

Therapy with omega-3 fatty acids for patients with chronic pain and anxious and depressive symptoms*

Uso de terapêutica com ácidos graxos ômega-3 em pacientes com dor crônica e sintomas ansiosos e depressivos

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ABSTRACT

BACKGROUND AND OBJECTIVES: Anxious and depressive disorders very often follow with chronic painful conditions and are associated to a range of negative outcomes. In spite of this association, both pain and these disorders are often inadequately managed, leading to labor incapacity, worsening of health and quality of life and increased health costs. A review was carried out of therapeutic actions of omega-3 (w-3) fatty acids to treat chronic pain patients with anxious and depressive symptoms.

CONTENTS: Studies are showing that anxious and depressive symptoms contribute to worsen pain and that chronic pain contributes for such disorders. It is possible that substances able to decrease pain may also relieve anxious and depressive symptoms. Omega-3 fatty acids may act on neuroprotection and mood stabilization, and may even decrease the inflammatory status common in chronic pain. Clinical trials have shown the effectiveness of fatty acids in patients with anxious and depressive symptoms and chronic pain.

CONCLUSION: Supplementation with w-3 fatty acids for chronic pain patients with anxious and depressive symptoms may be an effective strategy to improve both such symptoms and pain.

Keywords: Anxiety, Chronic pain, Depression, Omega-3.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Desordens ansiosas e depressivas muitas vezes ocorrem simultaneamente com condições dolorosas crônicas e são associadas a uma gama de desfechos negativos. Apesar desta associação, tanto a dor quanto essas desordens são frequentemente tratadas de forma inadequada, causando incapacidade laboral, redução da saúde, da qualidade de vida e aumento dos custos com a saúde. Foi realizada uma revisão das ações terapêuticas dos ácidos graxos ômega-3 no tratamento de pacientes com dor crônica que apresentam sintomas ansiosos e depressivos.

CONTEÚDO: Estudos vêm demonstrando que sintomas ansiosos e depressivos contribuem para exacerbar o quadro algíco e que a presença de dor crônica contribui para o surgimento destes transtornos. É possível que o emprego de substâncias capazes de reduzir os sintomas algícos possa aliviar os sintomas ansiosos e depressivos. O ácido graxo w-3 pode atuar na neuroproteção e estabilização do humor, e na redução do estado inflamatório, comum na dor crônica. Ensaios clínicos evidenciaram a eficácia do ácido graxo em pacientes com sintomas ansiosos e depressivos, e com dor crônica.

CONCLUSÃO: A suplementação com ácidos graxos w-3 em pacientes com dor crônica que apresentam sintomas ansiosos e depressivos pode ser uma estratégia efetiva tanto para a melhoria destes sintomas quanto do quadro algíco.

Descritores: Ansiedade, Depressão, Dor crônica, Ômega-3.

INTRODUCTION

Chronic pain is a health problem affecting one third of the adult population¹. Factors such as alcohol, smoking, older age, overweight, female gender, low socioeconomic condition, low education, physical inactivity, execution of manual works and marital status are positively associated to this morbidity, which is among the major causes of absenteeism and decreased productivity at work, medical leaves, retirement due to disease, labor indemnities, social security benefits and pensions²⁻⁵.

Chronic pain is often associated to psychiatric co-morbidities, such as depressive and anxious disorders. In approximately 40% of cases, mood changes are short-lasting, but most of the times they are recurrent and become chronic disorders for 5% to 30% of pa-

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Submitted in October 02, 2012.

Accepted for publication in February 28, 2013.

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tients⁶. However, in spite of this association, both pain and psychiatric disorders are in general inadequately managed, resulting in pain intensity worsening, labor incapacity, decreased health and quality of life (QL), thus increasing treatment costs^{7,8}.

Supplementation with omega-3 fatty acids (w-3), nutrient with nutraceutical properties, seems to attenuate pain and psychiatric disorders^{9,10}.

So, to analyze such hypothesis, therapeutic actions of w-3 fatty acids to treat chronic pain patients with anxious and depressive symptoms were reviewed in BBO, LILACS, Pubmed and Scielo databases being included studies carried out from 2000 to 2012.

ANXIOUS AND DEPRESSIVE SYMPTOMS IN CHRONIC PAIN PATIENTS

Evidences have confirmed that, even in predominantly organic cases, the influence of psychological aspects is relevant in pain complaints, with significant relationship between chronic pain and psychiatric disorders¹¹.

Pain may contribute to anxious responses because it acts as an alert system triggering fighting and escaping reactions. This is translated into fear and insecurity feelings faced to diagnostic unawareness. When the cause of pain is not overcome and becomes a chronic process, feelings such as hopelessness, helplessness and despair may give place to depressive symptoms or even to major depression¹².

