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Effect of Omega 3 fatty acid supplementation after traumatic spinal cord injury

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ABSTRACT

Background

Spinal cord injury is a life changing threatening neurological condition that completely changes subject's life. In medical management recent advances has significantly improved diagnosis, stabilization, survival rate and well-being of SCI patients, but there has been very small progression in its treatment, and some such as Stem cell transplantation etc. is very costly that is not possible for everyone to afford.So now a days major focus is on nutraceutical supplementation as they are easy to administer and easy to afford. Omega 3 fatty acid are important polyunsaturated fatty acids with some roles in normal cellular metabolism, they have Anti-inflammatory and antioxidant properties. Studies have proved its beneficial role in ameliorating inflammation in different diseases and thus plays role in improving neurological outcomes after neuronal injury.Fish are the best source of omega 3 fatty acid,EPA & DHA are two main types of omega 3 fatty acid and both the sources are found in fish, salmon, tuna, mackerel, and sardines fatty fish are good source of EPA & DHA,and high in protein content and low in saturated fat.In SCI,inflammatory events results in activating various inflammatory markers so PUFA 3 helps in suppressing their activity, for healthy adults, the daily recommended level of omega-3 fatty acid is 300 mg.Leukotriene-5, thromboxane-3, and prostaglandin-3 are derived from essential fatty acids, and are known to be therapeutically important in inflammatory conditions as well as for mental health. A marine crustacean Antarctic krill, Euphausia superba, has not been a traditional food in the human diet, its a rich source of high-quality protein, with the advantage over other animal proteins of being low in fat and a rich source of EPA and DHA. Antioxidant levels in krill are higher than in fish, suggesting benefits against oxidative damage. Finally, the waste generated by the processing of krill into edible products can be developed into value added products.

Material and method

Online literature search was undertaken in PUBMED library and PLOS ONE library ,Scopus with the key word Spinal cord injury & its prevalence, Epidemology of Spinal Cord Injury,Role of omega 3 fatty acid and its role in spinal cord inury,Potential health benefits of Omega 3 fatty acid etc.A systematic Literature Search was made upto 2023.Using the above mentioned database we selected 100 articles.

Result and Conclusion

Omega 3 fatty acid plays a role in regulating several pathways associated with the damage resulting from secondary SCI . Given the considerable health advantages, the consumption of EPA and DHA is encouraged, with fatty fishes such as salmon, mullet, and mackerel identified as prime sources of these beneficial acids. This emphasis on aquaculture industries is leading to increased attention. Consequently, this review aims to comprehensively explore the potential benefits of PUFA.

Keywords: Osteoporosis, Omega 3 fatty Acid, SCI, EPA, DHA, National Spinal Cord Injury Statistical Centre (NSCISC)

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INTRODUCTION

A spinal cord injury (SCI) is characterized by the deterioration in motor, sensory, and autonomic functions due to either total or partial damage to the spinal cord due to trauma. It changes the subjects' lives with lifelong treatment, and the patient is entirely dependent on others. It is a debilitating neurological condition with socio-economic implications for those affected and the health system. [1] According to the National Spinal Cord Injury Statistical Centre (NSCISC), 12,500 new cases of SCI are recorded each year in North America [2]. Patients with SCI over 60 years have significantly poorer results than younger patients [2]. Almost 90% of SCI cases are traumatic and occur due to road traffic accidents (RTA), falling from a height, falling of heavy objects such as wall or bullet fire injury [3]. Men are most often affected by SCI. Therefore, the ratio of men and women is affected by 2: 1, and adults are more affected than children. According to the demographics, men are most often involved in early and late adulthood (3rd and 8th decades of life) [3], while women are affected during puberty (15-19 years) [4].SCI can cause quadriplegia or paraplegia depending upon the level of injury. Paraplegia is caused by a lesion in the dorsal spine, while a lesion causes quadriplegia at the cervical level [5]. As per NSCISC [2], the cervical level of the spinal cord (50%) is typically affected in SCI, with the most commonly affected level being C_5 vertebrae while resting the thoracic level (35%) and the lumbar region (11%). Middleton et al. reported that the survival rates for SCI over 40 years were 47% and 62% for patients with quadriplegia and paraplegia, respectively [6]. The degree of injury and the functions retained after SCI determined SCI patients' life expectancy. Patients with an ASIA Impairment Scale (AIS) grade D have almost 90% normal life and a higher life expectancy than lower grades [7]. As spinal cord injury has catastrophic sequelae on individual suffering, it is imperative to resolve SCI's cellular and molecular mechanisms and develop new effective treatment modalities to curtain the suffering.There are four types of Traumatic spinal cord injury i.e Complete spinal cord injury(ASIA A) causes permanent damage to the area of the spinal cord that is affected and no motor or sensory function is preserved at this point.Incomplete Spinal cord injury(ASIA B):In this type of injury Sensory but not motor function is preserved below the neurological level.Incomplete Spinal cord injury(ASIA C): In this type of injury motor function is preserved below the neurological level, and half of key muscles below the neurological level a muscle grade less than 3(Grade 0-2),and if , and half of key muscles below the neurological level a muscle grade more than or equal to 3(Grade 0-3) then it is chategerised as ASIA D.

ASIA E:In this category both sensory and motor functions are normal.In human beings, polyunsaturated fatty acids (PUFA) or ω-3 acids are essential components of cell membranes. They facilitate normal functioning of the body, but most mammals are unable to synthesize it so they need a dietary source to meet their need. Three types of ω-3 acids include alpha linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) [8]. linoleic acid (C18:2n–6, LA) is the parent omega-6 fatty acid and α-linolenic acid (C18:3n–3, ALA) is parent omega-3 fatty acid, human can synthesize arachidonic acid (C20:4n–6; AA), one of the Omega-6 fatty acids from LA, and ALA can help in synthesizing omega-3 fatty acids, as eicosapentaenoic acid (C20:5n–3; EPA), docosapentaenoic acid (C22:5n–3, DPA) and docosahexaenoic acid (C22:6n–3, DHA), However the conversion of ALA into omega-3 fatty acids in EPA, DPA and DHA is quite very low therefore these fatty acids are considered as essential fatty acid too [9].According to nutrition experts suggested ratio of both fatty acid is 5:1(n–6:n–3 fatty acid) or less is desired [10].But nowadays western society food habits is characterized by high consumption of foods having a large amount of saturated fatty acids and very low proportion of PUFA like meat, seed oils, fast food (pizzas,hamburgers…) and snack food (cakes, biscuits…) [11]..Ratio of omega 6 to omega 3 fatty acid (n–6:n–3),value has been recorded upto 2: 1 in blood of people who consumes Japanese food or Mediterranean food as these food contains large amount of Fish,whereas this ratio is recorded 25:1,much higher than desires in people who mostly consumes fast food [9,13]. For that reason nutritionists advise to consume more fishy and green leafy vegetables in diet to prevent many diseases, especially cardiovascular diseases. Supplementation with omega-3 fatty acids helps to increase the concentration of antioxidant catalase (CAT) and superoxide dismutase (SOD) and suppresses the activity of the oxidative stress marker, i.e. Malondialdehyde (MDA) in the SCI rat model. n-3-acid supplementation also helps in reducing the expression of the enzyme glutamine synthetase, which is responsible for reducing the activity of glutamate-induced excitotoxicity in injured tissues. Elevated levels of glutathione (GSH) at the injury site

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are maintained by a diet high in -3 acids. Cell apoptosis is inhibited, which is a marker of improvement in motor function in rodents with SCI [14].Sabour H, et al. [15] state the effect of omega-3 fatty acids in their double-blind, randomized clinical study on 104 patients with spinal cord injury who gave an omega intervention (465 mg docosahexaenoic acid (DHA) and 63 mg eicosapentaenoic acid (EPA) two capsules each day for 14 months and showed that after 14 months intervention concentration of adiponectin was significantly reduced, but no effect on leptin concentration was observed, a linear relationship between weight and leptin concentration was found.In Europe and the USA, mainly functional foods were fortified with n3 fatty acids last year, the production of which is increasing, such as bread and baked goods, milk and derivatives, spreadable fats, eggs, juices, soft drinks, meat and poultry products, etc. The natural source of omega-3 fatty acids is fish oil, which is incorporated into conventional foods, with various strategies being followed to avoid important changes in the sensory quality of the products [16].

