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Complex regional pain syndrome (CRPS): The therapeutic role of Intralipid (soybean oil; linoleic acid) ?

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Abstract
Since 1929, when Burr and Burr first described a syndrome caused by stringent fat reduction in a diet (which manifested mostly as cutaneous symptoms, such as erythema with scaling, hair loss, itch, and increased water loss), it became clear that particular fat pay an essential role in skin structure. The word "essential" best describes these fats because of the inability of the human organism to synthesize them, which means they can only be provided through dietary intake.
Complex regional pain syndrome (CRPS) is usually triggered by trauma or a surgical procedure, and it typically becomes an established one after an intense inflammatory process with chronic pain and edema as the main symptoms. Available treatments for CRPS have low efficacy. This study aimed to evaluate the clinical and immunoregulatory effects of omega-3 polyunsaturated fatty acid (PUFA) supplementation on paw edema and anti- and pro-inflammatory cytokines and macrophage phenotypes in the chronic post-ischemia pain (CPIP) preclinical model of CRPS-Type I.
The results suggest that omega-3 PUFA supplementation has anti-inflammatory effects in the CPIP model of CRPS-Type I, significantly reducing paw edema and regulating concentrations of anti-inflammatory cytokines, including IL-4 and IL-10.
Key Words: *Complex regional pain syndrome (CRPS), Intralipid, Soybean oil, Linoleic acid.*

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Since 1929, when Burr and Burr first described a syndrome caused by stringent fat reduction in a diet (which manifested mostly as cutaneous symptoms, such as erythema with scaling, hair loss, itch, and increased water loss), it became clear that particular fat pay an essential role in skin structure [1,2]. The word "essential" best describes these fats because of the inability of the human organism to synthesize them, which means they can only be provided through dietary intake. The term essential fatty acids (EFAs) was formed and referred to two polyunsaturated fatty acids (PUFAs), linoleic acid (LA) and α-linolenic acid (ALA), initiating acids for the cascade of elongation to very long-chain PUFAs (more than 22 C-atoms). PUFAs are divided into two families, omega-3 (ω-3) and omega-6 (ω-6). ω-3 fatty acids (FAs) have in common a terminal carbon-carbon double bond in the omega three-position, the third bond from the methyl end of the acid, whereas, ω-6 acids have it in the omega six-position, the sixth bond from the methyl end of the fatty acid, respectively. LA is a member of the ω-6 family, whereas, ALA is classified as ω-3 PUFA. The double bonds in these EFAs are always in *cis*-configuration, which means there are two hydrogen atoms on the same side of the double bond [3]. Salubrious effects of PUFAs might be mediated through various mechanisms, including modifications in cell membrane lipid composition, gene expression, cellular metabolism, and signal transduction [4]. However, ω-3 and ω-6 FAs have antagonistic effects on metabolic functions in the human organism.

PUFAs are nowadays desirable components of "specialty oils", oils with special dietary, and functional properties that are used as nutraceuticals or cosmeceuticals. Due to the better understanding of their biological and functional properties, and their health benefits, PUFAs, specially ω-3 PUFAs are of great importance for health system, due to their potential applications in disease prevention, but also treatment of the most common chronic inflammatory diseases, including inflammatory skin diseases, such as atopic dermatitis (AD), psoriasis, and acne. Nowadays, clinicians have at the disposal useful tools like lipidomics and nutrilipomics that guide them to provide the most appropriate and individualized FAs supplementation in the treatment of their patients, but also the prevention of disease in various clinical fields, as well as the field of dermatology [5].

Immunoregulatory Effect of Preventive Supplementation of Omega-3 Fatty Acid in a Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS) is usually triggered by trauma or a surgical procedure, and it typically becomes an established one after an intense inflammatory process with chronic pain and edema as the

main symptoms. Available treatments for CRPS have low efficacy. This study aimed to evaluate the clinical and immunoregulatory effects of omega-3 polyunsaturated fatty acid (PUFA) supplementation on paw edema and anti- and pro-inflammatory cytokines and macrophage phenotypes in the chronic post-ischemia pain (CPIP) preclinical model of CRPS-Type I.

