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Review

Pathophysiology of spinal cord injury and potential health benefits of omega-3 fatty acid

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Spinal cord injury (SCI), is a life changing threatening neurological condition that completely changes patients' life. It has been shown that early treatment soon after the injury may improve neurological recovery. To date, no therapeutic modalities exist that have shown very positive effect on neurological outcomes. However, recent clinical and preclinical studies have shown little hope for the treatment of SCI. In medical management, recent advances have significantly improved diagnosis, stabilization, survival rate, and well-being of SCI patients, but there has been little progression in the treatment. An important strategy for SCI treatment is to reduce the levels of reactive oxygen species, and oxidative stress. Today, the main focus is on neutraceuticals as they are natural compounds, easy to accommodate and have high antioxidant properties which diminish the toxic effects of oxidative stress responsible for the progression of several pathologies of the nervous system. Omega-3 fatty acids are important polyunsaturated fatty acids (PUFA) with some roles in normal cellular metabolism. They have anti-inflammatory and antioxidant properties, and it has been proven to be beneficial in ameliorating inflammation in different diseases and thus improves neurological outcomes after neuronal injury. PUFA helps in suppressing the Inflammatory and oxidative stress markers responsible for SCI inflammatory events, 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. Fatty fishes such as salmon, mullet and mackerel are the best sources of EPA and DHA and thus have significant health benefits.

Key words: Osteoporosis, omega-3 fatty acid, spinal cord injury (SCI), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), National Spinal Cord Injury Statistical Center (NSCISC).

INTRODUCTION

A spinal cord injury (SCI) is characterized by the deterioration in motor, sensory, and autonomic functions caused by 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

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socio-economic implications for those affected and the health system (Tator, 1998; Dumont et al., 2001; Yılmaz et al., 2014; Alizadeh et al., 2019).

According to the National Spinal Cord Injury Statistical Center (NSCISC), 12,500 new cases of SCI are recorded each year in North America (Hachem et al., 2017). Patients with SCI over 60 years have significantly poorer results than younger patients (Hachem et al., 2017). 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 walls, or bullet injuries (WHO, 2013). Men are most often affected, with a ratio of 2:1 compared to women, and adults are more commonly affected than children. According to demographics, men are most often involved in early and late adulthood (3rd and 8th decades of life) (WHO, 2013), while women are affected during puberty (15-19 years) (Stein et al., 2015).

SCI can result in quadriplegia or paraplegia depending on the level of injury. Paraplegia is caused by a lesion in the dorsal spine, while quadriplegia occurs due to a lesion at the cervical level (Wilson et al., 2012). According to NSCISC (Hachem et al., 2017), the cervical level of the spinal cord (50%) is typically affected, with the most commonly affected level being the C5 vertebra, followed by the thoracic level (35%) and the lumbar region (11%). Middleton et al. (2012) reported survival rates for SCI over 40 years, with rates of 47% for patients with quadriplegia and 62% for those with paraplegia (Hachem et al., 2017; Middleton et al., 2012). The degree of injury and the functions retained after SCI determine patients' life expectancy. Patients with an ASIA Impairment Scale (AIS) grade D have almost a 90% normal life expectancy and a higher life expectancy than lower grades (Shavelle et al., 2015). Given the catastrophic sequelae of SCI on individuals, it is imperative to understand SCI's cellular and molecular mechanisms and develop new effective treatment modalities to alleviate suffering.

In all mammals, polyunsaturated fatty acids (PUFA) or ω-3 acids are essential components of cell membranes, facilitating normal body functioning. However, most mammals cannot synthesize them and rely on dietary sources to meet their needs. Three types of ω-3 acids include alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (Prasad et al., 2021).

Linoleic acid (C18:2n−6, LA) is the parent omega-6 fatty acid, and α-linolenic acid (C18:3n−3, ALA) is the parent omega-3 fatty acid. Humans can synthesize arachidonic acid (C20:4n−6; AA), one of the omega-6 fatty acids, from LA, and ALA can aid in synthesizing omega-3 fatty acids, including 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 like EPA, DPA, and DHA is relatively low, leading to these fatty acids being considered essential as well (Rubio-Rodríguez et al., 2010).

According to nutrition experts, the recommended ratio of the two fatty acids is 5:1 (n6:n3 fatty acid) or less, as desirable (WHO/FAO, 1994). However, the current food habits in Western societies are characterized by high consumption of foods rich in saturated fatty acids and low proportions of polyunsaturated fatty acids (PUFA), such as meat, seed oils, fast food (pizzas, hamburgers), and snack foods (cakes, biscuits) (Fernández-SanJuan, 2000). Compared to Japanese or Mediterranean diets, which typically contain a large amount of fish with a ratio close to 2:1, the composition of fast food consumption leads to a much higher ratio, up to 25:1 in the blood of subjects consuming fast food (Kamei et al., 2001; Ambring et al., 2006). As a result, adolescents who predominantly consume fast food have a significantly imbalanced fatty acid profile (Rubio-Rodríguez et al., 2010). This is why nutritionists recommend increasing consumption of fish and green leafy vegetables in the diet to prevent various diseases, especially cardiovascular diseases.

Supplementation with omega-3 fatty acids has been shown to increase the concentration of antioxidant enzymes such as catalase (CAT) and superoxide dismutase (SOD), while suppressing the activity of the oxidative stress marker malondialdehyde (MDA) in rat models of spinal cord injury (SCI) (Michael-Titus and Priestley, 2013; Figueroa et al., 2013). Additionally, n-3 acid supplementation helps reduce the expression of the enzyme glutamine synthetase, which is responsible for reducing the activity of glutamate-induced excitotoxicity in injured tissues. Diets high in omega-3 acids help maintain elevated levels of glutathione (GSH) at the injury site and inhibit cell apoptosis, which are markers of improved motor function in rodents with SCI (Michael-Titus and Priestley, 2013; Figueroa et al., 2013).

Sabour et al. (2015) investigated the effects of omega-3 fatty acids in a double-blind, randomized clinical study involving 104 patients with spinal cord injury (SCI). Participants received an omega intervention consisting of 465 mg of docosahexaenoic acid (DHA) and 63 mg of eicosapentaenoic acid (EPA) in two capsules daily for 14 months. The study found that after the 14-month intervention, the concentration of adiponectin was significantly reduced, although no significant effect on leptin concentration was observed. However, a linear relationship between weight and leptin concentration was identified. In Europe and the USA, there has been an increasing trend in fortifying functional foods with omega-3 fatty acids over the past year. This trend has led to the fortification of various food products such as bread and baked goods, milk and dairy derivatives, spreadable fats, eggs, juices, soft drinks, and meat and poultry products (Kolanowski and Laufenberg, 2006). The primary natural source of omega-3 fatty acids is fish oil, which is incorporated into conventional foods. Various strategies are employed to minimize significant changes in the sensory quality of these products (Jiménez-Colmenero, 2006).

PATHOPHYSIOLOGY OF SCI

The primary mechanical injury leading to spinal cord injury (SCI) can result from various mechanisms such as compression, contusion, transection, and shearing forces (Alizadeh et al., 2019). Historically, SCI was typically associated with a high-energy mechanism in young patients, resulting in severe cord damage and complete neurologic injury. However, there is now an increasing proportion of SCIs observed in older individuals due to minor traumas compounded by chronic compression from degenerative cervical myelopathy, often resulting in incomplete injuries (Wilson et al., 2020). Cord compression caused by primary mechanical insults initiates a complex cascade of molecular and cellular events known as secondary injury, which further exacerbates tissue damage. Early decompressive surgery is often performed to alleviate ongoing compression after SCI and mitigate the effects of secondary injury (Fehlings et al., 2012).

Secondary injury is triggered by the primary injury and involves various chemical and mechanical damage to spinal cord tissues. Delays in managing SCI after the initial insult can worsen the prognosis (Ding and Chen 2022; Rowland et al., 2008). This secondary injury progresses over several hours to weeks and is characterized by disruptions in ion homeostasis, the release of reactive oxygen species, and excessive release of excitatory neurotransmitters. These processes impair endogenous cellular repair systems, leading to inflammation, extensive neuronal and glial cell death, residual demyelination of nerve fibers, and significant neuronal apoptosis (Ding and Chen, 2022; Zechner et al., 2003; Crowe et al., 1997).

The inflammatory response plays a crucial role in secondary injuries following spinal cord injury (SCI). Microglia, astrocytes, T cells, and neutrophils from the lesion area release inflammatory factors such as matrix metalloproteinases, tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-12 (IL-12), which contribute to tissue damage, disruption of the blood-spinal cord barrier, and edema (Noble et al., 2002). Additionally, oxidative stress induced by microglial activation leads to peroxidation and disruption of the normal phospholipid structure of cell membranes, further damaging neuronal tissue (Ding and Chen, 2022).