Pathophysiology of SCI: The primary mechanical injury that leads to SCI may be because of a variety of mechanisms such as compression, contusion, transection, and shearing forces [4], Historically the typical phenotype of SCI was a high energy mechanism in young patients, resulting in severe cord damage and a complete neurologic injury. In older subjects, an increasing proportion of SCIs is seen due to minor traumas on a background of chronic compression from degenerative cervical myelopathy, resulting in incomplete injuries [16].

Cord compression because of primary mechanical insults activates a complex cascade of molecular and cellular events, termed as secondary injury, that further cause tissue damage, in order to suppress these effects, early decompressive surgery is performed for the setting of ongoing compression after SCI [17].

Secondary injury resulting from delay in SCI management after the initial attack affects the prognosis [18]. The secondary injury leads to progression in tissue injury that occurs in several hours to several weeks. It is characterized by the sudden change in ion homeostasis, the release of reactive oxygen species, and excess excitatory neurotransmitters release. It affects endogenous cellular repair systems leading to inflammation, extensive neuronal and glial cell death, residual demyelination of nerve fibre, and severe neuronal apoptosis.The inflammatory response plays a vital role in secondary injuries. microglial nuclear (astrocytes), T cells and neutrophils from the lesion area, begins with the release of inflammatory factors such as matrix metalloproteinases, which break down extracellular matrix components, which leads to tissue damage, disruption of the blood-spinal cord barrier and oedema, tumor necrosis factor- (TNF-), IL-1, IL-12. In addition, oxidative stress through activation of microglia causes peroxidation and disruption of the normal phospholipid structure of the cell membrane, which leads to damage to the neuronal tissue. In the spinal cord, the excitatory neurotransmitter is directly influenced by N-methyl-D-aspartate (NMDA) receptors, studies in animal models have shown that by blocking this NMDA receptor, protection against secondary damage due to trauma and ischemia is achieved. With the help of NMDA antagonists, neurological functions can be improved and the incidence of oedema reduced.A spinal canal hematoma arises from the compression of the spinal cord due to mechanical injury in the initial stages of SCI. This compression causes bleeding, subsequently leading to an interruption in blood supply, resulting in hypoxia and localized ischemic infarction. These two factors contribute to damage in the gray substance, where metabolic functions are notably high,Thus, neurons in the damaged area are physically broken and the thickness of the myelin sheath is reduced, including a deterioration in neuronal transmission can be exacerbated by oedema and the accumulation of macrophages in the damaged tissue [18].The release of inflammatory cytokines and free radicals leads to activation of apoptosis after SCI, which leads to inflammation and excitotoxicity, apoptosis occurs in the areas around the injured spinal cord tissue between 3 hours and 8 weeks after SCI. Many studies have shown that demyelination is exacerbated by the apoptosis of the oligodendrocytes after several weeks of injury [18], a study by David et al. [18] showed that oligodendrocyte changes occur in response to SCI.Neurotransmitters, Catecholamines play an important role in the Nervous system,At the site of injury the level of norepinephrine (NE) gradually increases and this catecholamine can cause the abnormal contraction of vascular smooth muscle, leading to vascular lumen stenosis and blood flow obstruction.Whereas the contents of neurotransmitter such as prostaglandin (PE), 5-hydroxytryptamine(5-HT), and dopamine (DA),

increases and together play an important role in the severe contraction of blood vessels, promote platelet aggregation, and induce spinal cord ischemia [19].Lipid peroxidation occurs after SCI, lipid peroxides are mainly produced by the peroxidation of injured and ruptured phospholipid cell membranes or by cytotoxicity (neutrophils, macrophages, astrocytes, polymorphonuclear granulocytes, and glial cells),Peroxides further worsen SCI by disrupting the cell membrane and blood–brain barrier,due to microcirculatory disturbances, Metabolic waste cannot be effectively removed that emhances in the rise of concentration of free radicals,Cell membrane continuity, intracellular electrolyte imbalance, and Ca2+ flow,is also interrupted by Lipid peroxidation, leading to necrosis and apoptosis because of changes in the local environment and increased cell permeability, electrolyte imbalances occur after SCI, including plasma imbalances of K+, Na+, Mg2+, and Ca2+, especially imbalances in Ca2+ pathways involved in cell death, thus aggravating secondary SCI,As soon as the spinal cord tissue is injured, ischemia and hypoxia occur,followed by an imbalance of cell energy transmission, the abnormal opening of ion pumps (Na+-K+ and Ca2+ pump) on the cell membrane, and Ca2+ flow into the cytoplasm,and glutamic acid an excitatory amino acids also increases and corresponding receptor interactions induce an intracellular Ca2+ overload, destroying the cell membrane, cytoplasm, and organelles, finally leading to cell autolysis and death [19].Soon after the SCI,Apoptosis is activated due to the release of inflammatory cytokines and free radicals, that leads to to inflammation and excitotoxicity[20],Soon after the spinal cord injury,apoptosis begins around the injured area between 3 h and 8 weeks[20]. In case of SCI, This phenomenon negatively impacts the condition through the loss of neurons. Studies have shown that cell death known as apoptosis is the cause of microglia deterioration, promoting additional inflammation. [20].**mTOR pathway**: mTOR, a conserved serine/threonine protein kinase, is the core of signaling networks, a central controller of cell growth, and belongs to the phosphoinositol 3-kinase (PI3K)-related protein kinase family. It interacts with several proteins, including subunits Raptor and Rictor, to form two different complexes (containing mLST8 subunits) known as mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) protein complexes,The mTORC1 protein kinase complex plays a central role in regulating cell growth and metabolism by promoting translation, ribosomal biogenesis, and autophagy. mTORC1 phosphorylates downstream effectors, such as P70 ribosomal S6 protein kinase (p70S6K), and further regulates mRNA translation [21],In case of SCI,the action of mTOR depends on the time phase after SCI [42],In acute Phase of SCI, key functions associated with secondary injury, such as cell death and inflammatory responses are regulated by mTOR pathway. In the subacute/chronic stage, mTOR signaling regulates the regeneration of damaged nerve tissue and glial scar formation,by inhibiting this pathway it was observed that there is reduction in apoptosis-related proteins via the mitochondrial pathway after SCI and prevent neuronal apoptosis [21],Expression of Beclin-1 protein is increased by inhibiting the mTOR pathway ultimately leading to decreased apoptosis levels [21], Activation of microglia neutrophils and macrophages in traumatic SCI can lead to local inflammatory responses. Activation of the mTOR pathway has been reported to stimulate synergism with mTOR/MEK1/ERK1/2/IKKβ/IκB-α/NF-κB, and multiple pathways enhance cytokine-induced pro-inflammatory markers and NO synthase activity in microglia [21],Inhibiting the mTOR pathway can regulate neuroinflammation in SCI,can reduce nerve cell death and other inflammatory process after SCI. Study by Cordaro M [22] demonstrated that in comparison to novel synthetic mTOR inhibitor rapamycin and temsirolimus, **KU0063794** dual mTORC1 and mTORC2 inhibitor is best to Promote neuroprotective function at the lesion site after SCI by reducing neuronal loss and cell mortality after SCI.After SCI, axonal regeneration can be promoted by inhibiting mTOR signaling pathway.