Female Swiss mice were supplemented with omega-3, corn oil, or saline and then submitted to the CPIP model of ischemia/reperfusion (I/R) injury. Supplementation was carried out for 30 days prior to and up to 2 or 15 days after the induction of CPIP, according to experimental protocols. The supplementation protocol included 1,500 mg/kg of omega-3 or corn oil through an intragastric route (gavage). Paw edema, interleukin-(IL-) 4, IL-10, transforming growth factor-β1 (TGF-β1), monocyte chemotactic protein-1 (MCP-1), and tumor necrosis factor (TNF) were then measured in the paw skin and muscle by enzyme-linked immunosorbent assay (ELISA), and macrophage phenotypes (M1 and M2) assessed in the paw muscle by Western blotting.

The CPIP model induced an increase in paw thickness up to 72 h post-I/R. Mice supplemented with omega-3 compared to the saline group displayed reduced edema but neither altered skin IL-4 or skin and muscle TGF-β1, TNF, and MCP-1 concentrations, nor did they exhibit significantly altered muscle macrophage phenotype on the 2nd-day post-CPIP. However, omega-3 supplementation reversed the I/R-related reduction in IL-4 in the paw muscle compared to groups supplemented with saline and corn oil. Furthermore, omega-3 promoted the reduction of IL-10 levels in the paw skin, compared to animals with lesions supplemented with saline, until the 2nd-day post-CPIP. On the 15th day post-CPIP, IL-10 was significantly increased in the muscle of animals supplemented with omega-3 compared to the saline group.

The results suggest that omega-3 PUFA supplementation has anti-inflammatory effects in the CPIP model of CRPS-Type I, significantly reducing paw edema and regulating concentrations of anti-inflammatory cytokines, including IL-4 and IL-10 (6).

Omega−3 fatty acids, also called Omega-3 oils, ω−3 fatty acids or *n*−3 fatty acids,[7] are polyunsaturated fatty acids (PUFAs) characterized by the presence of a double bond, three atoms away from the terminal methyl group in their chemical structure.[8] They are widely distributed in nature, being important constituents of animal lipid metabolism, and they play an important role in the human diet and in human physiology.[9][10] The three types of omega−3 fatty acids involved in human physiology are α-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). ALA can be found in plants, while DHA and EPA are found in algae and fish. Marine algae and phytoplankton are primary sources of omega−3 fatty acids.[11] DHA and EPA accumulate in fish that eat these algae.[12] Common sources of plant oils containing ALA include walnuts, edible seeds, and flaxseeds, while sources of EPA and DHA include fish and fish oils.[7]

Mammals are unable to synthesize the essential omega−3 fatty acid ALA and can only obtain it through diet. However, they can use ALA, when available, to form EPA and DHA, by creating additional double bonds along its carbon chain (desaturation) and extending it (elongation). Namely, ALA (18 carbons and 3 double bonds) is used to make EPA (20 carbons and 5 double bonds), which is then used to make DHA (22 carbons and 6 double bonds).[7][8] The ability to make the longer-chain omega−3 fatty acids from ALA may be impaired in aging.[13] In foods exposed to air, unsaturated fatty acids are vulnerable to oxidation and rancidity.[8][14]

Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS) is a chronic pain condition often involving hyperalgesia and allodynia of the extremities. CRPS is divided into CRPS-I and CRPS-II. Type I occurs when there is no confirmed nerve injury. Type II is when there is known associated nerve injury. Female gender is a risk factor for developing CRPS. Other risk factors include fibromyalgia and rheumatoid arthritis. Unfortunately, the pathogenesis of CRPS is not yet clarified. Some studies have demonstrated different potential pathways. Neuropathic inflammation, specifically activation of peripheral nociceptors of C-fibers, has been shown to play a critical role in developing CRPS. The autonomic nervous system (ANS) is involved. Depending on whether it is acute or chronic CRPS, norepinephrine levels are either decreased or increased, respectively. Some studies have suggested the importance of genetics in developing CRPS. More consideration is being given to the role of psychological factors. Some association between a history of depression and/or post-traumatic stress disorder (PTSD) and the diagnosis of CRPS has been demonstrated. Treatment modalities available range from physical therapy, pharmacotherapy, and interventional techniques. Physical and occupational therapies include mirror therapy and graded motor imagery. Medical management with non-steroidal anti-inflammatory drugs (NSAIDs) has not shown significant improvement. There have been supporting findings in the use of short-course steroids, bisphosphonates, gabapentin, and ketamine. Antioxidant treatment has also shown some promise. Other pharmacotherapies include low-dose naltrexone and Botulinum toxin A (BTX-A). Sympathetic blocks are routinely used, even if their short- and long-term effects are not clear. Finally, spinal cord stimulation (SCS) has been used for decades. In conclusion, CRPS is a multifactorial condition that still requires further studying to

better understand its pathogenesis, epidemiology, genetic involvement, psychological implications, and treatment options. Future studies are warranted to better understand this syndrome. This will provide an opportunity for better prevention, diagnosis, and treatment of CRPS (15).

Diagnosis of Complex regional pain syndrome (CRPS) is made primarily on a clinical basis, and no specific test is known to confirm or exclude CRPS diagnosis. That is, there aren't specific diagnostic tools and instrumental tests are made only for identifying an etiology at the basis of the CRPS. Numerous therapeutic methods have been introduced, but none have shown definitive results. When symptoms persist, patients experience permanent impairment and disability. Therefore, early recognition of CRPS, along with proper treatment, is important for minimizing permanent loss of function. As there is no gold standard test for CRPS, several clinical diagnostic criteria have been introduced and applied in various studies. However, to date, no formal or standardized diagnostic criteria for CRPS have been widely accepted. However, the Budapest diagnostic criteria have recently increased in popularity and are frequently used in scientific studies. The goal for management of CRPS is the return of normal limb function. No specific technique has been shown to prevent CRPS following surgery, but avoidance of prolonged immobilization may be important. Therefore, initiating early post-surgical rehabilitation, where possible, is important. A multidisciplinary approach would seem to be optimal, above all things objectives of physical and occupational therapy are fulfilled with combination pharmacotherapy due to provide pain relief to facilitate physical rehabilitation. Future research using large randomized controlled trials should focus on collecting strong evidence for the etiology of CRPS, testing pharmacological effects, and determining appropriate combination treatment strategies (16).

Complex regional pain syndrome type 1: Analysis of 108 patients

Complex regional pain syndrome (CRPS) type 1 is characterized by the presence of pain, edema, functional impotence, impaired mobility, trophic changes, vasomotor instability and bone demineralization.

We carried out a retrospective and prospective, descriptive, observational study of 108 patients over 18 years of age with suspected CRPS who met Doury's criteria. We recorded demographic data, clinical characteristics, comorbidities, previous predisposing conditions and triggering factors, such as injury or fracture. We evaluated laboratory data, serial plain X-rays, 3-phase bone scintigraphy with technetium 99 and bone density scan, as well as drug treatment, rehabilitation and disease course.

In all, 89% of the 108 patients were women with an average age of 54.8±12.4 years. The time between the onset of the symptoms and the first visit to a physician was 3.1 months. The most common triggering factor was injury (91.7%). The most frequent psychological factor was anxiety (42.6%). All the patients reported pain and 99.07% had impaired mobility. The most frequently affected part of the body was the hand (75%; 81/108 patients) followed by the shoulder, in the shoulder-hand syndrome. All the patients had serial X-rays and changes were observed in 93.5%. Three-phase bone scintigraphy revealed evidence of disease in all 32 of the patients who underwent this study. Bone density scanning was performed in 54 patients (50%). All the patients were treated with nonsteroidal anti-inflammatory drugs, mainly diclofenac (60%). Calcium therapy was initiated in 106 patients (98.2%) and vitamin D3 therapy in 97.2%. All the patients received bisphosphonates, primarily alendronate and ibandronate (67.6% and 27.8%, respectively). Thirty-six patients (33.3%) received corticosteroids. All of the evaluated patients underwent rehabilitation involving occupational therapy. The average time to recovery was 6.31 months (range, 4-24). The outcome was favorable in 88.9% of the patients.