Excitatory neurotransmission in the spinal cord is directly influenced by N-methyl-D-aspartate (NMDA) receptors. Animal studies have demonstrated that blocking these NMDA receptors can provide protection against secondary damage from trauma and ischemia. NMDA antagonists have been shown to improve neurological function and reduce edema incidence (Akhmetzyanova et al., 2018; Aguiar et al., 2018; Tang et al., 2019; Arabi et al., 2019).

Spinal canal hematoma results from compression of the spinal cord due to mechanical damage. During the early phase of SCI, bleeding occurs, followed by interruption of blood supply, resulting in hypoxia and local ischemic infarction. These factors contribute to damage to the gray matter, where metabolic function is high. Neurons in the affected area undergo physical damage, and the thickness of the myelin sheath is reduced, leading to deterioration in neuronal transmission. Edema and the accumulation of macrophages in damaged tissue can exacerbate neuronal damage (Austin et al., 2012; Yezierski, 2000; Nickel and Gu, 2018; Fehlings and Agrawal, 1995).

The release of inflammatory cytokines and free radicals following spinal cord injury (SCI) triggers apoptosis, leading to inflammation and excitotoxicity. Apoptosis occurs in the areas surrounding the injured spinal cord tissue between 3 h and 8 weeks after SCI. Several studies have demonstrated that oligodendrocyte apoptosis exacerbates demyelination several weeks post-injury (Burnside et al., 2018; Casper et al., 2018; David et al., 2018). David et al. (2018) specifically showed that oligodendrocyte changes occur in response to SCI (Table 1).

EPIDEMIOLOGY: INDIAN EPIDEMIOLOGICAL DATA

Chhabra et al. (2021) conducted a retrospective study covering data from 2000 to 2016, involving 758 subjects, of which 39% (294) were quadriplegics and 61% (464) were paraplegics. During this period, the mortality rate was recorded at 10%. Among the subjects, approximately 81% were male, with quadriplegics experiencing a higher death rate of 22% compared to 3% for paraplegics.

In contrast, Jha et al. (2021) conducted a prospective study from March 2019 to March 2020, revealing that the primary cause of spinal cord injury (SCI) was road traffic accidents (RTA) (70%), followed by falls from height (28%). The most affected age group was 20 to 39 years, followed by 50 to 59 years, with falls being the predominant cause of injury in the latter age group. Males were found to be more susceptible to SCI. Among the 198 cases analyzed, 68 had thoracic spine injuries, 86 had lumbar spine injuries, and 22 had cervical spine injuries, with 22 cases involving injuries at multiple segments. Most cases (138) were within the age range of 25 to 50 years.

Devkota et al. (2013), in a study conducted in western Nepal, identified falls as the major cause of injury, followed by RTAs, with the lumbar spine being the most commonly affected site. The study also observed a higher male-to-female ratio among those affected.

Jain et al. (2021), in a retrospective observational study conducted in East India, collected data from August 15, 2018, to August 14, 2019, involving 103 patients with spinal cord injuries. The primary cause of injury in their study was road traffic accidents (37.9%), with a male-to-female ratio of 5.87:1. The most common age group affected was 31 to 40 years, followed by 21 to 30 years and 41 to 50 years.

Table 1. Progressive damage in the injured spinal cord that occurs following traumatic spinal cord injury.

No.	Damage
1	Vascular disruption, eschemia
2	Ionic imbalance
3	Oxidative stress
4	Glial activation
5	Matrix remodelling
6	Glial scar formation
7	Cell death
8	Axon degeneration and demylination
9.	Lipid peroxidation
10	Neuroinflammation
11	Infarction
12	Vascular disruption, eschemia
13.	Excess of nitrous oxide

This table shows the key pathophysiological events that occur after primary injury and lead to progressive tissue degeneration.
Source: Alizadeh et al. (2019).

Mittal S et al (2021) demonstrated that Fall from height were the predominant type of injury in women, while road traffic accidents (RTA), is more common in male. The thoracolumbar junction (D10-L2) (37.5%) followed by the cervical spine (25.3%) were the most common sites of injury, with variations observed between the age groups, particularly among individuals aged 16 to 30 years.

Mathur et al. (2015) demonstrated in their study that occupational hazards such as falls from height (53%) and road traffic accidents (23%) were common causes of spinal cord injury, along with carrying heavy objects overhead (3.0%) and falls following electric shock (4.0%). They found that married individuals were at a higher risk for SCI compared to singles, with 58.3% of subjects being married, consistent with findings from Western countries.

Rai and Ganvir (2019) also reported a higher percentage of married individuals compared to singles (70%) in their study on spinal cord injury.

Nirmala et al. (2020) described the sociodemographic characteristics of subjects in their study, revealing that out of 60 subjects, 36 were men (60%). A significant proportion of subjects had completed secondary school (38.3%) or primary education (31.7%), while 11.7% had completed university education, and 10.0% were illiterate. The occupations of the subjects varied, with 28.3% being students, 26.7%-day laborers, and 21.7% housewives. The majority of patients (58.3%) were married, and more patients came from middle-income families (53.3%) than from low-income families (45.0%). Both traumatic and non-traumatic spinal cord injuries were more prevalent in rural communities compared to urban areas.

Krishnamurthy et al. (2020), in their hospital-based cross-sectional study, found that younger age groups (20 to 49 years) were most commonly affected by spinal cord injuries compared to older age groups (50 years and over). The thoracic level was the most common site of injury (64.3%), followed by the lower cervical level (21.4%). They observed that patients with incomplete spinal cord injuries (39.2%) were more prevalent than those with complete injuries (60.8%).

Yusuf et al. (2019), in a study on 133 patients with traumatic paraplegia, reported that the majority of patients were younger, with road traffic injuries accounting for 72.2% of cases. The cervical spine was the most common site of injury (62%), and complete spinal cord injury was the most common type (52.6%).

Kumar et al. (2015), in their study involving 152 cases of spinal cord injury, found that adolescents were the most affected group, with 71.7% of cases occurring in construction workers. Falls from a great height were a common cause of injury (61.2%), with cervical spine injuries accounting for 44.1% of cases.

Ning et al. (2012), in a review, reported that in Asia, the incidence rates of traumatic spinal cord injury ranged from 12.06 to 61.6 million-1, with a mean age ranging from 26.8 to 56.6 years. Male subjects were at higher risk compared to females, with motor vehicle collisions and falls being the common types of injuries. War injuries were reported as the leading cause in most countries. The neurological level and extent of injury varied, with subjects classified based on AIS/Frankel grade.

Chacko et al. (1986) reported on 218 subjects with spinal cord injuries admitted to a general hospital in rural India. Among them, 125 subjects had a neurological deficit, with infections and pressure ulcers being common complications. Patients with cervical spine injuries were particularly affected, highlighting the lack of facilities in general hospitals for managing such cases.

Sridharan et al. (2015) conducted a study on 245 indoor patients at the Rajiv Gandhi Government General Hospital in Chennai, India, revealing that males (216) were predominantly affected compared to females. The male-to-female ratio was 8.8:1.2, with the most common age group affected being 20 to 40 years old. Falls from a height were identified as the most common type of injury. Among men, injuries to the cervical spine (C5 and C6) were frequent, followed by injuries to the dorsal and lumbar spine segments, while women commonly experienced lumbar spine injuries.

According to Pandey et al. (2007), road traffic accidents (RTAs) represent the second largest mode of injury in spinal cord injuries. This is attributed to the increasing number of vehicles in metropolitan cities in developing countries like India. To mitigate traffic-related accidents, stricter traffic rules must be enforced.

In a retrospective study by Lalwani et al. (2014), 341 cases were identified between January 2008 and December 2011, with 288 male and 53 female patients. The majority of patients were aged 25 to 64 years, followed by young adults aged 16 to 24 years. The male-

to-female ratio was 5.4:1. Isolated spinal injuries were observed in 55% of cases, with cervical spine injuries being most prevalent (75.95%). Thoracic spine injuries were observed in 16.42% of patients, and thoracic and lumbar spine injuries were observed in 7.62% of patients. Falls from a height (44.28%) and RTAs (41.93%) were the most common types of injuries. The majority of patient deaths occurred in phase IV (secondary to tertiary complications of trauma), with fewer deaths in phases I (brought dead or survived 3 to 24 h) and III (>24 hours to 7 days).

WORLDWIDE EPIDEMIOLOGICAL DATA

In a recent retrospective study by Chen et al. (2021) conducted in the Chinese province of Guangdong, traumatic spinal cord injury (TSCI) was investigated, revealing a male-to-female ratio of 3.4:1. Of the 482 cases analyzed, 384 were male and 112 were female. The age group most affected was 45-60 years (41.7%), followed by 31-45 years (23.8%). Falls from a height accounted for the most common type of injury (49.3%), followed by motor vehicle collisions (34.8%). The cervical spinal cord, particularly the C4-C6 region, was the most commonly injured site, comprising 39.8% of cases.

