increase of 136.4% in the patient group when compared to healthy controls. Anti-inflammatory cytokines: There was a statistically significant decrease among the patient group when compared to healthy controls.
7	Lundh et al.[15]	Chronic pelvic pain (32) Healthy controls (37)	Testosterone; MIF (factor of inhibition of the migration of macrophages); cytokines (TNF-α, TNF-β, IL-2, IL-1β); salivar cortisol.	MIF: Significantly higher in patients than in control. Testosterone: Less in patients than in control TNF-α: significantly higher in patients than in control.
8	Koike et al.[16]	Burning mouth Syndrome (47) Healthy controls (47)	Adrenaline; noradrenaline; ACTH; plasma cortisol.	Adrenaline: significantly lower in patients. Depression levels significantly associated with plasma levels of noradrenaline and cortisol.
9	Sturgill, McGee and Menzies[17]	Fibromyalgia (105)	Cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-13, IL -17, G-CSF, GM-CSF, IFN-y and TNF-α); chemokines (CXCL8, CCL2 (MCP1) e CCL4 (MIP1β)).	There were no significant correlations between cytokine levels and fatigue, depression or stress; there is a trend of significance when we compare levels of cytokines and pain. After post-hoc analysis, there was a marked reduction of IL-4, IL-5, and IL-13 cytokines.
10	Ciszek et al. [18]	Vulvodynia (33), vulvodynia and irritable bowel syndrome (23) Healthy control (22)	Cytokines (MCP-1, MIP-1α, MIP-1β, RANTES, ENA-78, FGF basic, G-CSF, GM-CSF, IFN-γ, IL-1α, IL-1β, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-17, TNF-α, Thrombopoietin, VEGF endothelial growth factor); RNA expression.	RNA expression: deregulation of miRNA in VBD affects relevant estrogen pathways, whereas, in generalized pain, it is related to muscle, nerve cells, and glial cells. IL-8 and IL-1ra were statistically significant between the groups, being higher in the patient group. Women with VBD and VBD + IBS have increased expression of proinflammatory cytokines.
11	Nenke et al.[19]	Chronic pain (26)	Salivar cortisol; plasma cortisol.	Plasma cortisol: significant reduction in opioid users when compared to control, especially at 60 and 120 min. There was no difference in salivary cortisol.
12	Bäckryd et al.[20]	Neuropathic chronic pain (14) Healthy control (17)	Cytokines (IL-1, IL-6, IL-8, and GM-CSF).	IL-6: significantly higher in patients than in controls. IL-1, IL-8, and GM-CSF: no difference between the two groups. A multivariate analysis showed a tendency for patients to have higher GM-CSF plasma levels than controls.
13	Park and Chung[21]	Temporomandibular pain (40) Healthy control (20)	Cytokines (IL-1β, IL-6, IL-10, and TNF-α); C-Reactive protein	Patients with major changes had higher scores on pain and sleep scores. The patient group had statistically higher levels of cytokines than the control group. Cytokines had a significant positive relationship with the Pittsburgh Sleep Quality Index (PSQI). IL-10 and TNF-α were associated with the sleepiness scale.

DISCUSSION

The present scoping review sought to understand the changes in plasma levels of biomarkers cytokines, nitric oxide, bradykinin, MMP, and cortisol presented in patients with chronic pain. In this review, thirteen articles were found to address these questions. A greater number of articles with cytokines were identified, followed by cortisol, only one article regarding NO and none for the other biomarkers.