This paper describes the clinical characteristics, therapeutic features and outcome of CRPS type 1 in 108 patients. This syndrome is known to be heterogeneous, and does not always present with the well-known symptoms. We recommend establishing a differential diagnosis including other infectious and inflammatory conditions, and point out the importance of early referral, which enables early treatment (17).

Do omega-6 and trans fatty acids play a role in complex regional pain syndrome?

The study aims to compare the omega-6 (n-6) and omega-3 (n-3) highly unsaturated fatty acids (HUFA), and trans fatty acid (trans FA) status of Complex Regional Pain Syndrome (CRPS) patients to pain-free controls.

Case control study. Setting. The setting was at a multidisciplinary rehabilitation center.

Twenty patients that met the Budapest research diagnostic criteria for CRPS and 15 pain-free control subjects were included in this study. Outcome Measures. Fasting plasma fatty acids were collected from all participants. In CRPS patients, pain was assessed using the McGill Pain Questionnaire-Short Form. In addition, results from the perceived disability (Pain Disability Index), pain-related anxiety (Pain Anxiety Symptom Scale Short Form), depression (Center for Epidemiologic Studies Depression Scale Short Form), and quality of life (Short Form-36 [SF-36]) were evaluated.

Compared with controls, CRPS patients demonstrated elevated concentrations of n-6 HUFA and trans FA. No differences in n-3 HUFA concentrations were observed. Plasma concentrations of the n-6 HUFA

docosatetraenoic acid were inversely correlated with the "vitality" section of the SF-36. Trans FA concentrations positively correlated with pain-related disability and anxiety.

These pilot data suggest that elevated n-6 HUFA and trans FA may play a role in CRPS pathogenesis. These findings should be replicated, and more research is needed to explore the clinical significance of low n-6 and trans FA diets with or without concurrent n-3 HUFA supplementation, for the management of CRPS (18).

New approach to peripheral nerve injury: nutritional therapy

There is no review in the literature on the effect of nutrition-related factors on peripheral nerve injuries. Therefore, it is aimed to evaluate the effect of nutritional factors on nerve injuries in this compilation.

Although there are several fundamental mechanisms by which nutrients and nutritional factors influence individuals, their exact impacts on neurogenesis have not been clearly identified. Recently, some studies showed that some nutrients have an important role in nerve injuries due to their neuroprotective properties. In addition to surgical treatment, in peripheral nerve injuries, these nutrients also may play a role in preserving nerve function and health, as well as in the recovery of an injured nerve tissue. Omega 3 and omega 6 fatty acids, group B vitamins, antioxidants, several minerals, phenolic compounds, and alpha lipoic acid are thought to have impacts on the nervous system. In addition to all of these, gut microbiota has effects on the nervous system, and some nutrient-related factors can also affect neurogenesis via gut microbiota.

Peripheral nerve injury is a condition in which the nerves in the peripheral nervous system become damaged. After the trauma, the peripheral nerve is hardly repaired due to the following reasons; the disability of the regeneration of motor neurons, the lack of a survival environment for Schwann cells, and the poor ability of the nerves to regenerate. Nutrition-related factors, the effects of which were described in recent years, should be more taken into account more (19).

The Role of Dietary Nutrients in Peripheral Nerve Regeneration.