In a descriptive cross-sectional study from Korea by Kim et al. (2021), which included 221 patients with spinal cord injury (161 traumatic and 60 non-traumatic), the most frequently affected age group was between 40 and 49 years. For non-traumatic spinal cord injury, the affected age group was between 70 and 79 years. Tripping was the main cause of injury, especially among the elderly. Traumatic spinal cord injuries were mainly observed in male subjects, with falls being the most common cause (37.3%), followed by car accidents (35.4%), and stumbling (19.3%). Non-traumatic spinal cord injury was predominantly caused by neoplasia (35.0%).

Johansson et al. (2021), in a prospective cohort study conducted in Finland over a four-year period, enrolled 346 subjects with spinal cord injury. They found that low-level falls (36.2%), high-level falls (25.5%), and transport-related accidents (19.2%) were the leading causes of injury. Fall from height was the common mode of injury among subjects aged above 60 years, while alcohol-related incidents accounted for 47.4% of cases in subjects below 60 years of age. Cervical injury was more common in subjects above 60 years of age (77.1%), compared to those below 60 years of age (59.6%). The incidence of traumatic spinal cord injury was higher in the summer and autumn seasons (Tables 1 to 3).

MISCALLENEOUS ROLE OF PUFA 3

Shehab et al. (2021) demonstrated that omega-3 fatty acids help improve vitamin D and calcium levels in women of childbearing potential. In their study, women were administered omega-3 fatty acid supplements (1000 mg) twice a day for 12 weeks, resulting in beneficial effects on vitamin D levels, calcium levels, and cardioprotective effects. Reductions in levels of harmful lipids such as cholesterol and LDL-c were also observed, highlighting omega-3's role in promoting bone health.

Matsumura et al. (2021) 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 abusive behaviors towards children, such as beating and violent shaking, and reduce tendencies to leave the baby alone at home.

In a double-blind cross-over design study by Kumar et al. (2015), it was found that obese adolescents have lower serum concentrations of omega-3 polyunsaturated fatty acids (PUFA) compared to normal weight adolescents, contributing to inflammatory activity and endothelial dysfunction. However, supplementation with omega-3 did not show significant differences in various health parameters, including cholesterol levels, blood pressure, and vascular structure.

In their study, participants were randomized to receive either a placebo or 1.2 g/day of omega-3 fatty acids for 3 months. However, no significant differences were observed between the omega-3 group and the placebo group in terms of total cholesterol, triacylglycerol, HDL cholesterol, anthropometry, blood pressure, pulse wave velocity, or vascular structure.

It is noteworthy that a majority of the American population has low consumption of omega-3 fatty acids, as highlighted in studies by Cholewski et al. (2018), Richter et al. (2017), and Zhang et al. (2018). Low levels of omega-3 fatty acids have also been implicated in painful disorders such as migraine headache, as demonstrated by Ramsden et al. (2013).

Furthermore, after burn injuries, levels of omega-3 fatty acids tend to decline, potentially contributing to increased susceptibility to infection and mortality. In cases of secondary spinal cord injury (SCI), ion imbalance and excitotoxicity in excitatory cells are hallmark factors. Excessive activation of relevant amino acid receptors leads to excitotoxicity, resulting in neuronal necrosis and apoptosis, which in turn can lead to demyelination after injury, as discussed in studies (Ahuja et al., 2017; Silva et al., 2014).

In a double-blind randomized controlled study by Rajaei et al. (2016) on rheumatoid arthritis (RA), an autoimmune inflammatory disease, participants who received an omega-3 supplement (2 capsules daily containing 1.8 and 2.1 grams of EPA and DHA) for twelve weeks showed reduced dependence on concomitant medication without weight change. Additionally, the omega-3-treated group experienced reductions in pain and morning stiffness.

Miles et al. (2012) suggest that marine n-3 PUFAs (EPA

Table 2. Major phase of traumatic SCI

Primary injury	Secondary injury/acute (second to minutes	Secondary injury/sub acute(minutes to week)	Secondary injury /chronic phase (months to year
Impact plus persistent compression	Vasospasm	Cellular apoptosis	Demylination of surviving axons
Impact alone with transient compression	Dearangement in ionic homeostasis	Neurite growth inhibitory factors,glial scar formation	Apoptosis
Distraction	Ischemia	Dearangement in ionic homeostasis	Maturation of glial scar
Lacertion/Transection	Accumulation of Neurotransmitter	Accumulation of neurotransmitter	Alteration of Ion channels and receptors
	Oedema	Glutamatergic excitotoxicity	Continue central Cavitation
	Plasma membrane compromise /permeability	Plasma membrane compromise /permeability	Altered neurocircuits
		Lipid peroxidation and nitrous oxide excess	Astroglial scar launch
		Vertebral compression	Syrinx formation
		Inflammatory mediated cell death	Chairi malformation
		Wallerian degeneration,Axonal dieback	
		Matrix remodelling	
		Evolution of glial scar around injury site	

This table shows the changes that occurs in the phases of spinal cord injury: Primary injury, secondary injury (acute, sub-acute and chronic phases of secondary SCI.

and DHA) found in oily fish and fish oils decrease the levels of n-6 PUFA arachidonic acid (ARA) within cells, which serves as a precursor to inflammatory eicosanoids, thereby potentially mitigating inflammation associated with RA.

A meta-analysis conducted by Goldberg and Katz (2007) demonstrated the beneficial effects of omega-3 fatty acid supplementation in reducing inflammation. Omega-3 supplementation is considered an attractive adjunctive treatment for alleviating joint pains associated with RA, inflammatory bowel disease, and dysmenorrhea.

Qi et al. (2016) observed postburn elevation in free fatty acid (FFA) levels, which subsequently returned to baseline over time. Their study concluded that after burn injury, alterations in lipid profile occur; suggesting that key lipids could serve as potential diagnostic and outcome indicators in critically injured patients. Low levels of omega-3 fatty acids may contribute to worsened pain outcomes after burn injury.

In both preclinical and clinical study models, supplementation with omega-3 fatty acids and their pro-resolving lipid mediators has been shown to reduce pain (Ramsden et al., 2013; Xu et al., 2013; Hill et al., 2016; Zhang et al., 2018). Lukaschek et al. (2016), in their cross-sectional study involving 142 community-dwelling older adults aged 60-85 years with subjective memory complaints, concluded that higher dietary intake of omega-3 long-chain polyunsaturated fatty acids (LCPUFA) was associated with better cognitive and physical function, highlighting the significant role of omega-3 fatty acids in optimizing age-related physical and cognitive health.

Berbert et al. (2005), in their prospective, double-blind, randomized study on rheumatoid arthritis, conducted a24-week trial of dietary supplementation with two different dosages of fish oil and one dosage of olive oil on 49 subjects. Clinical evaluations were performed at baseline and every 6 weeks, while immunological variables were measured at baseline and after 24 weeks of the study. The subjects were divided into three groups: twenty patients consumed daily dietary supplements of omega-3 fatty acids containing 27 mg EPA and 18 mg/kg 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 g of oleic acid.

They demonstrated that subjects who consumed fish oil experienced greater clinical benefits from dietary supplementation with omega-3 fatty acids over longer time intervals than those previously studied. Additionally, certain immune changes were observed in subjects who received olive oil supplementation.

CHRONIC USE OF OMEGA-3 FATTY ACIDS

Clinical and animal studies have shown that to reduce cardiovascular disease (CVD) morbidity

Table 3. The rich sources of Omega 3 fatty acid in different food sources.