Epidemiology

Indian epidemiological data: According to Chhabra HS [23] his retrospective study showed that (data between 2000 and 2016) during the study period the mortality rate was 10%, while the data from 16 years (758) subjects, quadriplegics and paraplegics were 39% (294) or 61% (464). 679 subjects were approximately 81% male; the death rate from quadriplegia and paraplegia was 22% and 3%, respectively. Respiratory disease is the leading killer of hospital deaths Due to the death rate in hospitals, there is a need to focus on respiratory management and the prevention of infections, especially in quadriplegics.Jha RK, et al [24], demonstrated in his prospective study that major cause of spinal cord injury is RTA (road traffic accident) along with hills, roof, trees, electricity pole, and stairs (70%) followed

by fall from height, including trees, hills, stairs or roof of home (28%),most common age group is s 20-39 years followed by 50-59 years, cause of injury in age group 50-59 years is because of fall. Male is more prone to SCI, they collected data from march 2019 to march 2020 total 198 cases (68 cases had thoracic injury. 86 patients had lumbar spine injury and 22 patients had cervical spine injury and rest 22 patients had spine injury at more than one segment),138 cases fall under the age group 25 to 50 years,whereas remaining 41 subjects were below 25 years of age and 19 subjects were found in 50 plus age group.out of 198 cases,136 cases were of RTA,52 cases were of fall from height,8 cases were of assault, 2 cases came after trivial injury who were later found to have atlanto axial dislocation.Sengupta D et al. [25] showed in his descriptive retrospective study that in patients with cervical spinal cord injury in low-middle-income countries (LMIC), ventilation exposure, hospitalization and mortality are high and the main cause of mortality among them is due to poor AIS values, extended VD, intensive care and hospital stays, comprehensive CSCI rehabilitation programs are required to overcome this situation.Jain M. et al. [26], in its retrospective observational study in the population of East India, collected data on August 15, 2018 and August 14, 2019 by including 103 patients with the injury in their study followed by RTA (37.9%), the ratio of men to Women (M: F) 5.87: 1, the most common age group in their study is 31-40 years, followed by 21-30 years and 41-50 year olds.Mittal S., et al is the most common type of injury in men and FFH is the most common type of injury in women The thoracolumbar junction (D10-L2) (37.5%) followed by the cervical spine (25.3%) is the most common injury site, and variations between the age group was 16-30 years were also observed in their study. Men were mainly affected in May / June (monsoons), while women mainly suffered trauma in March / April (summer). Mathur and colleagues (2015) demonstrated in his study that occupational hazards like FFH (53%) & RTA (23%), carrying heavy object overhead (3.0%), and fall following electric shock (4.0%),and married couples are at high risk for spinal cord injury in comparison to singles, in their study married subjects were 58.3% which is similar to the studies from the Western countries (57.7%)(Migliorini CE, et al 2009).Another study by Rai S et al [27], also reported that percentage of married couples were more in comparison to singles (70%).Nirmala BP et al. [28] describe the sociodemographics of the subjects and showed that of 60 subjects, 36 were men (60%), while 23 subjects (38.3%) completed secondary school and 19 (31.7%) completed primary education level, 7 (11.7%) subjects have completed a university education, 6 (10.0%) were illiterate. Students, day laborers, and housewives were 17 (28.3%), 16 (26.7%) and 13 (21.7%), respectively. 35 patients (58.3%) were married. 27 (45.0%) came from low-income families and 32 (53.3%) came from middle-income families. Both patients with traumatic SCS and non-traumatic SCS belong to the rural community compared to the urban community.Krishnamurthy G, et al. [29] in his hospital-based cross-sectional study showed that younger age groups (20 to 49 years of age) were most often affected compared to older age groups of 50 years and over, while the most common injury site was at the level of the thorax (64.3%) followed by a lower cervical level in 21.4% of the cases. Patients with incomplete SCI (39.2%) were stronger compared to a complete spinal cord. People with injuries (60.8%). A study by Yusuf et al. [30] on 133 patients with traumatic paraplegia came to the conclusion that the majority of the patients were younger, in 72.2% of the cases road traffic injuries were the most common type of injury, the most common injury site is the cervical spine (62%) and complete Spine injury (52.6%) is the most common type of injury in their study.While in another study by Aswani Kumar et al. [31] in 152 SCI cases, adolescents were most affected, in which 71.7% of the cases were construction workers, this means in their study that a fall from a great height is a common form of injury (61.2%). Cases of cervical spine injury were 44.1%.GZ et al. [32] showed in his review that in Asia the incidence rates of traumatic spinal cord injuries ranged from 12.06 to 61.6 per million and the mean age ranged from 26.8 to 56.6 years when male subjects were exposed to high risk are female and common types of injuries are motor vehicle collisions (MVCs) and falls, however most countries have reported war injuries as the leading cause. The neurological level and extent of injury were mixed and subjects were classified based on AIS / Frankel grade A.Chacko V. et al. [33] showed that of 218 subjects with spinal cord injuries who were admitted to a general hospital in rural India, 125 subjects were characterized by a neurological deficit. Infections and pressure ulcers were reported, patients with injuries to the cervical spine were mostly eliminated, so their study emphasizes that general hospitals have no facilities.Sridharan N, et al. [34] examined the epidemiology of spinal cord injuries in indoor patients (245) of the Rajiv Gandhi Government General Hospital, Chennai, India and showed in their

study that men are most affected compared to women (216 men). Subjects), the ratio between the male and female population is 8.8: 1.2, and the most common age group is ages 20 to 40 and the most common type of injury is a fall from a height, such as the injury in men is in Area of the cervical spine (C5 and C6) was high, followed by injuries in the segments at the dorsal level and on the lumbar spine, whereas in women the most common injury site was on the lumbar spine.According to Pandey V et al [35], RTA is the second largest mode of injury in SCI it is because of increased number of vehicles in metropolitan cities of a developing country like India so to minimize this traffic related accidents strict traffic rules must be enforced on public.In another retrospective study by Lalwani S et al. [36] a total of 341 such cases were identified between January 2008 and December 2011, of which 288 people were male and 53 people were female, most people were between 25 and 64 years old, followed in young adults between 16 and 24 years of age (19, 35%) the ratio between men and women is 5.4: 1, 55% of the cases had isolated spinal injuries, Cases had isolated spine injuries, cervical spine injury was observed in 259 patients (75.95%), thoracic spine injury was observed in 56 patients (16.42%) and thoracic spine injury was observed in 26 patients (7.62%) a thoracic and lumbar spine was observed. A higher drop in energy (44.28%) is the most common type of injury, followed by an RTA (41.93%); the patient's death mostly occurred in phase IV (secondary to tertiary complications of the trauma, ie> 1 week), while in phase I forty patients died (brought dead or survived 3 to 24 h) and 70 in phase III (> 24 h to 7 days).