Peripheral nerves are highly susceptible to injuries induced from everyday activities such as falling or work and sport accidents as well as more severe incidents such as car and motorcycle accidents. Many efforts have been made to improve nerve regeneration, but a satisfactory outcome is still unachieved, highlighting the need for easy to apply supportive strategies for stimulating nerve growth and functional recovery. Recent focus has been made on the effect of the consumed diet and its relation to healthy and well-functioning body systems. Normally, a balanced, healthy daily diet should provide our body with all the needed nutritional elements for maintaining correct function. The health of the central and peripheral nervous system is largely dependent on balanced nutrients supply. While already addressed in many reviews with different focus, we comprehensively review here the possible role of different nutrients in maintaining a healthy peripheral nervous system and their possible role in supporting the process of peripheral nerve regeneration. In fact, many dietary supplements have already demonstrated an important role in peripheral nerve development and regeneration; thus, a tailored dietary plan supplied to a patient following nerve injury could play a non-negotiable role in accelerating and promoting the process of nerve regeneration (20).

Complex regional pain syndrome

Is a chronic pain condition

Complex regional pain syndrome is a chronic pain condition characterized by autonomic and inflammatory features. It occurs acutely in about 7% of patients who have limb fractures, limb surgery, or other injuries. Many cases resolve within the first year, with a smaller subset progressing to the chronic form. This transition is often paralleled by a change from "warm complex regional pain syndrome," with inflammatory characteristics dominant, to "cold complex regional pain syndrome" in which autonomic features dominate. Multiple peripheral and central mechanisms seem to be involved, the relative contributions of which may differ between individuals and over time. Possible contributors include peripheral and central sensitization, autonomic changes and sympatho-afferent coupling, inflammatory and immune alterations, brain changes, and genetic and psychological factors. The syndrome is diagnosed purely on the basis of clinical signs and symptoms. Effective management of the chronic form of the syndrome is often challenging. Few high quality randomized controlled trials are available to support the efficacy of the most commonly used interventions. Reviews of available randomized trials suggest that physical and occupational therapy (including graded motor imagery and mirror therapy), bisphosphonates, calcitonin, subanesthetic intravenous ketamine, free radical scavengers, oral corticosteroids, and spinal cord stimulation may be effective treatments. Multidisciplinary clinical care, which centers around functionally focused therapies is recommended. Other interventions are used to facilitate engagement in functional therapies and to improve quality of life (21).

COMPLEX REGIONAL PAIN SYNDROME INDUCED BY EXTRAVASATION OF PROPOFOL

Complex Regional Pain Syndrome (CRPS) is a chronic disabling painful pathological condition that persists long after the initial injury to the affected limb, triggering characterized by constant pain, allodynia, hyperalgesia, edema, trophic changes, vasomotor dysregulation, and motor deficiency. Usually, the cause is a physical, chemical, or mechanical injury; other times no apparent cause can be identified that could justify the disease. A specific continuing pain is the symptomatology, which is not specific and appears disproportionate to any inciting the initial traumatic event.

Case presentation: A 36-year-old woman with a history of dysphagia, heartburn, abdominal pain and persistent cough underwent to EGDS with the suspect of a hiatal hernia. During the induction phase of anesthesia by intravenous administration of Propofol, an intravenous anesthetic agent, the extravasation of this drug occurred in the upper right limb tissue. Ten months later further EMG/NCS showed an antalgic reduction of the voluntary recruitment pattern lacking peripheral neuropathy signs. Continuing pain disproportionate to the incidental event, allodynia, temperature asymmetry and alteration of the skin color at the right arm lacking evidence of nerve lesions, confirmed the diagnosis of complex regional pain syndrome type 2. Conclusion: In case of CPRS, the forensic pathologist has to determine the cause in order to prevent a medical malpratice claim, and also it is useful to well known the clinical features to evaluate a state of permanent invalidity. Difficult diagnosis plays a crucial role in the onset of the high disability that the disease causes if it is not recognized on time. The causes of CPRS may be the consequences of a medical error (in the specific case the extravasation of an irritant substance, Propofol) and from subsequent diagnostic delay a very debilitating morbid picture can occurs. For medico-legal purposes, it becomes essential to know the syndrome, and especially to diagnose it in a short time (22).