Fish	EPA (%)	DHA (%)	DPA (%)	ALA (g/100-g sample)	Reference
Menhaden oil	18.3	9.6	1.8	-	Ackman (2005)
Herring oil	7.5	6.8	0.75	-	Ackman (2005)
Cod liver oil	12.2	12.7	1.7	-	Copeman and Parrish (2004)
Cod flesh oil	19.1	32.6	2	-	Copeman and Parrish (2004)
Capelin oil	9.3	4.1	0.9	-	Copeman and Parrish (2004)
Skipjack tuna oil	11.1	29.1	0	-	Tanabc et al. (1999)
Butterfish oil	5.1	10.8	2.4	-	Budge et al. (2002)
Yellowtail flounder oil	15	18.7	3.3	-	Budge et al. (2002)
Winter flounder oil	14.4	20.1	3.8	-	Budge et al. (2002)
Haddock oil	14.8	24.8	1.9	-	Budge et al. (2002)
Halibut oil	9.6	30.6	2.6	-	Budge et al. (2002)
Mackerel oil	8	19.3	1.6	-	Budge et al. (2002)
Salmon oil	9.1	6.2	1.8	-	Aursand et al. (1994)
Flaxseed oil	-	-	-	53.368	Health Can. (2016)
Chia seed	-	-	-	17.83	Health Can. (2016)
Walnut oil	-	-	-	10.4	Health Can. (2016)
Canola oil	-	-	-	9.137	Health Can. (2016)
Hemp seed	-	-	-	8.56	Health Can. (2016)
Soybean oil	-	-	-	6.789	Health Can. (2016)
Mustard oil	-	-	-	5.899	Health Can. (2016)
Hickory nuts, dried	-	-	-	1.047	Health Can. (2016)
Pistachio nuts, raw	-	-	-	0.259	Health Can. (2016)
Pumpkin and squash seed kernels, dried	-	-	-	0.12	Health Can. (2016)
Almonds, dried, unbalanced, unroasted	-	-	-	0.003	Health Can. (2016)
Bearded seal oil	9.27	13.38	4.76	-	-
Grey seal oil	5.23	7.12	4.97	-	Shahidi (1998)
Common octopus	16.1	20.6	1.8	-	Arts et al. (2001)
European squid	14.3	31.6	0.4	-	Arts et al. (2001)
Squid	13.9	16.9	1.3	-	Arts et al. (2001)

and mortality, a diet containing fatty fish, fish oils (FOs), or individual omega-3 fatty acids could help eliminate these complications. However, the concentrations of omega-3 fatty acids in plasma and their content in cells and tissues react slowly over time to the uptake of omega-3 fatty acids, typically taking around 3 months to increase the concentration of docosahexaenoic acid (DHA) in plasma and red blood cells (RBCs).

Kew et al. (2004) conducted a placebo-controlled, double-blind parallel study on 42 healthy volunteers who were randomly assigned to receive supplementation with placebo (olive oil), eicosapentaenoic acid (EPA) (4.7 g/day), or DHA (4.9 g/day) for 4 weeks. Blood samples were taken before and after supplementation. They found that T lymphocyte activation was reduced by DHA supplementation, while no significant effect was observed in the EPA-supplemented group on phagocytosis of monocytes or neutrophils, or on cytokine production or the expression of adhesion molecules by peripheral blood mononuclear cells.

Furthermore, in rats, it has been observed that after 8 weeks of oral intake, there is maximum incorporation of omega-3 fatty acids into cardiac phospholipids (Ayalew-Pervanchon et al., 2007).

Therefore, oral ingestion or ingestion of omega-3 fatty acid supplements require a longer time to achieve substantial cellular accumulation, through which they can have protective effects on CVD, typically occurring over days to weeks.

In their study, Moghadam et al. (2012) observed the beneficial role of n-3 PUFA supplementation in type 2 diabetes mellitus (T2DM). They included 84 subjects aged between 45 and 85 years with at least a 2-year history of T2DM. The participants were supplemented with three n-3 capsules per day containing EPA 1,548 mg, DHA 828 mg, and other n-3 fatty acids 338 mg, while the control group received three placebo capsules containing sunflower oil 2,100 mg for 8 weeks. They

demonstrated that the n-3 supplemented group had suppressed levels of serum TNF-α concentration by 8% ($p < 0.01$).

In a study by Mori et al. (1999), overweight men with hyperlipidemia were supplemented with 4 g/day for 6 weeks with either EPA, DHA, or olive oil (as a control group). The beneficial effects were observed in the EPA group. This finding indicates that the beneficial effects of omega-3 fatty acids are responsive to the vasculature, altering endothelial dysfunction and hypertension. Both EPA and DHA have different hemodynamic effects.

Green tea polyphenol epigallocatechin gallate (EGCG) was used to prepare esters of DHA, having high stability and antioxidant properties. Studies using NVivo have shown that Institute of Cancer Research (ICR) mice suffering from colon tumorigenesis have been protected by these esters (Shahidi and Ambigaipalan, 2018).

The richest sources of ω-3 PUFAs are marine organisms, although some plants also serve as sources of omega-3 fatty acids, such as flax, chia, and canola seeds (good sources of ALA). ALA serves as a precursor to the synthesis of LC PUFAs in the human body, although its synthesis in the body is limited to rates of less than 4% at best. Therefore, humans need dietary sources to increase its concentration in the body (Shahidi and Ambigaipalan, 2018).

Heterotrophic fungus-like microorganisms, called Thraustochytrids, are responsible for PUFA production at an industrial scale. Some of its genera like Schizochytrium, Thraustochytrium, and Ulkenia are of great importance because of the high content of omega-3 fatty acids in their oil (Patel et al., 2021).

On the basis of age and gender, the required level of ALA varies between 1.1 and 1.6 g/day according to the Dietitians of Canada (2013). Dietitians also recommend consuming 2 fish per day to acquire nearly 0.3-0.45 g of EPA and DHA per day (FAO, 2010).

According to the Food and Agriculture Organization of the United Nations (FAO, 2010), the recommended dose of ALA is 0.5 to 0.6% per day to prevent deficiency symptoms in adults, with a total ω-3 PUFA intake of 0.5 to 2% (FAO, 2010).

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 (Hixson et al., 2016).

According to Waliullah et al. (2014), osteoporosis, a muscular disorder, is characterized by low bone mineral density, and post-menopausal osteoporosis is highly prevalent in Indian females. They are often unaware of it because of its silent presentation, so proper guidance and awareness of nutritional supplementation may help to avoid it among females. Studies have demonstrated that consumption of omega-3 fatty acids helps in the prevention of osteoclastogenesis, and increased consumption of omega-3 fatty acids in comparison to omega-6 fatty acids helps in the prevention of loss of bone mass (Casado-Díaz et al., 2013).

INFLAMMATORY PATHWAYS

Inflammatory processes are influenced by omega-3 fatty acids 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 and docosanoids (Witte et al., 2010). The 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 is downregulated by omega-3 fatty acids (Zirpoli et al., 2020; Campos-Staffico et al., 2019). NF-B, when translocated into the nucleus, is used to activate gene expression of numerous proinflammatory cytokines, including TNF-, interleukin 1 beta (IL-1), and interleukin 6 (IL-6) (Campos-Staffico et al., 2019). In aging patients with chronic inflammation who were supplemented with bioactive derivatives of omega-3 fatty acids such as eicosanoids and docosanoids (Campos-Staffico et al., 2019), suppressed inflammation markers (Tan et al., 2018; Zúñiga et al., 2011), peroxisome proliferator-activated receptors alpha and gamma were found in their serum. Investigated PPAR is activated by omega-3, which helps to reduce the expression of inflammatory genes by inhibiting NF-B activation (Duda et al., 2007; Kiecolt-Glaser et al., 2012). Adiponectin is 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 increases adiponectin levels (Zirpoli et al., 2020; Duda et al., 2007) in middle-aged to adults.

Late adult patients receiving EPA + DHA therapy show a significant reduction in circulating levels of proinflammatory cytokines compared to those receiving placebo therapies as markers of inflammation (Tan et al., 2018). Kiecolt-Glaser et al. (2012) in their randomized controlled trial on 138 participants (45 men and 93 women), ranged in age from 40 to 85, were randomly divided into 3 groups, viz 2.5 g/day n-3 PUFAs, or (2) 1.25 g/day n-3 PUFAs, or (3) placebo capsules that mirrored the proportions of fatty acids in the typical American diet, for 4 months, and observed suppressed serum interleukin 6 and TNF alpha levels. Depressive symptoms were quite low at baseline and did not change significantly in response to supplementation.

STRUCTURE OF PUFA

This is characterized by the presence of a carboxylic acid (COOH) at one end of the molecule, a methyl end (-CH3) at the other end, and there must be at least two double bonds in the chain (Bentsen, 2017), based on the presence of the number of carbons in their chain and the

number of double bonds. PUFA is mainly identified as LA (C18:2), arachidonic acid (AA; C20:4), EPA (C20:5), and DHA (C22:6). The molecular formula and molecular weight of omega-3 fatty acids are C60H92O6 with a molecular weight of 909.39 g/mol. These have an initial double bond on the third carbon atom from the methyl or omega-end of the fatty acid, while omega-6 fatty acids have the empirical formula and molecular weight C38H64O4 or 584.9, and the first double bond is on the sixth carbon atom from the methyl terminus (Bentsen, 2017). The presence of a high concentration of n-3 in plasma is associated with a reduced risk of neurodegenerative diseases (Jovanović et al., 2011). 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, that is, synapses, also consist of DHA-enriched membranes (Kidd, 2007).