Worldwide epidemiological data

One of the most recent retrospective studies by Chen J, et al. [37] in the Chinese province of Guangdong via TSCI showed that the male to female ratio was 3.4: 1, meaning that of 482 cases, 384 subjects were male and 112 were female. The most affected age group was 45-60 years (41.7%), followed by 31-45 years (23.8%), the most common type of injury was a fall from a height (49.3%), followed by motor vehicle collisions (MVCs)) (34.8%), and the most common injury site was the cervical spinal cord, C4-C6, which accounted for 39.8%.Another descriptive cross-sectional study from Korea by Kim HS et al. [38] has shown that of 221 patients with spinal cord injury (161 traumatic and 60 non-traumatic) the most frequently affected age group was between 40 and 49 years, while in the case of non-traumatic SCI the age group affected by traumatic SCI was between 70 and 79 years. Male subjects were mainly affected by TSCI, compared to non-TSCI, while the most common cause of TSCI was a drop (37.3%), followed by a car accident (35.4%). %) and stumbling (19.3%) and, in non-traumatic SCI, neoplasia (35.0%). Tripping is the main cause, especially in the elderly.Johansson E, et al [39] in his prospective cohort study on SCI subjects from Finland in a 4 year period they enrolled 346 subjects and observed that leading cause of injury were low-level falls (36.2%), high-level falls (25.5%), and transport-related accidents (19.2%), fall from height is common mode of injury in subjects above 60 years of age, whereas in subjects below 60 years of age 47.4% cases were alcohol-related. Cervical injury is the most common type of injury in subjects above 60 years of age (77.1%), while less common in subjects below 60 years of age (59.6%), In Summer and Autumn season the incidence of TSCI is high.Gautam S et al [40],in his descriptive cross-sectional study on 465 Patients demonstrated that in Nepal out of 465 Patients, 316 patients were of TSCI,and most common mode of Injury was fall from height(243 Patients),and the mean age of patients was 43.13±16.55 years.Similarly in Bangladesh Raihan Habib et al [41],in his Prospective study observed that male subjects are more effected in comparison to female,and the most common mode of injury is RTA(47.7%), followed by falls (25.7%) and violence (15.6%).In their study most common level of injury is cervical level (50.9%), followed by the thoracic spine (37.2%) and lumbar spine (11.9%),and Most of the patients were of Complete injury(ASIA A) and the mortality rate was 9.6%.

Singh R,et al[42] in his epidemiological study in Haryana state demonstrated that out of 483 Subjects,there were 361 males and 122 female and most prevalent age group was 20-29 followed by 30-39. Most common mode of injury was Fall from height (roof, trees, electricity pole (44.5%) followed by motor vehicle accidents (34.7%).Complete Paraplagia subjects were more followed by tetraplegia, Dorsolumbar spine injury was the commonest with first lumbar being the most common fractured vertebra followed by twelfth dorsal vertebra, cervical spine injury was next with most common site being fifth and sixth cervical vertebrae.Among European countries, where the incidence of TSCI is between 15 and 30 per million population, the incidence of TSCI in Estonia is among the highest, Youngest Men are significantly higher in comparison to women and the leading cause of TSCI is fall and alcohol consumption

is the main reason in Estonia before trauma.Most common site of injury in Estonia is cervical region 59.4% followed by thoracic level in 18.3% and at lumbar or sacral level in 22.3%,Patients above 60 years of age had cervical SCI in 80% of cases. 53%of cases were of complete Paraplagia(ASIA A& B),followed by 47% of cases of Incomplete Paraplagia (ASIA C& D).

Miscalleneous role of PUFA 3

Shehab R, et al. [43] showed that omega-3 fatty acid helps improve vitamin D and calcium levels in women of childbearing potential 3 fatty acid (1000 mg) twice a day for 12 weeks, and they observed a beneficial effect of omega on the vitamin D level, calcium in addition to cardioprotective effects was also seen as reducing levels of bad lipids like cholesterol, LDL-c, risk factor and had rewarding effects on blood clotting. So this study proves Omega's golden role in strengthening bone health.Matsumura Ket al [44] proved the beneficial effect of omega-3 fatty acids on maternal absorption; their study showed that high levels of omega-3 fatty acid absorption by the mother can lead to abuse of children such as beating, violent shaking and will reduce leaving the baby alone at home.Dangardt F, et al. [45] state in their double-blind cross-over design study that obese adolescents compared to normal weight adolescents have lower serum concentrations of omega-3 (n3) polyunsaturated fatty acids (PUFA), which contribute to inflammatory activity and endothelial dysfunction, in their study included 25 adolescents (14 women, 11 men, age 15.7 1.0 years, BMI 33.8 3.9). They were randomized to receive either placebo or 1.2 g / day for 3 months. as well as in the n3 group no difference in terms of total cholesterol, triacylglycerol, HDL cholesterol, anthropometry, blood pressure, pulse wave velocity or vascular structure was observed.Majority of American population have low consumption of Omega 3 fatty acid [46].In painful disorders like migraine headache [47], it is mostly because of low levels of omega 3 fatty acid. After burn injury levels of omega 3 fatty acid almost declines that give rest to infection and mortality. After secondary SCI ion imbalance is an hallmark, Toxicity in Excitatory cell is another factor contributing in SCI, excitatory toxicity is caused due to excessive activation of relevant amino acid receptors that produce excitatory toxicity leading to neuronal necrosis and apoptosis, that results in demyelination after injury [47].Study by Rajaei E [48] in their double-blind randomized controlled study on rheumatoid arthritis, an autoimmune, inflammatory disease that an omega-3 supplement (2 capsules daily containing 1.8 and 2.1 grams of EPA and DHA) for Twelve weeks helped her dependence on concomitant medication without weight change, and pain and morning stiffness were also reduced in the omega-3-treated group.Study by Miles EA et al [49],states that in RA Marine n-3 PUFAs (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) found in oily fish and fish oils decrease the contents of n-6 polyunsaturated fatty acid (PUFA) arachidonic acid (ARA) into cells which is precursor of inflammatory Eicosanoids. Meta-analysis by Goldberg RJ [50], demonstrated the beneficial effect of omega 3 fatty acid supplementation against inflammation, and states that it is an attractive adjunctive treatment for getting relief from joint pains associated with RA, inflammatory bowel disease, and dysmenorrhea.Study by Abdullahi A, et al [51] demonstrated that as postburn elevation in FFAs level were seen and returned to baseline over time. Thus their study concluded that after burn injury alteration in lipid profile are seen characterizing key lipids as potential diagnostic and outcome indicators in critically injured patients. Worsen pain outcomes after burn injury is because of low levels of omega 3 fatty acid, In Preclinical &clinical study model it has been shown that supplementation with O3FAs and their pro-resolving lipid mediators help in reducing pain [51].Lukaschek K, et al [52] in his cross sectional study on 142 community-dwelling older adults (60-85 years) with subjective memory complaints and concluded that higher dietry intake ω-3 LCPUFA was associated with better cognitive and physical function, proving that omega 3 fatty acid plays major role in optimizing age related physical and cognitive health.Berbert AA, et al [53] In their prospective, double-blind, randomized study on rheumatoid arthritis a 24 week trial of dietary supplementation with 2 different dosages of fish oil and 1 dosage of olive oil, on 49 subjects, they performed clinical evaluation at baseline and every 6 weeks whereas immunological variables were measured at baseline and after 24 weeks of study,they divided subjects into three groups i.e. Twenty patients consumed daily dietary supplements of n3 fatty acids containing 27 mg eicosapentaenoic acid (EPA) and 18 mg kg docosahexaenoic acid (DHA) (low dose), 17 patients ingested 54 mg/kg EPA and 36 mg/kg DHA (high dose), and 12 patients ingested olive oil capsules containing 6.8 gm of oleic acid, they demonstrated that subjects who consume fish oil have higher clinical

benefits of dietary supplementation with omega3 fatty acids for time intervals that are longer than those previously studied.Whereas certain immune changes have been observed in subjects with olive oil supplementation.