Among the articles which included cytokines, it was possible to observe that cytokines were the most evaluated biomarker, mainly IL-6, IL-2, and IL-10. However, the one that had the strongest relationship to chronic pain was IL-6[6]. Interleukin-6 is related to both the innate and adaptive immune response. It arises in response to microorganisms, but also to stimulation by other cytokines such as IL-1 and TNF-α. It is also considered the main myosin produced by active skeletal muscles and has an acute pro-inflammatory effect, but its presence stimulates the increase of other interleukins, such as IL-10, which presents a chronic anti-inflammatory effect[22]. In studies by Koch et al.[8] and Malhotra et al.[14], a direct relationship was found between the concentration of pro-inflammatory interleukins, mainly IL-6, and the severity of chronic pain. Pro-inflammatory cytokine concentrations in this review were related to the presence of chronic pain, as six articles have shown that these cytokine concentrations were higher in patients with chronic pain than in healthy controls[13]. These studies presented different chronic pain charts, so this finding may be related to chronic musculoskeletal pain of different origins. Another relationship found in the cytokine and chronic pain ratio was the decrease of anti-inflammatory cytokines in patients with chronic pain when compared to controls[13,14,17,19]. This information may facilitate the modification of pain perception, since IL-10, for example, plays an important role as a pain perception blocker[23].

Concerning NO, only one article was found to evaluate plasma dosage. A study by Koch et al.[8] showed that serum NO levels increase in patients with chronic pain at all severity levels when compared to healthy controls. However, although these authors also find modifications in the dosages of cytokines, there are no references as to the correlation between these variables. It is known that NO plays an important role in the synthesis of cytokines and inhibitory factors involved in inflammation[24].

Regarding plasma cortisol levels, five studies with this type of analysis were found. Among them, only Vaisberg et al.[10] evaluated plasma cortisol and cytokine levels for chronic pain in athletes, but it did not show a relationship between the two biomarkers. In Vaisberg et al.[10], no significant changes were found between the groups with chronic pain or chronic pain in serum cortisol levels. Additionally, no studies showed a relationship between cytokines and cortisol. Cytokines can aid in the activation of the neuroendocrine axis, increasing the cortisol secretion, and a modification in this system, due to the cytokines, the increase could explain a chronic release and increase in plasma cortisol[7].

Among the five articles that measured plasma cortisol, three presented significant changes. Wingenfeld et al.[11] showed higher concentrations of plasma cortisol in the fibromyalgia group than in the other groups, which is related to a difficulty in responding to stress. Koike et al.[8] reported a direct relationship between depressive symptoms and serum cortisol rates. Nenke et al.[19] showed that patients on opioids treatment had reduced cortisol rates. In this view, it seems that patients experiencing chronic pain with emotional changes may present changes in plasma cortisol levels.

Taken together, our findings provide evidence that chronic musculoskeletal pain can increase pro-inflammatory cytokines, mainly IL-6 and NO in serum, as well as decrease IL-10. Cortisol seems to be related to the presence of anxiety and depression symptoms, which may make it difficult for these patients to cope in the face of chronic pain[25]. Another important aspect is the type of chronic pain evaluated. The most cited were not fibromyalgia and chronic pelvic pain but unspecified chronic pain. This aspect identifies many possible factors that develop chronic pain, which, after being established, becomes a health problem itself, with its own particularities[26].

No study was found in the literature to have measured plasma MMP or bradykinin content in patients with chronic musculoskeletal pain. This may be related to the fact that MMP and bradykinins influence the local inflammatory process when patients present tissue injury, but this not always happens in patients with chronic pain[27]. However, it would be important to understand the systemic impact of the presence of these biomarkers and their impact on chronic pain processes when acute tissue injury ceases.

In this review, it was found that most of the articles deal with a cross-sectional observational study, which is justified by the guiding question used since this study sought to identify the modifications in the biomarkers in patients with chronic pain. However, despite being observational studies, they presented a high level of evidence, which makes it possible to use them as scientific evidence for these biomarkers modifications.

Because of the guiding question, this study did not include randomized clinical trials that could better explain the relationships between these biomarkers as well as factors that aggravate or ameliorate clinical symptoms and possibly modify biomarker dosages. Further studies are required to understand the relationship between biomarkers and other problems associated with chronic pain, such as psycho-social aspects.

CONCLUSION

This scoping review can conclude that there are changes in inflammatory and anti-inflammatory cytokine plasma levels of patients with chronic pain, and that cortisol is related to anxiety and depression symptoms. Regarding NO, bradykinin, and MMP, it was not possible to establish this relationship due to the absence of studies.

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