DESATURASE AND ELONGASE

LA and ALA are the precursors or building blocks for the synthesis of other PUFAs, allowing humans to consume food sources or synthesize them from precursors through the participation of various desaturases in conjunction with elongases (Bentsen, 2017). Desaturases are enzymes that remove two hydrogen atoms from a fatty acid to introduce a carbon/carbon double bond towards the carboxyl end of the molecule, while enzymes that catalyze the carbon chain extension of a fatty acid by the addition of two carbons to the molecule are called elongases (Yilmaz and Lim, 2017). The precursor to omega-6 fatty acid is LA, and to omega-3 fatty acid is ALA. Increased dietary intake of LA leads to less conversion of ALA into longer-chain n-3 PUFA. The intake of LA has the potential to convert to EPA and does not increase AA in the tissue, while the conversion of LA to AA is low in diets high in meat and poultry. The numerous double bonds in AA give membranes mobility, flexibility, and fluidity (Figure 1).

Role of omega 3 and 6 fatty acid in SCI

King et al. (2006) state in their study that after lateral hemisection of the spinal cord, omega-3 fatty acids such as linolenic acid and DHA were injected into rats 30 min after the injury. 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, was observed. Decreased oxidation of RNA/DNA suggests a neuroprotective effect of omega-3 fatty acids, proving their antioxidant nature. In contrast, omega-6 fatty acids like arachidonic acid worsened the results, highlighting a striking difference between the two fatty acids. Bi et al. (2019) using the SCI rat model show the therapeutic effect of omega-3 fatty acids. They divided rats into four groups: sham, control, SCI plus 50 mg/kg omega-3 fatty acids, and SCI plus 100 mg/kg omega-3 fatty acids. They observed that the group supplemented with omega-3 fatty acids suppressed TNF and interleukin-6 (IL-6) levels by more than 50%. The mRNA expression of TNF and IL-6 was also reduced, while in the control rat group, there was an increase in the expression of Caspase3-, p53-, Bax, and proNGF mRNA levels by around 1.3, 1.4, 1.2, and protein expression by more than 30%, and proNGF mRNA by more than 40%, and an increased expression of bcl2 mRNA by 286.9%, with reduced expression of Bax also observed. These results indicate that omega-3 fatty acid supplementation helps reduce oxidative stress, apoptosis, and levels of inflammatory markers in rats with ischemic reperfusion (Figure 2).

Baazm et al. (2021) state that omega-3 fatty acid supplementation supports neurological function in the event of neuronal injury and suppresses the activity of inflammatory markers. Mahadewa et al. (2017) state that the intervention of both alpha-tocopherol and omega-3 fatty acids (30 mg/kg + 5 ml/kg for 2 weeks) resulted in the highest BBB score in the combination treatment group. Their results suggest that the combination of both drugs shows promising therapy for SCI. In Huntington's disease (HD), a neurodegenerative disease caused by mutations on chromosome sequence 4, abnormal reproduction leads to an excess of cytosine-adenine-guanine (CAG) repeats in HD patients, with a higher number of CAG repeats correlating with more severe disease. Suspecting involvement of certain omega-3-responsive signaling pathways, British researchers found promising therapy in HD using EPA in its ethyl ester form (Ethyl-EPA) (Puri et al., 2002). Zanarini and Frankenburg (2003), in a double-blind placebo control study, 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) for two months, demonstrating promising results against aggression and depression compared to women who received a placebo. Lim et al. (2012) found in animal models of SCI that mice with Caenorhabditis elegansfat-1, responsible for increased endogenous production of omega-3 acids, exhibited rapid recovery of motor function, increased numbers of neurons and oligodendrocytes, and a simultaneous decrease in the number of macrophages and concentrations of inflammatory cytokines compared to control groups fed different diets.

Omega-3 fatty acids play an important role in anxiety and depression, as several studies have shown. A study by Javidan et al. (2014) conducted a double-blind randomized clinical study where patients with traumatic paraplegia were supplemented with omega-3 fatty acids (435 mg DHA and 65 mg EPA) for 14 months. They found no significant improvement in disability scores on

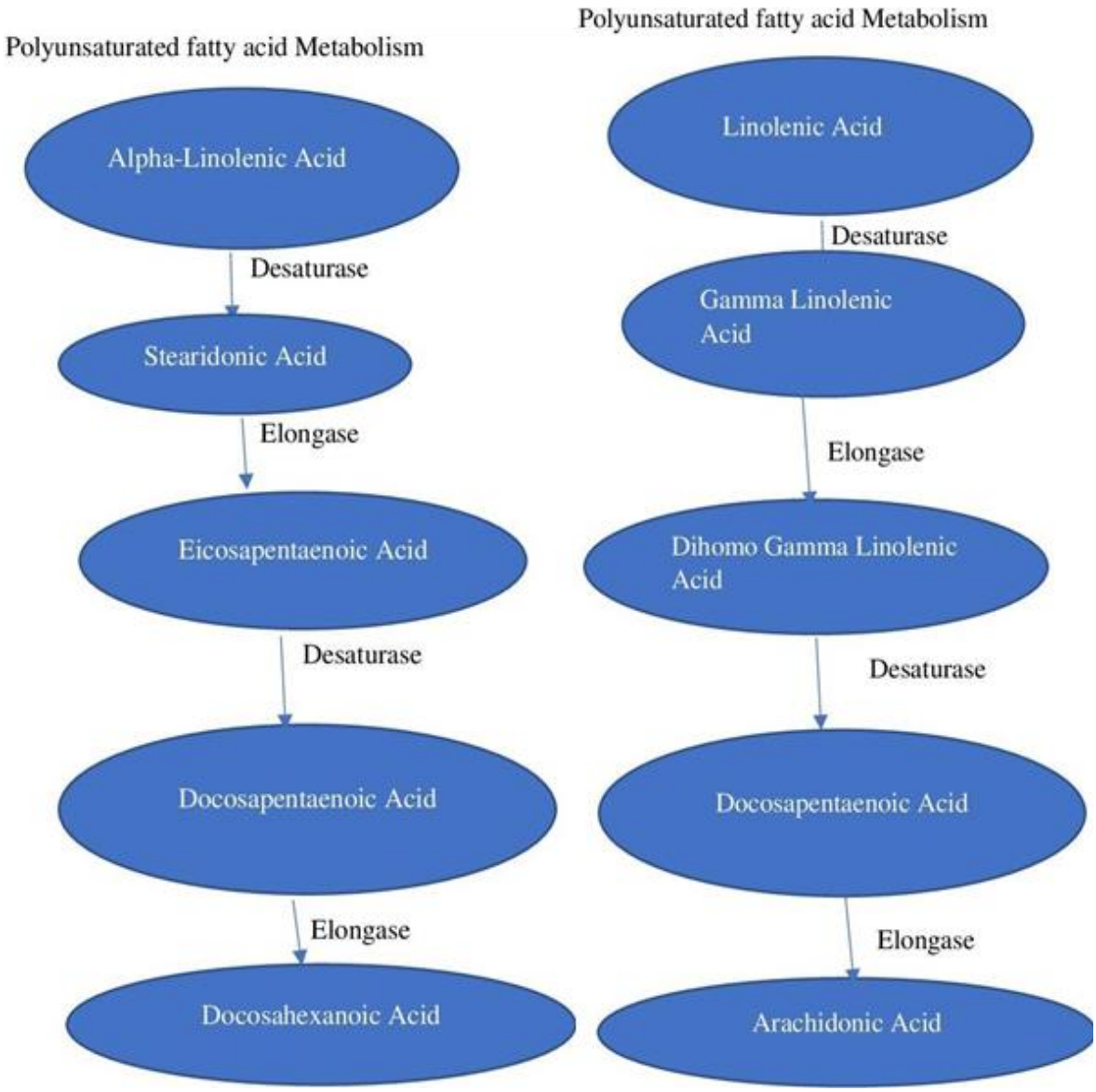

Figure 1. Polyunsaturated fatty acid metabolism.

the locomotion subscale or in sphincter control, indicating that omega-3 fatty acids exert their neuroprotective effect only in the acute phase of SCI, with no effect in chronic SCI cases. Reduced spinal cord edema, white matter cavitation, demyelination, and vessel ingrowth were observed on the 35th day after SCI in mice fed with an omega-3 diet (Emon et al., 2010). Similar effects were observed in mice fed with omega-3 acids prior to planned SCI, indicating the preventive action of omega-3 fatty acids against inflammation following neurotrauma. Ward et al. (2010) noted the beneficial effect of DHA intervention in an SCI rat model, observing that white matter damage was prevented after DHA supplementation and reduced axonal dysfunction was seen. One study showed no difference in the likelihood of depression, anxiety, or stress among respondents in traumatic SCL and non-traumatic SCL cases, with depression at 37%, anxiety at 30%, and clinically significant stress at 25% (Migliorini et al., 2009). 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 an oil-derived LC-O3PUFAs supplementation for 8 weeks prior to spinal contusion, LC-O3PUFAs were observed to regulate important biochemical signatures associated with amino acid metabolism and free radical capture. This dietary supplement helped increase reduced glucose levels (48%) and polar uncharged/hydrophobic amino acids (less than 20%), while enhancing the content of antioxidant/anti-inflammatory amino acids and peptide