Chronic Use Of Omega-3 Fatty Acids

Clinical and animal studies have shown that to reduce CVD morbidity and mortality, a diet containing fatty fish, fish oils (FOs), or individual omega-3 FAs could help eliminate these complications, The concentrations of omega-3 FA in plasma and their content in cells and tissues, however, react slowly over time to the uptake of omega-3 FA, 3 months to increase the concentration of DHA in plasma and in RBC increase.Kew S. et al. [54] in their placebo-controlled, double-blind parallel study on 42 healthy volunteers who were randomly assigned received supplementation with placebo (olive oil), EPA (4.7 g / d) or DHA (4.9 g / d) for 4 weeks. Before and after the supplementation, blood samples were taken. T lymphocyte activation was reduced by DHA supplementation, while no significant effect on phagocytosis of monocytes or neutrophils, or on cytokine production or the expression of adhesion molecules by peripheral blood mononuclear cells was observed in the EPA-supplemented group.It has been observed in rats that after 8 weeks of oral intake a maximum incorporation of omega-3 FA into cardiac phospholipids occurs [55]. Thus, oral ingestion or ingestion of omega-3 FA supplements require a longer time to achieve substantial cellular accumulation through which they can have protective effects on CVD; i.e. over days to weeks. In their study Moghadam et al [56], observed the beneficial role of n-3 PUFA supplementation in type 2 diabetes mellitus (T2DM) 84 subjects, aged between 45-85 years with at least a 2 year history of T2DM,supplemented with three n-3 capsules per day (EPA 1,548 mg; DHA 828 mg; other n-3 fatty acids 338 mg), and control were supplemented with three placebo capsules (sunflower oil 2,100 mg) for 8 weeks, they demonstrated that n-3 supplemented group have suppressed level of serum TNF-α concentration by 8%($p < 0.01$).Study by Mori et al. [57] overweight men with hyperlipidaemia was supplemented with 4 g/ day for 6 weeks with either EPA, DHA or olive oil (as a control group). Such effects were observed in the EPA group, this finding indicates the beneficial effects of omega-3 FS is responsive to the vasculature that alters endothelial dysfunction and hypertension, and both EPA and DHA have different hemodynamic effects.Green tea polyphenol [epigallocatechin gallate (EGCG), was used to prepared esters of DHA, having high stability and antioxidant property, invivo studies have shown ICR (Institute of Cancer Research) mice, suffering from colon tumorigenesis has been protected by these esters [58].Richest source of ω-3 PUFAs, are marine organism though some plants are also source of omega 3 fatty acid like flax, chia, and canola seeds (good source of ALA),ALA severs as a precursor to the synthesis of LC PUFAs in the human body, though its synthesis in the body is limited to rates of less than 4% at best, so human need dietry source to increase its concentration in body [59].Heterotrophic fungus-like microorganisms, called Thraustochytrids are responsible for PUFA production at industrial scale, some of its genera like Schizochytrium,Thraustochytrium, and Ulkenia, is of great importance because of high content of omega 3 fatty acid in their oil [60]. On the basis of age and gender the required level of ALA varies between 1.1 and 1.6 g/day (Dietitians of Canada (2013), Dieticians also recommended to take 2 fish per day so to acquire nearly 0.3-0.45 g of EPA and DHA per day [61]. According to the Food and Agricultural Organization of the united nation (FAO 2010), the recommended dose of ALA is 0.5-0.6% per day to prevent deficiency symptoms in adults, with a total ω-3 PUFA intake of 0.5-2% [61]. Using genetic modification LC ω-3 PUFAs such as EPA and DHA are incorporated into flax and Brassica species, thus oils obtained from these genetically modified sources are free from any fishy odor [62].According to Waliullah S [63] Osteoporosis a muscular disorder is characterized by low bone mineral density and post-menopausal osteoporosis is highly prevalent in Indian females and they are unaware of it because of its silent presentation so proper guidance and awareness of nutritional supplementation may help to avoid it among females, So studies have demonstrated that consumption of omega 3 fatty acid helps in prevention of osteoclastogenesis and increased consumption of omega 3 fatty acid in comparison to omega 6 fatty acid helps in prevention of loss of bone mass [64].Inflammatory processes are influenced by omega-3 FA either directly through modulation of transcription factors and gene expression or indirectly through inflammation-dissolving lipid mediators or bioactive derivatives of omega-3 fatty acids such as eicosanoids, docosanoids [65]. Activity of the core factor kappa B (NF-B), one of the most important transcription regulators of inflammatory reactions involved in the pathogenesis of CVD, its

activity is downregulated by omega-3 FA [66], NF-B, as it is translocated into the nucleus, is used to activate gene expression of numerous proinflammatory cytokines, including tumor necrosis factor alpha (TNF-), interleukin 1 beta (IL-1), and interleukin 6 (IL-6) [66]. In aging patients with chronic inflammation who were supplemented with bioactive derivatives of omega-3 fatty acids such as eicosanoids and docosanoids [66], suppressed inflammation markers [87-88], peroxisome proliferator-activated receptors alpha and gamma were found in their serum. investigated (PPAR, PPAR) is activated by omega-3, which helps to reduce the expression of inflammatory genes by inhibiting NF-B activation [66].Adiponectin, a cardioprotective adipocyte-derived hormone used to modulate the activity of NF-B, and dose-dependent supplementation with omega-3 fat derivatives in animals and humans to increase adiponectin levels [66], middle-aged to adults late adult patients receiving EPA + DHA therapy have a significant reduction in circulating levels of proinflammatory cytokines than those receiving placebo therapy as markers of inflammation [66].Kiecolt-Glaser et al [67] in his randomized controlled trial on 138 participants (45 men and 93 women), ranged in age from 40 to 85,were randomly divided in 3 groups, viz 2.5 g/d n-3 PUFAs, or (2) 1.25 g/d n-3 PUFAs, or (3) placebo capsules that mirrored the proportions of fatty acids in the typical American diet, for 4months,and observed suppressed serum interlukin 6,TNF alpha levels, Depressive symptoms were quite low at baseline and did not change significantly in response to supplementation.Nie J,et al[68], demonstrated in his study the beneficial role of PUFA in animal model that high omega 3 fatty acid supplemented group had showed improved motor function recovery,High expression level of spinal cord repair-related protein such as MBP, Galc and GFAP, High omega 3 fatty acid supplemented group had improved autophagy ability and inhibited activity of the mTORC1 signaling pathway.Study by William Davis and colleagues demonstrated that Omega 3 fatty acid along with Vitamin D supplement when given to asymptomatic adults then a decrease coronary calcium scores has been recorded in these adults.Subjects on Dialysis when consume omega-3 fatty acids,had high level of fetuin-A a liver derived Plasma protein,which is an inhibitor of vascular calcification,and further elevated level of vitamin (1,25 (OH)D) was also observed in dialysis patients [69].Study by An et al., 2012 observed that when Subjects on Dialysis were given omega-3 fatty acid supplementation for 6 months can change the fatty acid content in Erythrocyte by suppressing the level of total trans fatty acid and transoleic acid and elevating the level of omega-3 fatty acid such as linoleic acid,palmitoleic acid, and lignoceric acid [70].A Cross Sectional Study by Son et al., 2012 on Hemodialysis Subjects reported that oleic acid and monounsaturated fatty acid (MUFA) were significantly high in the erythrocyte membrane of patients suffering from vascular calcification in comparison to controls.Study by Farina EK et al 2012 in the Framingham osteoporosis study, observed that subjects who consume high fish diets have high Bone Mineral density of hip bones, Another Study by Moon et al on Korean postmenopausal women observed that high erythrocyte level of DHA with EPA in these women have less chances of Osteoporosis[71].Study by Chen et al on Chinese Population demonstrated that due to high intake of fish diet by Chinese had reduced risk of developing Osteoporosis.