Another way to understand the effects of anxiety and depression is to study them on the stress process. It has been proposed that vulnerability factors, such as anxiety and depression, may negatively affect patients by increased exposure or responsiveness to stress, thus increasing pain reports¹³. It is possible that anxiety is manifested by physical excitation, increased sensitivity to pain or interpretation of sensations as painful; and that depression is expressed by lack of pleasure, being able to increase vulnerability to pain during stress¹⁴.

A study¹⁵ aiming at identifying the frequency of anxious and depressive symptoms in patients with peripheral neuropathy has shown the presence of anxious symptoms in 68.5%, and of depressive symptoms in 51.9% of evaluated patients.

Another study with the Israelite population has shown that chronic pain is significantly associated to higher probability of anxious and depressive disorders. Anxious disorders were three times more common and depressive disorders were twice as common in chronic pain patients as compared to pain-free patients⁷.

A study⁸ evaluating 400 chronic pain patients has identified a high prevalence of anxiety and depression (70% and 60%, respectively). It has also observed that co-morbidities associated to anxiety, depression and chronic pain were significantly higher than those associated just to chronic pain, and that individuals with anxiety and depression had poorer QL as compared to individuals without anxiety and depression.

A study⁵ has evaluated 1209 individuals participating in the *Netherlands Study of Depression and Anxiety* to determine the impact of pain on the course of anxious and depressive disorders and has observed that high number of pain sites, joint pain, daily use of painkillers and more severe pain levels were associated to poorer course of such disorders.

In a different study¹⁴, prevalence of depression in rheumatoid arthritis (RA) was much higher than that reported by the general community, but was similar to other chronic diseases. RA depression is associated to higher levels of disease activity, pain, fatigue, labor incapacity, poor treatment compliance and higher risk of mortality and suicide.

Other authors¹ have evaluated the effect of isolated chronic musculoskeletal pain, or associated to anxiety and depression. For such, participants of the study were divided in 4 groups: Group P (pain), group PD (pain and depression), group PA (pain and anxiety) and group PDA (pain, depression and anxiety). Authors have observed that group P patients had lower pain intensity as compared to PDA group. Depression and anxiety were strongly related to the number of days individuals were absent from their routine activities (school, work) as consequence of pain, being a mean of 18 days for group P, 32 days for group PA, 38 days for group PD and 42.6 days for group PDA.

So, it is observed that the presence of such psychiatric co-morbidities contributes for a poorer course of disease in chronic pain patients, becoming unquestionable the need of for follow up by a mental health specialist and a multidisciplinary team⁷.

Considering that anxiety and depression symptoms are commonly found in those patients and that the real cause and consequence relationship is still not well established, it is possible that resources able to contribute to treat the painful process be also able to help eliminating such symptoms, especially when pain is the major trigger of psychic disorders. Similarly, it is plausible that the use of agents decreasing anxious and depressive disorder symptoms may also cooperate in decreasing pain.

THERAPY WITH OMEGA-3

Several non pharmacological alternatives have been used to help managing chronic pain and its consequences. Among them there is the use of nutrients with effects similar to non-steroid anti-inflammatory drugs (NSAIDs), such as w-3 fatty acids⁹.

Polyunsaturated fatty acids, group to which w-3 belongs, act on cell signaling, enzyme regulation, eicosanoid synthesis, neuronal migration regulation, determination of synaptic plasticity and modulation of cytokines with neuromodulating and neurotransmitting activity¹⁶. Currently, several benefits of w-3 ingestion are reported, being related to prevention and treatment of cardiovascular diseases, gastrointestinal inflammatory diseases, infections, lesions and immune changes¹⁷.

Several mechanisms are suggested to explain the relationship of w-3 and psychiatric disorders including: membrane function changes; mood stabilization; increased BDNF expression (Brain-Derived Neurotrophic Factor), protein involved in neuroprotection, including neuronal survival, dendritic arborization, synaptic plasticity and neurodevelopment; inflammation improvement and change in eicosanoid, docosatrienes and central nervous system genes synthesis. Docosahexaenoic acid (DHA), one w-3 component, when incorporated to neuronal cell membranes, may lead to a better binding of neurotransmitters to their receptors. The eicosapentaenoic acid (EPA), another w-3 component, seems to increase brain oxygen and glucose supply and to protect against oxidative stress¹⁸.

DHA and EPA supplementation during critical development periods (gestation and lactation) is essential for cortical maturation, synaptogenesis and myelination, and may also decrease the risk of cognitive and psychopathological deficits in adult life¹⁹.