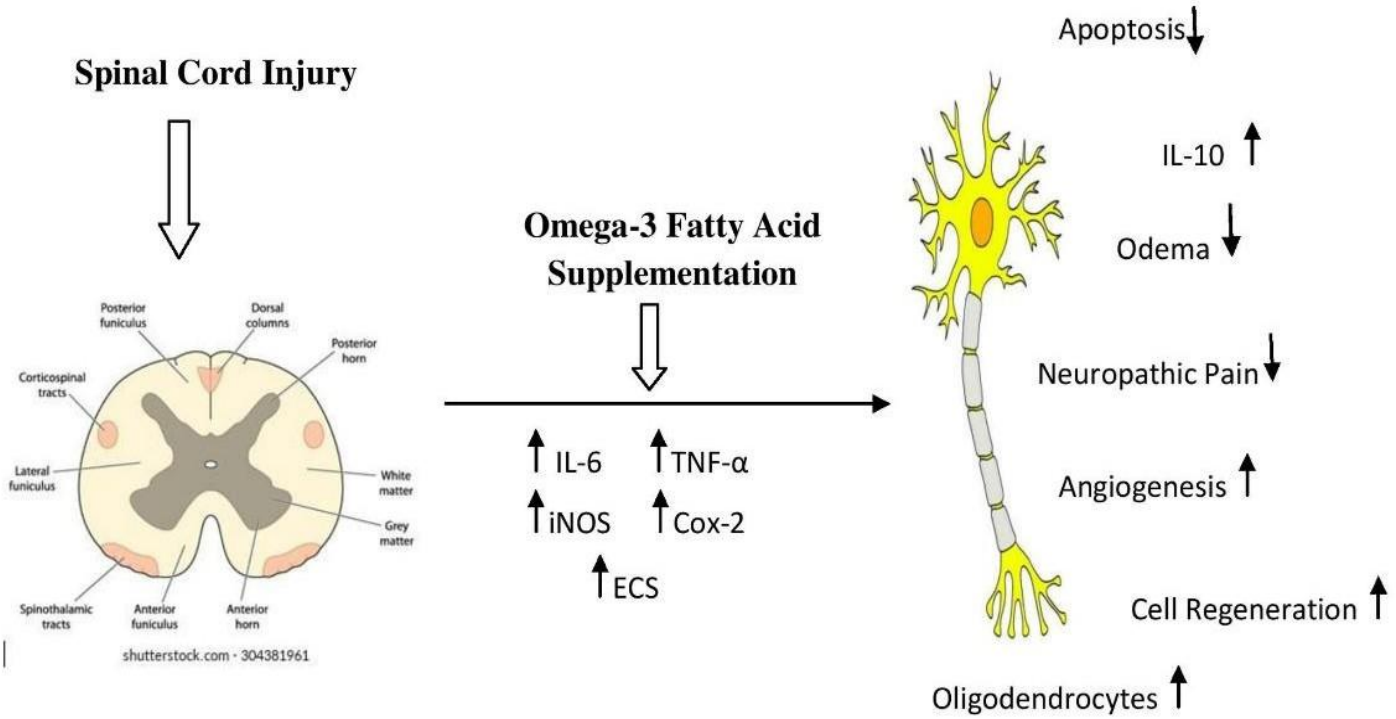

Figure 2. Role of omega-3 fatty acid supplementation after spinal cord injury in rodent model.

metabolites such as alanine (+24%), carnosine (+33%), homocarnosine (+27%), and kynurenine (+88%) compared to animals on a normal diet. An increase in neurotransmitters and mitochondrial metabolism, such as N-acetylglutamate (+43%) and acetyl-CoA levels (+27%), was reported in the PUFA supplementation group. Therefore, dietary PUFA intervention in SCI helps target global correction and improves the pro-oxidative metabolic profile characterizing SCI-mediated sensorimotor dysfunction (Figueroa and De Leon, 2014).

Mills et al. (2011) highlight the positive role of omega-3 fatty acid supplementation against diffuse axonal damage in rats. They divided the rats into three groups, with the first and second groups receiving 10 or 40 mg/kg/day omega-3 fatty acid supplementation, respectively, while the third group received no supplementation (fish oil). After 30 days of supplementation, increased omega-3 fatty acid serum levels were observed, along with a decreased number of positive axons as indicated by immunohistochemical analysis of amyloid beta precursor protein in the supplemented groups. Paterniti et al. (2014) found in an in vivo study that DHA supplementation in acute SCI helps reduce spinal cord inflammation and tissue damage. DHA supplementation led to decreased expression of proinflammatory cytokines (TNF-α), glial fibrillary acid protein (GFAP), nitrotyrosine formation, and apoptosis (Fas-L, Bax, and Bcl-2 expression), thereby aiding in the restoration of limb function. Additionally, DHA promoted neurite length and branching in the spinal ganglion, mitigating the effects of oxidative stress. Several studies have indicated that elevated EPA levels are associated with less atrophy of the grey matter in the hippocampus, parahippocampus, and amygdala in individuals over 65 years of age, and slower cognitive decline has been reported (Samieri et al., 2012).

Inflammatory/Immunological reactions

Cells of the immune system are rarely found in the central nervous system (CNS), 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 (Schwab and Zhang, 2014). 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 (Plemel et al., 2014; Popovich, 2014). However, it is assumed that it occurs in the early phase of SCI exerting a certain neuroprotective effect, which can lead to oedema and leukocyte migration, apoptosis (Yune et al., 2003), while increasing the synthesis of IL-10 and stimulating the regeneration of the axon. It also exerts a neuroprotective effect against reactive oxygen radicals (Chen et al., 2015). 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. Such that the arrest status can lead 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 (Casado-Díaz et al., 2013). 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 (Casado-Díaz et al., 2013). The aforementioned signalling 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.

Conclusion

This review primarily underscores the beneficial effects of omega-3 fatty acid supplementation, its structural aspects, and its potential health benefits across various diseases. It particularly Focus into the pathophysiology of spinal cord injury (SCI) and the impact of omega-3 fatty acid supplementation as a nutritional intervention, highlighting its ease of administration, safety, and affordability. The antioxidant and anti-inflammatory properties of polyunsaturated fatty acids (PUFAs) contribute to their neuroprotective effects against various neurodegenerative conditions such as Parkinson's disease, ischemia, and optic neuropathy. While many studies have been conducted using animal models, some investigations into cardiovascular diseases (CVDs) have involved human subjects to demonstrate effectiveness. However, despite the wealth of evidence regarding omega-3 fatty acids in SCI animal models, determining the optimal dose and duration of treatment remains a challenge, leaving researchers to rely on somewhat arbitrary criteria.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

REFERENCES

Aguiar SA, Baker SN, Gant K, Bohorquez J Thomas CK (2018). Spasms after spinal cord injury show low-frequency intermuscular coherence. Journal of Neurophysiology 120:1765-1771.

Ahuja CS, Nori S, Tetreault L, Wilson J, Kwon B, Harrop J, Choi D, Fehlings MG (2017). Traumatic spinal cord injury—repair and regeneration. Neurosurgery 80(3S):9-22. 10.1093/neuros/nyw080

Akhmetzyanova ER, Mukhamedshina YO, Zhuravleva MN, Galieva LR, Kostennikov AA, Garanina EE, Rizvanov AA (2018). Transplantation of microglia in the area of spinal cord injury in an acute period increases tissue sparing, but not functional recovery Frontiers in Cellular Neuroscience 12:5072018.

Alizadeh A, Dyck SM, Karimi-Abdolrezaee S (2019). Traumatic spinal cord injury: an overview of pathophysiology, models and acute injury mechanisms. Frontiers in Neurology 10:282.

Ambring A, Johansson M, Axelsen M, Gan L, Strandvik B, Friberg P (2006). Mediterranean-inspired diet lowers the ratio of serum phospholipid n–6 to n–3 fatty acids, the number of leukocytes and platelets, and vascular endothelial growth factor in healthy subjects. The American Journal of Clinical Nutrition 83(3):575-581. 10.1093/ajcn.83.3.575

Aarabi B, Olexa J, Chryssikos T, Galvagno SM, Hersh DS, Wessell A, Sansur C, Schwartzbauer G, Crandall K, Shanmuganathan K, Simard JM (2019). Extent of spinal cord decompression in motor complete (American Spinal Injury Association Impairment Scale Grades A and B) traumatic spinal cord injury patients: post-operative magnetic resonance imaging analysis of standard operative approaches. Journal of Neurotrauma 36:862-876.