Structure of PUFA

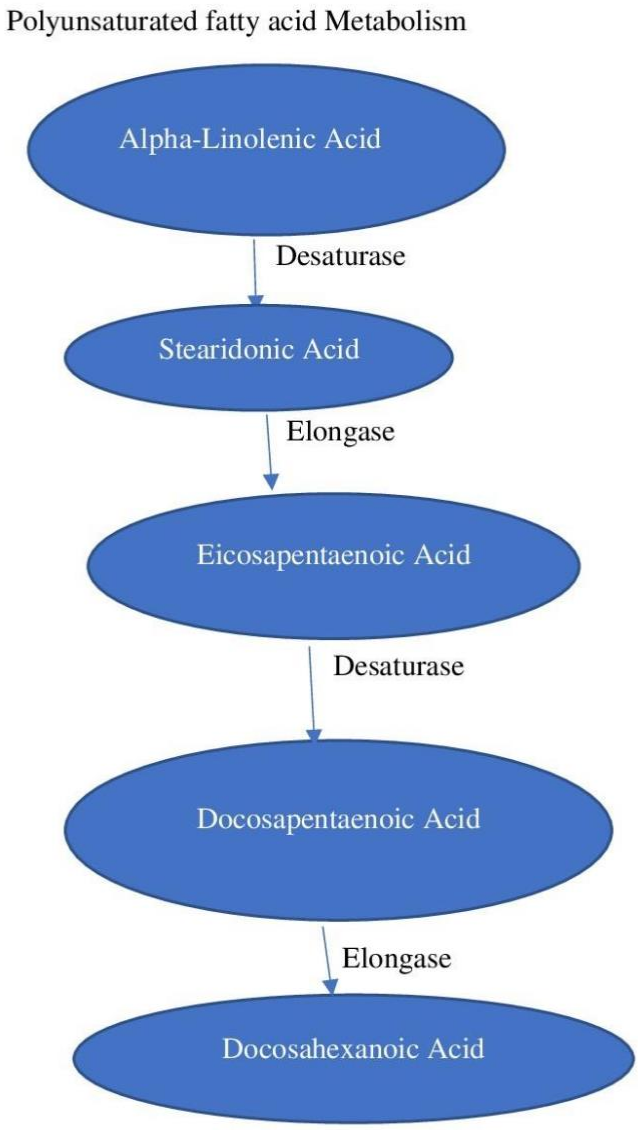
It is characterized by the presence of carboxylic acid (COOH) at one end of the molecule, a methyl end (-CH_3) at the other end, and there must be at least two double bonds in the chain[72] , on the basis of the presence of the number of Carbons in their chain and number of double bonds PUFA is mainly identified as linoleic acid (LA; C18: 4); Arachidonic acid (AA; C20: 4); Eicosapentaenoic acid (EPA; C20: 5) and docosahexaenoic acid (DHA; C22: 6). The molecular formula & molecular weight of omega-3 fatty acid is $C_{60}H_{92}O_6$ with a molecular weight of 909.39 g / mol, has an initial double bond on the third carbon atom of methyl or omega -End of the fatty acid, while omega-6 fatty acid has the empirical formula & molecular weight $C_{38}H_{64}O_4$ or 584.9, and the first double bond is on the sixth carbon atom from the methyl terminus, presence of a high concentration of n-3 in plasma are associated with one associated reduced risk of neurodegenerative diseases [72],Omega 3 fatty acid(EPA,DHA),protects us from various metabolic disorders[72],Brown,Green and red algae are the richest source of Omega 3 Fatty acid especially from the algae of Australia (North Queensland),Red Seaweeds(Champia parvula) have highest content of EPA ((3.30mg/g DW).Women who consume large amount of diet enriched in Omega 3 fatty acid in comparison to Omega 6 fatty acid have reduced risk of having Breast cancer [72]. DHA is enriched in the formation of axons in most tissues in the body, including the myocardium, retina, and brain. The

growing membrane is relatively fluid, which is due to DHA and its high level of unsaturation. The primary functional units of the brain circuits, i.e. Synapses also consist of DHA-enriched membranes [73].

Desaturase and elongase

Linoleic acid (LA) and alpha linolenic acid (ALA) are the precursors or building blocks for the synthesis of other PUFAs, so that humans can consume food sources or synthesize them from precursors through the participation of various desaturases in conjunction with elongases [73]. that removes two hydrogen atoms from a fatty acid to introduce a carbon / carbon double bond towards the carboxyl end of the molecule is called a desaturase, while an enzyme that catalyzes the carbon chain extension of a fatty acid by the addition of two carbons to the molecule is called an enolase [94], The precursor to omega-6 fatty acid is LA, and to omega-3 fatty acid is ALA. Increased dietary intake of LA, the less ALA is converted into longer-chain n-3 PUFA. The intake of LA has the potential to EPA and does not increase AA in the tissue while the conversion of LA to AA is low (a diet high in meat and poultry). The numerous double bonds in AA give membranes mobility, flexibility and fluidity.

Omega 3&6 Fatty Acid



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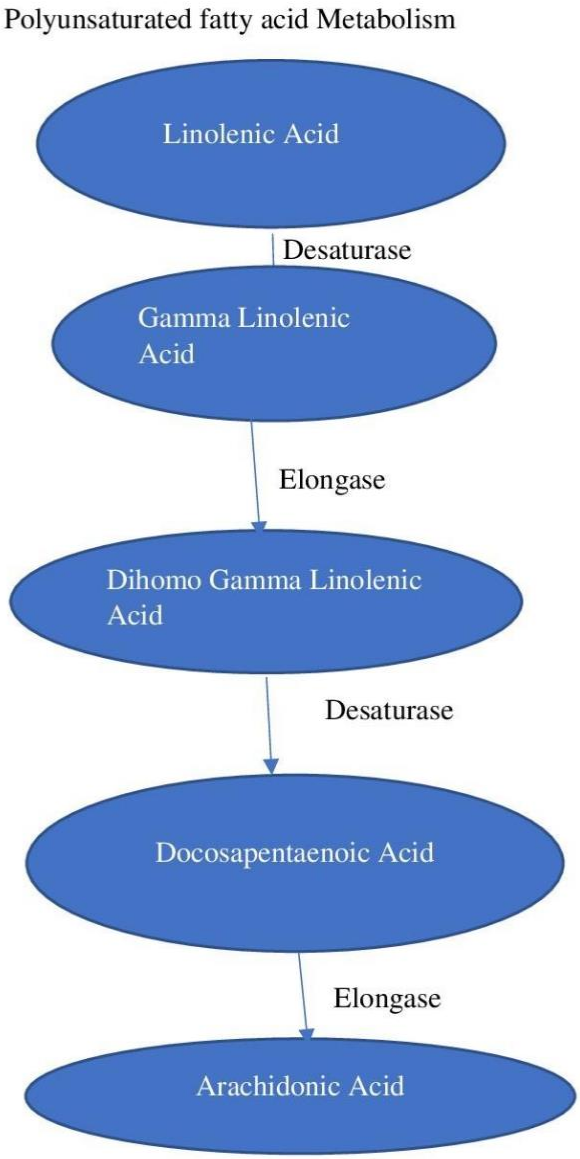