Changes in immune and glial markers in the CSF of patients with Complex Regional Pain Syndrome

Complex Regional Pain Syndrome is a severe chronic pain condition characterized by sensory, autonomic, motor and dystrophic signs and symptoms. The pain in CRPS is continuous, it worsens over time, and it is usually disproportionate to the severity and duration of the inciting event. This study compares cerebrospinal fluid (CSF) levels of pro- and anti-inflammatory cytokines, chemokines and several biochemical factors (glial fibrillary acidic protein (GFAP), the nitric oxide metabolites (nitrate plus nitrite), the excitatory amino acid neurotransmitter glutamate, calcium, total protein and glucose) in patients afflicted with CRPS to levels found in patients suffering with other non-painful or painful conditions. The aim of the study is to determine the degree of involvement of glial cells and immune system mediators in the pathophysiology of CRPS. There was no elevation or reduction of a CSF marker that was specific for CRPS patients. However, there were several patterns of markers that could be helpful in both elucidating the mechanisms involved in the disease process and supporting the diagnosis of CRPS. The most common pattern was found in 50% (11 out of 22) of the CRPS patients and consisted of; elevated IL-6, low levels of IL-4 or IL-10, increased GFAP or MCP1 and increases in at least two of the following markers NO metabolites, calcium or glutamate. The results from this and other similar studies may aid in elucidating the mechanisms involved in the pathophysiology of CRPS. A better understanding of these mechanisms may lead to novel treatments for this very severe, life-altering illness (23).

Differential expression patterns of cytokines in complex regional pain syndrome

Complex regional pain syndromes (CRPS) are characterized by persistent and severe pain after trauma or surgery. Neuro-immune alterations are assumed to play a pathophysiological role. Here we set out to investigate whether patients with CRPS have altered systemic pro- and anti-inflammatory cytokine profiles compared to controls on mRNA and protein level. We studied blood cytokine mRNA and protein levels of the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF), interleukin-2 (IL-2) and IL-8 and the anti-inflammatory cytokines IL-4, IL-10, and transforming growth factor-beta1 (TGF beta 1) in 40 prospectively recruited patients with CRPS I, two patients with CRPS II, and 34 controls. Quantitative real-time PCR and enzyme linked immunosorbent assay were used. Additionally, the patients underwent quantitative sensory testing and were assessed with the McGill pain questionnaire and the Hospital anxiety and depression scale. Patients with CRPS had higher blood TNF and IL-2 mRNA levels ($p=0.005$; $p=0.04$) and lower IL-8 mRNA levels ($p<0.001$) than controls. The mRNA for the anti-inflammatory cytokines IL-4 and IL-10 was reduced in the patient group ($p=0.004$; $p=0.006$), whereas TGF beta 1 mRNA levels did not differ between groups. These results were paralleled by serum protein levels, except for TGF beta 1, which was reduced in patients with CRPS, and for IL-8, which gave similar protein values in both groups. Sensory testing showed a predominant loss of small fiber-related modalities in the patient group. The shift towards a pro-inflammatory cytokine profile in patients with CRPS suggests a potential pathogenic role in the generation of pain (24).

The brain in chronic CRPS pain: abnormal gray-white matter interactions in emotional and autonomic regions

Chronic complex regional pain syndrome (CRPS) is a debilitating pain condition accompanied by autonomic abnormalities. We investigated gray matter morphometry and white matter anisotropy in CRPS patients and matched controls. Patients exhibited a disrupted relationship between white matter anisotropy and whole-brain gray matter volume; gray matter atrophy in a single cluster encompassing right insula, right ventromedial prefrontal cortex (VMPFC), and right nucleus accumbens; and a decrease in fractional anisotropy in the left cingulum-callosal bundle. Reorganization of white matter connectivity in these regions was characterized by branching pattern alterations, as well as increased (VMPFC to insula) and decreased (VMPFC to basal ganglion) connectivity. While regional atrophy differentially related to pain intensity and duration, the strength of connectivity between specific atrophied regions related to anxiety. These abnormalities encompass emotional, autonomic, and pain perception regions, implying that they likely play a critical role in the global clinical picture of CRPS (25).