Ayalew-Pervanchon A, Rousseau D, Moreau D, Assayag P, Weill P, Grynberg A (2007). Long-term effect of dietary α-linolenic acid or decosahexaenoic acid on incorporation of decosahexaenoic acid in membranes and its influence on rat heart *in vivo.* American Journal of Physiology-Heart and Circulatory Physiology 293(4):H2296-H2304. 10.1152/ajpheart.00194.2007

Baazm M, Behrens V, Beyer C, Nikoubashman O, Zendedel A (2021). Regulation of Inflammasomes by Application of Omega-3 Polyunsaturated Fatty Acids in a Spinal Cord Injury Model. Cells 10(11):3147.

Bentsen H (2017). Dietary polyunsaturated fatty acids, brain function and mental health. Microbial Ecology in Health and Disease 28:1281916. 10.1080/16512235.2017.1281916

Berbert AA, Kondo CR, Almendra CL, Matsuo T, Dichi I (2005). Supplementation of fish oil and olive oil in patients with rheumatoid arthritis. Nutrition 2:131-136. 10.1016/j.nut.2004.03.023

Bi J, Chen C, Sun P, Tan H, Feng F, Shen J (2019). Neuroprotective effect of omega-3 fatty acids on spinal cord injury induced rats. Brain and Behavior 9(8):e01339.

Burnside ER, De Winter F, Didangelos A, James ND, Andreica EC, Layard-Horsfall H, Muir EM, Verhaagen J, Bradbury EJ (2018). Immune-evasive gene switch enables regulated delivery of chondroitinase after spinal cord injury. Brain 141(8):2362-2381.

Campos-Staffico AM, Costa AP, Carvalho LS, Moura FA, Santos SN, Coelho-Filho OR, Nadruz W, Quinaglia e Silva JC, Sposito AC, Brasilia Heart Study (2019). Omega-3 intake is associated with attenuated inflammatory response and cardiac remodeling after myocardial infarction. Nutrition Journal 18:1-8.

Casado-Díaz A, Santiago-Mora R, Dorado G, Quesada-Gómez JM (2013). The omega-6 arachidonic fatty acid, but not the omega-3 fatty acids, inhibits osteoblastogenesis and induces adipogenesis of human mesenchymal stem cells: potential implication in osteoporosis. Osteoporosis International (24):1647-1661.

Casper DS, Zmistowski B, Schroeder GD, McKenzie JC, Mangan J, Vatson J, Hilibrand AS, Vaccaro AR, Kepler CK (2018). Preinjury patient characteristics and postinjury neurological status are associated with mortality following spinal cord injury. Spine 43(13):895-899.

Chacko V, Joseph B, Mohanty SP, Jacob T (1986). Management of spinal cord injury in a general hospital in rural India. Spinal Cord 24(5):330-335.

Chen J, Chen Z, Zhang K, Song D, Wang C, Xuan T (2021). Epidemiological features of traumatic spinal cord injury in Guangdong Province, China. The Journal of Spinal Cord Medicine 44(2):276-281. 10.1080/10790268.2019.1654190

Chen WF, Chen CH, Chen NF, Sung CS, Wen ZH (2015). Neuroprotective effects of direct intrathecal administration of granulocyte colony-stimulating factor in rats with spinal cord injury. CNS Neuroscience and Therapeutics 21(9):698-707. 10.1111/cns.12429.

Chhabra HS, Sharawat R, Vishwakarma G (2022). In-hospital mortality in people with complete acute traumatic spinal cord injury at a tertiary care center in India—a retrospective analysis. Spinal Cord 60(3):210-

215. 10.1038/s41393-021-00657-x
Cholewski M, Tomczykowa M, Tomczyk M (2018). A comprehensive review of chemistry, sources and bioavailability of omega-3 fatty acids. Nutrients 10(11):1662. 10:1662. 10.3390/nu10111662
Crowe MJ, Bresnahan JC, Shuman SL, Masters JN, Beattie MS (1997). Apoptosis and delayed degeneration after spinal cord injury in rats and monkeys. Nature Medicine 3(1):73-76.
David S, Kroner A, Greenhalgh AD, Zarruk JG, Lopez-Vales R (2018). Myeloid cell responses after spinal cord injury. Journal of Neuroimmunology (321):97-108.
Devkota P, Manandhar HK, Khadka PB (2013). Spinal Injuries in a Tertiary Care Referral Center of Western Nepal. Nepal Journal of Medical Sciences 2(2):156-159.
Ding Y, Chen Q (2022). mTOR pathway: A potential therapeutic target for spinal cord injury. Biomedicine and Pharmacotherapy 145:112-430.
Duda MK, O'Shea KM, Lei B, Barrows BR, Azimzadeh AM, McElfresh TE, Stanley WC (2007). Dietary supplementation with ω-3 PUFA increases adiponectin and attenuates ventricular remodeling and dysfunction with pressure overload. Cardiovascular Research 76(2):303-310.
Dumont RJ, Verma S, Okonkwo DO, Hurlbert RJ, Boulos PT, Ellegala DB, Dumont AS (2001). Acute spinal cord injury, part II: contemporary pharmacotherapy. Clinical Neuropharmacology 24(5):265-279.
Emon ST, Irban AG, Bozkurt SU, Akakin D, Konya D, Ozgen S (2011). Effects of parenteral nutritional support with fish-oil emulsion on spinal cord recovery in rats with traumatic spinal cord injury. Turkish Neurosurgery 21(2).
FAO (2010). Fats and fatty acids in human nutrition: report of an expert consultation. Rome: FAO: Fats and fatty acids in human nutrition. report of an expert consultation.
Fehlings MG, Agrawal S (1995). Role of sodium in the pathophysiology of secondary spinal cord injury. Spine 20(20):2187-2191.
Fehlings MG, Vaccaro A, Wilson JR (2012). Early versus delayed decompression for traumatic cervical spinal cord injury: results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). PloS one 7(2) e32037. 10.1371/journal.pone.0032037
Fernández PM, Juan S (2000). Fatty acid composition of commercial Spanish fast food and snack food. Journal of Food Composition and Analysis 13(3):275-281. 10.1006/jfca.2000.0893
Figueroa JD, De Leon M (2014). Neurorestorative targets of dietary long-chain omega-3 fatty acids in neurological injury. Molecular Neurobiology 50:197-213. 10.1007/s12035-014-8701-1
Figueroa JD, Cordero K, Llán MS, De Leon M (2013). Dietary omega-3 polyunsaturated fatty acids improve the neurolipidome and restore the DHA status while promoting functional recovery after experimental spinal cord injury. Journal of Neurotrauma 30(10):853-868. 10.1089/neu.2012.2718
Goldberg RJ, Katz J (2007). A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain. Pain 129(1-2):210-223. 10.1016/j.pain.2007.01.020
Hachem LD, Ahuja CS, Fehlings MG (2017). Assessment and management of acute spinal cord injury: From point of injury to rehabilitation. The Journal of Spinal Cord Medicine 40(6):665-675.
Hill CL, March LM, Aitken D, Lester SE, Battersby R, Hynes K., Jones G (2016). Fish oil in knee osteoarthritis: a randomised clinical trial of low dose versus high dose. Annals of the Rheumatic Diseases 75(1):23-29.
Hixson SM, Shukla K., Campbell LG, Hallett RH, Smith SM, Packer L, Arts MT (2016). Long-chain omega-3 polyunsaturated fatty acids have developmental effects on the crop pest, the cabbage white butterfly Pieris rapae. PLoS One 11(3):e0152264, 10.1371/journal.pone.0152264.
Hulbert AJ, Turner N, Storlien LH, Else PL (2005). Dietary fats and membrane function: implications for metabolism and disease. Biological reviews of the Cambridge Philosophical Society 80(1):155-69. 10.1017/S1464793104006578.
Jain M, Mohanty CR, Doki SK, Radhakrishnan RV, Khutia S, Patra SK, Biswas M (2021). Traumatic spine injuries in Eastern India: A retrospective observational study. International Journal of Critical Illness and Injury Science 11:79. 10.4103/IJCIIS.IJCIIS_95_20.
Javidan AN, Sabour H, Latifi S (2014). Does consumption of polyunsaturated fatty acids influence on neurorehabilitation in traumatic spinal cord-injured individuals? a double-blinded clinical trial. Spinal Cord 52(5):378-82. 10.1038/sc.2014.30.
Jha RK, Gupta R (2021). Traumatic Spinal Cord Injury, an Overview of Epidemiology and Management in Vindhya Region 12(2):304-307. 10.37506/ijphrd.v12i2.14136
Jiménez CF (2006). Healthier lipid formulation approaches in meat-based functional food. Technological options for replacement of meat fats by non-meat fats. Trends in Food Science and Technology 18:567-578 10.1016/j.tifs.2007.05.006
Johansson E, Luoto TM, Vainionpää A (2021). Epidemiology of traumatic spinal cord injury in Finland. Spinal cord 59(7):761-768. 10.1038/s41393-020-00575-4
Jovanović S, Savić M, Aleksić S (2011). Production standards and the quality of milk and meat products from cattle and sheep raised in sustainable production systems. Biotechnology in animal husbandry 27(3):397-404.
Kamei M, Ki M, Kawagoshi M, Kawai N (2002). Nutritional evaluation of Japanese take-out lunches compared with Western-style fast foods supplied in Japan. Journal of food composition and analysis 15(1):35-45. 10.1006/jfca.2001.1021
Kew S, Mesa MD, Tricon S (2004). Effects of oils rich in eicosapentaenoic and docosahexaenoic acids on immune cell composition and function in healthy humans. The American Journal of Clinical Nutrition 79(4):674-681. 10.1093/ajcn/79.4.674.
Kidd PM (2007). Omega-3 DHA and EPA for cognition, behavior, and mood: clinical findings and structural-functional synergies with cell membrane phospholipids. Alternative Medicine Review 712(3):207.
Kiecolt-Glaser JK, Belury M (2012). Omega-3 supplementation lowers inflammation in healthy middle-aged and older adults: A randomized controlled trial. Brain, Behavior, and Immunity 26(6):988-995. 10.1016/j.bbi.2012.05.01
Kim HS, Lim KB, Kim J, Kang J, Lee H, Lee SW, Yoo J (2021). Epidemiology of spinal cord injury: changes to its cause amid aging population, a single center study. Annals of Rehabilitation Medicine 45(1):7-15. 10.5535/arm.20148
King VR, Huang WL, Dyall SC (2006). Omega-3 fatty acids improve recovery, whereas omega-6 fatty acids worsen outcome, after spinal cord injury in the adult rat. Journal of Neuroscience 26(17):4672-80. 10.1523/JNEUROSCI.5539-05.
Kolanowski W, Laufenberg G (2006). Enrichement of food products with polyunsaturated fatty acids by fish oil addition. European Food Research and Technology pp. 472-477. 10.1007/s00217-005-0089-8.
Krishnamurthy G, Kumar G (2020). A hospital based cross-sectional study on clinical profile of patients with spinal cord injuries. MRIMS Journal of Health Sciences 8(3):61. 10.4103/mjhs.mjhs_19_20.
Kumar KA, Subrahmanyam BV, Phanidra SV, Kumar SS, Harish PN, Ramamohan P, Agrawal A (2015). Demographic Pattern, Clinical Profile and Outcome of Traumatic Spinal Cord Injuries at a Tertiary care Hospital. Romanian Neurosurgery 15:312-317.
Kumar KA, Subrahmanyam BV, Phanidra SV, Kumar SS, Harish PN, Ramamohan P, Agrawal A (2012). The relationship between localized subarachnoid inflammation and parenchymal pathophysiology after spinal cord injury. Romanian Neurosurgery 29:1838-1849.
Lalwani S, Singh V, Trikha V (2014). Mortality profile of patients with traumatic spinal injuries at a level I trauma care centre in India. The. Indian Journal of Medical Research 140(1):40.
Leaf A, Xiao YF, Kang JX (2005). Membrane effects of the n-3 fish oil fatty acids, which prevent fatal ventricular arrhythmias. The Journal of Membrane Biology 206:129-39.
Lim SNL, Gladman SJ, Dyall SC (2013). Transgenic mice with high endogenous omega-3 fatty acids are protected from spinal cord injury. Neurobiology of Disease 51:104-112. 10.1016/j.nbd.2012.10.021.
Lukaschek K, von Schacky C, Kruse J (2016). Cognitive impairment is associated with a low omega-3 index in the elderly: results from the KORA-age study. Dementia and Geriatric Cognitive Disorders 42(3-4):236-245. 10.1159/000448805
Mahadewa TG, Wardana WA, Wardhana W (2017). The difference in motor improvements related to combination of omega-3