It is also stated that DHA deficiency is associated to dysfunctions in neuronal membrane stability, neuroplasticity and serotonin, norepinephrine and dopamine transmission, which may be related to the etiology of mood disorders and to cognitive manifestation of depression. EPA, for its anti-inflammatory action, may be associated to somatic symptoms of depression¹⁰.

The association between w-3 consumption and the presence of depressive and anxious symptoms is being investigated and it has been noticed that societies with high w-3 consumption have lower prevalence of depression. It has also been observed that patients with more severe depression have lower w-3 body levels and that there is a significant negative correlation between such levels and the severity of depressive symptoms¹⁰.

Confirming such observations, a study²⁰ has indicated that clinical depression is followed by a lower w-3 erythrocyte level, as well as by lower plasma and brain levels of this fatty acid. In addition, they state that high arachidonic acid (AA) concentration or high blood, plasma and erythrocyte AA/EPA ratio is associated to increased severity of depressive symptoms.

In spite of these positive evidences, some studies show no significant beneficial effects of w-3 ingestion to protect against the risk of developing depressive symptoms^{21,22}. A meta-analysis²³ carried out to evaluate the effects of w-3 on depression has shown that there are no significant fatty acid effects with regard to placebo, suggesting that studies which have found beneficial relationships had methodological failures. On the other hand, a different recent meta-analysis²⁴ has observed that the effectiveness of w-3 is related to the EPA/DHA ratio of the product, evidencing that those studies where supplemented w-3 had a minimum of 60% EPA have shown significant beneficial results.

A study²⁵ carried out with adult individuals of South Korea, has shown that erythrocyte levels of w-3 and of EPA and DHA alone were significantly lower in patients with depression as compared to those without depression.

This relationship is also being studied in adolescents. The status of w-3 and w-6 was investigated in adolescents with eating disorders and depressive symptoms and it was observed that these individuals had significantly lower w-3 and w-6 levels and higher omega 6/omega 3 ratio than adolescents with eating disorders and without depressive symptoms²⁶. These results were confirmed by a study carried out with Australian adolescents, where it was observed that patients with eating disorders and depressive symptoms had significantly lower w-3 ingestion than those with eating disorders alone²⁷.

Few studies have investigated the action of this fatty acid on anxiety disorders, although it has been suggested that w-3 could interfere with this disorder due to the similarity of some pathophysiological mechanisms between anxiety and depression. It has been reported that individuals without depression, but with social anxiety, have lower w-3 levels in erythrocyte membranes, high omega 6/omega 3 ratio and negative correlation between w-3 levels and anxiety scores as compared to control group²⁴.

Experimental animal studies^{28,29} have observed that diet poor in w-3 is associated to the presence of anxiety, and that supplementation of this fatty acid has promoted improvement both in anxiety and in anxiety-related parameters. A different study³⁰ has shown that w-3 supplementation in early brain development phases in rats was successful in decreasing anxiogenic effects of stressing events.

A clinical trial³¹ has evaluated the effects of w-3 supplementation in students and has observed that 2.5 g/day supplementation for 12 weeks was able to decrease anxiety scores.

However, when it comes to anxiety and depression of chronic pain patients, beneficial w-3 actions gain new aspects.

Consistent evidences show competitive interactions between w-3 and w-6 in the formation of eicosanoids. Increased w-3 consumption results in its increase in inflammatory cells phospholipids, so, due to the lower amount of substrate available for eicosanoid synthesis as from w-6, w-3 supplementation in human diet has resulted in decreased production of prostaglandins, second series thromboxanes and fourth series leukotriens, all potent inflammatory agents^{16,31-33}.

In addition, it is said that anxious and depressive symptoms may increase inflammatory cytokines expression, which would contribute to pain worsening, and that inflammatory mechanisms are involved in the pathophysiology of such symptoms, in a vicious cycle. Since w-3 consumption results in decreased pro-inflammatory cytokines production, there would be decrease in hyperalgesia and anxious and depressive symptoms³¹.

So, taking into consideration the already established association between pain and anxious and depressive symptoms, it is possible that improvement of psychological symptoms could be related to the direct w-3 action at brain level, or indirect action, by the action of this fatty acid on the attenuation of the inflammatory process leading to pain.

CONCLUSION

Both for its direct actions on brain structures and its anti-inflammatory characteristic, w-3 supplementation may become a beneficial strategy to improve anxious and depressive symptoms and pain of chronic pain patients.

Well-conducted clinical trials are needed to evaluate the usefulness of this supplementation to treat patients with such symptoms, as well as to establish dose and supplementation time needed to reach positive results.

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