Role in Spinal Cord Injury

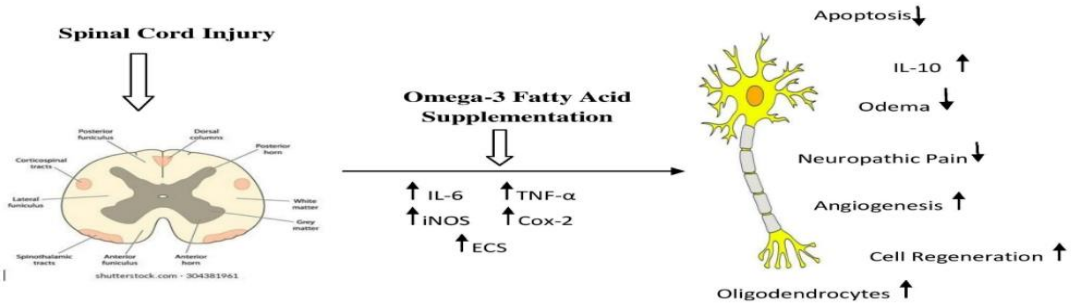
Spinal cord injury(SCI) is a life-threatening process; it greatly impacts subjects' quality of life and families. within developed nation annual cases of SCI are 11.5–53.4 cases per million, whereas alone in North America, over 1 million people are affected with direct lifetime costs around $1.1–4.6 million USD each [74].Study by King VR, et al. [75] state in their study that after lateral hemisection of the spinal cord, omega-3 fatty acids such as linolenic acid and docosahexaenoic acid (DHA) were injected into rats 30 minutes after the injury, with a significant improvement in locomotor performance within 6 weeks after the injury and neuroprotection, including decreased lesion size and apoptosis and increased neuronal and oligodendrocyte survival has been observed, decreased oxidation of RNA / DNA suggests a neuroprotective effect of omega-3 fatty acids and proves their antioxidant nature. In contrast, omega- 6 fatty acids like arachidonic acid worsened the results, so the study shows a striking difference between the two fatty acids.Another study by Bi J, et al. [76] using the SCI rat model shows the therapeutic effect of omega-3 fatty acids. They divided rats into four groups, such as sham, control, spinal cord injury plus 50 mg / kg omega-3 fatty acids and spinal cord injury plus 100 mg / kg omega-3 fatty acids, they observed that the group that supplemented with omega-3 fatty acids was suppressed tumor necrosis factor alpha (TNF) and terleukin6 (IL6) levels by> 50%, the mRNA expression of TNF and IL6 was also reduced, while in the control rat group an increase in the expression of Caspase3-, p53-, Bax and proNGF mRNA levels around 1.3, 1.4, 1.2 and protein expression by> 30% and proNGF mRNA by> 40% and

an increased expression of bcl2 mRNA by 286.9 % and reduced expression of Bax was also observed. The above result indicated that omega-3 fatty acid supplementation helps reduce oxidative stress, apoptosis, and levels of inflammatory markers in rats with ischemic reperfusion.Study by Baazm M, et al. [77] states that omega-3 fatty acid supplementation supports neurological function in the event of neuronal injury and suppresses the activity of inflammatory markers.Mahadewa Tjokorda GB et al. [78] states that the intervention of both alphatocopherol and omega-3 fatty acids (30 mg / kg + 5 ml / kg for 2 weeks) and the highest BBB score found in the combination treatment group, so their results match the Combination of both drugs show promising therapy for SCI.In Huntington's disease (HD), one of the neurodegenerative disease mutations occurs on chromosome sequence 4, so due to abnormal reproduction, there are a dozen pairs of cytosine-adenine-guanine (CAG) in HD patients, the higher the number of CAGs the more severe the disease. Suspecting that certain omega-3-responsive signaling pathways might be involved, British researchers using EPA in its ethyl ester form (Ethyl-EPA) found promising therapy in Huntington's disease [79].The study by Zanarini MC et al. In its double-blind placebo control study, [80] showed the beneficial effect of omega-3 fatty acids against borderline personality disorder in 30 female volunteers with moderate BPD when they were supplemented with only 1 g / day of EPA (as ethyl EPA) two months showed promising results against aggression and depression compared to women who received a placebo.Study by S.-N. Lim et al. [81] found in animal models that, according to SCI, in mice with Caenorhabditis elegansfat-1. a rapid recovery of motor function, as well as an increased number of neurons and oligodendrocytes with a simultaneous decrease in the number of macrophages and concentrations of inflammatory cytokines was observed gene (fat-1 mice), gene responsible for an increased endogenous production of 3 acids, compared to mice fed a -3-acid-poor diet, a standard laboratory diet, or a diet with an increased percentage of omega 6 acids.Omega-3 fatty acids play an important role in anxiety and depression, as several studies have shown. A study by Javidan AN [82] showed in its double-blind, randomized clinical study that after 14 months of supplementation with omega-3 fatty acids (435 mg docosahexaenoic acid and 65 mg eicosapentaenoic acid), in patients with traumatic paraplegia, the longer than Lasted 1 year after an injury, and found no significant omega supplementation in their disability scores either on the locomotion subscale or in sphincter control, hence they conclude that omega-3 fatty acids exert its neuroprotective effect only in the acute phase of SCI , but has no effect in chronic SCI cases.Reduced spinal cord edema white matter cavitation, demyelination, and vessel ingrowth were observed on 35th day after SCI in mice fed with omega 3 diet [83].Similar effects were observed in mice who were fed with ω-3 acids prior to planned SCI, these findings indicate the preventive action of omega 3 fatty acid against inflammation following neurotrauma.Ward RE,et al [84] states beneficial effect of DHA intervention in SCI rat model and observed White matter damage is prevented after DHA supplementation, reduced axonal dysfunction was seen. One of the studies showed that there is no difference in the likelihood of depression, anxiety or stress among respondents in the case of traumatic SCL and NON-traumatic SCL, depression 37%, anxiety 30% and clinically significant stress 25% [85]. Omega-3 fatty acids play an important role in anxiety and depression, as several studies have shown.In the treatment and prevention of spinal cord-associated neurological deficits, long-chain omega-3 polyunsaturated fatty acids (LC-O3PUFAs) play a therapeutic role in oil-derived LC-O3PUFAs for 8 weeks prior to spinal contusion and have been observed to be in Both cases and controls regulate important biochemical signatures associated with amino acid metabolism and free radical capture, The dietary supplement of LC-O3PUFAs helps in increasing the reduced glucose level (48%) and polar uncharged / hydrophobic amino acids (less than 20%), while the content of antioxidant / anti-inflammatory amino acids and peptide metabolites such as - alanine (+24%), Carnosine (+ 33%), homocarnosine (+ 27%), kynurenine (+ 88%), compared to animals with a normal diet, An increase in neurotransmitters and mitochondrial metabolism such as N-acetylglutamate (+ 43%) and acetyl-CoA levels (+ 27%) was reported in the group with PUFA supplementation. Thus, the dietary intervention of PUFA in SCI helps to target the global correction and improve the pro-oxidative metabolic profile that characterized SCI-mediated sensorimotor dysfunction [85].Mills JD et [86] point to the positive role of O3FA supplementation against diffuse axonal damage in rats. They divided the rats into 3 groups, the first and second groups received 10 or 40 mg / kg / day O3FA and the third group received no

supplementation (fish oil), increased O3FA serum levels, decreased number of positive axons after 30 days of supplementation Amyloid beta precursor protein in the supplemented group as shown by immunohistochemical analysis.Study by Paterniti I [87], found in his in vivo study that in acute SCI, DHA supplementation helps to reduce the degree of spinal cord inflammation and tissue damage, the expression of proinflammatory cytokine (TNF-), glial fibrillary acid Protein (GFAP.)), Formation of nitrotyrosine, apoptosis ((Fas-L, Bax and Bcl-2 expression) and helps restore limb function, and DHA also promotes neurite length and branching in the spinal ganglion, reducing the effects of oxidative stress. Many studies have shown that elevated EPA levels were associated with less atrophy of the gray matter of the hippocampus, parahippocampus, and amygdala in people over 65 years of age, and slower cognitive decline has been reported [88].