A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain

Between 40% and 60% of Americans use complementary and alternative medicine to manage medical conditions, prevent disease, and promote health and well-being. Omega-3 polyunsaturated fatty acids (omega-3 PUFAs) have been used to treat joint pain associated with several inflammatory conditions. We conducted a meta-analysis of 17 randomized, controlled trials assessing the pain relieving effects of omega-3 PUFAs in patients with rheumatoid arthritis or joint pain secondary to inflammatory bowel disease and dysmenorrhea. Meta-analysis was conducted with Cochrane Review Manager 4.2.8. for six separate outcomes using standardized mean differences (SMDs) as a measure of effect size: (1) patient assessed pain, (2) physician assessed pain, (3) duration of morning stiffness, (4) number of painful and/or tender joints, (5) Ritchie articular index, and (6) nonselective nonsteroidal anti-inflammatory drug consumption. Supplementation with omega-3 PUFAs for 3-4 months reduces patient reported joint pain intensity (SMD: -0.26; 95% CI: -0.49 to -0.03, p=0.03), minutes of morning stiffness (SMD: -0.43; 95% CI: -0.72 to -0.15, p=0.003), number of painful and/or tender joints (SMD: -0.29; 95% CI: -0.48 to -0.10, p=0.003), and NSAID consumption (SMD: -0.40; 95% CI: -0.72 to -0.08, p=0.01). Significant effects were not detected for physician assessed pain (SMD: -0.14; 95% CI: -0.49 to 0.22, p=0.45) or Ritchie articular index (SMD: 0.15; 95% CI: -0.19 to 0.49, p=0.40) at 3-4 months. The results suggest that omega-3 PUFAs are an attractive adjunctive treatment for joint pain associated with rheumatoid arthritis, inflammatory bowel disease, and dysmenorrhea (26).

Changes in consumption of omega-3 and omega-6 fatty acids in the United States during the 20th century

The consumption of omega-3 (n-3) and omega-6 (n-6) essential fatty acids in Western diets is thought to have changed markedly during the 20th century.

We sought to quantify changes in the apparent consumption of essential fatty acids in the United States from 1909 to 1999.

We calculated the estimated per capita consumption of food commodities and availability of essential fatty acids from 373 food commodities by using economic disappearance data for each year from 1909 to 1999. Nutrient compositions for 1909 were modeled by using current foods (1909-C) and foods produced by traditional early 20th century practices (1909-T).

The estimated per capita consumption of soybean oil increased >1000-fold from 1909 to 1999. The availability of linoleic acid (LA) increased from 2.79% to 7.21% of energy ($P < 0.000001$), whereas the availability of α-linolenic acid (ALA) increased from 0.39% to 0.72% of energy by using 1909-C modeling. By using 1909-T modeling, LA was 2.23% of energy, and ALA was 0.35% of energy. The ratio of LA to ALA increased from 6.4 in 1909 to 10.0 in 1999. The 1909-T but not the 1909-C data showed substantial declines in dietary availability (percentage of energy) of n-6 arachidonic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Predicted net effects of these dietary changes included declines in tissue n--3 highly unsaturated fatty acid status (36.81%, 1909-T; 31.28%, 1909-C; 22.95%, 1999) and declines in the estimated omega-3 index (8.28, 1909-T; 6.51, 1909-C; 3.84, 1999).

The apparent increased consumption of LA, which was primarily from soybean oil, has likely decreased tissue concentrations of EPA and DHA during the 20th century (27).

CONCLUSION

Complex regional pain syndrome (CRPS) **treatment by intralipid (soybean oil, linoleic acid)** is first suggested in the medical literature.

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