Inflammatory / immunological reactions

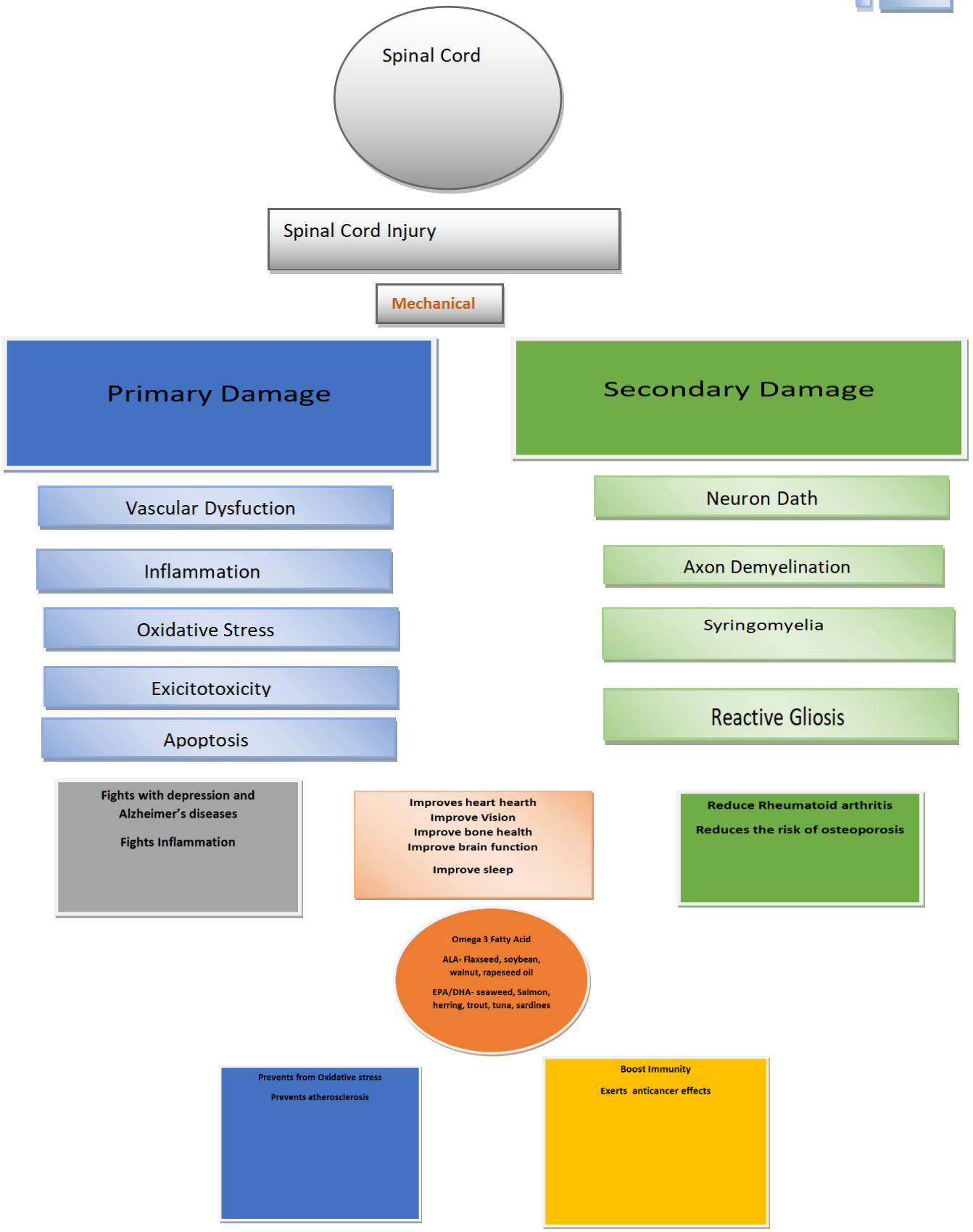
Cells of the immune system are rarely found in the CNS system, after SCI mechanical trauma activates microglia and secretes cytokines, after SCI in the CSF an increase in arachidonic acid metabolites leukotriene C4 and thromboxane B2 has been reported five to nine times ,One hour after the trauma, however, the TNF-alpha level rises in the spinal cord, while the role of TNF-alpha in the CNS is still unknown [89]. However, it is assumed that it occurs in the early phase of SCI exerts a certain neuroprotective effect, can lead to edema and leukocyte migration, apoptosis,while by increasing the synthesis of IL-10 and stimulating the regeneration of the axon it also exerts a neuroprotective effect against reactive oxygen radicals [89].The development of various neoplastic cells in the body is inhibited when there is an increased proportion of 3-acids in the cell membrane, many studies have proven that the presence of omega-3 fatty acids in the cell membrane restricts cell division in tumors during the synthesis phase (S phase), so that the initiation of the (G2 phase) of the cell cycle is prevented, so that the arrest status leads to apoptosis of neoplastic cells for a longer period of time,Omega-3 fatty acids activate sphingomyelinase (SMYase) on the cell membrane, which in turn increases the synthesis of ceramide [83], ceramide inhibits the phosphorylation of the retinoblastoma protein (pRb) alternately via the activation of phosphatase 1 (PP1) and 2A (PP2A) proteins and p21 protein, which further restricts cell division within the tumor [83]. The above signaling pathways may only lead to apoptosis of neoplastic cells, as some studies show. In healthy cells of the retina, heart or neurons, the presence of omega-3 fatty acids has a protective property that inhibits programmed cell death. But this duality needs further research,Source of below figure(Wojdasiewicz et al 2020)



Role of Omega-3 Fatty Acid Supplementation after Spinal Cord Injury in Rodent Model

CONCLUSION

This review mainly emphasizes the beneficial effects of omega-3 fatty acid supplementation, its structure and potential health benefits in various diseases and we mainly focus on the pathophysiology of spinal cord injury and the effects of omega-3 fatty acid supplementation on it, As a nutritional supplement is easy to administer and the safest, easiest and most affordable. The antioxidant and anti-inflammatory effect of PUFA, exerts a neuroprotective effect against various neurodegenerative diseases such as PD, ischemia, optic neuropathy. Most of the studies are done on animal models. In the case of CVDs, some of the studies were done on human models to prove their effectiveness. Despite the well-documented role of omega-3 fatty acids in the SCI animal model, research does not provide an answer to the main question of the optimal dose and duration of treatment, hence a demanding task can be based on arbitrary criteria.



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