polyunsaturated fatty acid and alpha-tocopherol supplementations diet of weight-dropped induced spinal cord injury in rats. Bali Medical Journal 6(3):S22-S25.
Matsumura K, Hamazaki K, Tsuchida A, Inadera H (2023). Omega-3 fatty acid intake during pregnancy and risk of infant maltreatment: a nationwide birth cohort–the Japan Environment and Children's Study. Psychological Medicine 53(3):995-1004.
Michael-Titus AT, Priestley JV (2014). Omega-3 fatty acids and traumatic neurological injury: from neuroprotection to neuroplasticity? Trends in Neurosciences 37(1):30-38.
Middleton JW, Dayton A, Walsh J (2012). Life expectancy after spinal cord injury: a 50-year study. Spinal Cord 50(11):803-811. 10.1038/sc.2012.55
Migliorini CE, New PW, Tonge BJ (2009). Comparison of depression, anxiety and stress in persons with traumatic and non-traumatic post-acute spinal cord injury. Spinal Cord 47(11):783-788.
Miles EA, Calder PC (2012). Influence of marine n-3 polyunsaturated fatty acids on immune function and a systematic review of their effects on clinical outcomes in rheumatoid arthritis. British Journal of Nutrition 107(S2):S171-S184.
Mills JD, Bailes JE, Sedney CL (2011). Omega-3 fatty acid supplementation and reduction of traumatic axonal injury in a rodent head injury model. Journal of Neurosurgery 114(1):77-84.
Mittal S, Rana A, Ahuja K, Ifthekar S, Kandwal P (2021). Pattern of spine fracture in Sub-Himalayan region: A prospective study. Journal of Clinical Orthopaedics and Trauma 15:27-32.
Moghadam AM, Saedisomeolia A, Djalali M, Djazayery A, Pooya S, Sojoudi F (2012). Efficacy of omega-3 fatty acid supplementation on serum levels of tumour necrosis factor-alpha, C-reactive protein and interleukin-2 in type 2 diabetes mellitus patients. Singapore Medical Journal 53(9):615-619.
Mori TA, Bao DQ, Burke V, Puddey IB, Beilin LJ (1999). Docosahexaenoic acid but not eicosapentaenoic acid lowers ambulatory blood pressure and heart rate in humans. Hypertension 34(2):253-260.
Nickel M, Gu C (2018). Regulation of central nervous system myelination in higher brain functions. Neural Plasticity.
Ning GZ, Wu Q, Li YL (2012). Epidemiology of traumatic spinal cord injury in Asia: a systematic review. The Journal of Spinal Cord Medicine 35(4):229-239.
Nirmala BP, Srikanth P, Janardhana MN (2020) Clinical and sociodemographic profiles of persons with spinal cord injury. Journal of Family Medicine and Primary Care 9(9):4890.
Noble LJ, Donovan F, Igarashi T (2002) Matrix metalloproteinases limit functional recovery after spinal cord injury by modulation of early vascular events. Journal of Neuroscience 22(17):7526-7535.
Pandey VK, Nigam V, Goyal TD, Chhabra HS (2007). Care of post-traumatic spinal cord injury patients in India: an analysis. Indian Journal of Orthopaedics 41(4):295.
Patel A, Karageorgou D, Katapodis P, Sharma A, Rova U, Christakopoulos P, Matsakas L (2021). Bioprospecting of thraustochytrids for omega-3 fatty acids: A sustainable approach to reduce dependency on animal sources. Trends in Food Science and Technology 115:433-444.
Paterniti I, Daniela I, Rosanna Di P, Emanuela E, Stacy G, Ping Y, John VP, Adina T. Michael-Titus, Salvatore C (2014). Docosahexaenoic acid attenuates the early inflammatory response following spinal cord injury in mice: *in-vivo* and *in-vitro* studies. Journal of Neuroinflammation 11:1-18.
Plemel JR, Yong VW, Stirling DP (2014). Immune modulatory therapies for spinal cord injury–past, present and future. Experimental Neurology 258:91-104.
Popovich PG (2014). Neuroimmunology of traumatic spinal cord injury: a brief history and overview. Experimental Neurology 258:1-4.
Prasad P, Anjali P, Sreedhar RV (2021). Plant-based stearidonic acid as sustainable source of omega-3 fatty acid with functional outcomes on human health. Critical Reviews in Food Science and Nutrition 61(10):1725-1737. 10.1080/10408398.2020.1765137
Puri BK, Bydder GM, Counsell SJ, Corridan BJ, Richardson AJ, Hajnal JV, Horrobin DF (2002). MRI and neuropsychological improvement in Huntington disease following ethyl-EPA treatment. Neuroreport 13(1):123-126.
Qi P, Abdullahi A, Stanojcic M, Patsouris D, Jeschke MG (2016). Lipidomic analysis enables prediction of clinical outcomes in burn patients. Scientific Reports 6(1):38707.
Rai S, Ganvir S (2019). A retrospective study of demographic profile of patients with spinal cord injury admitted in a tertiary care hospital in Ahmadnagar, International Journal of Physiotherapy and Research 7(2):1034-39.
Rajaei E, Mowla K, Ghorbani A, Bahadoram S, Bahadoram M, Dargahi-Malamir M (2016). The effect of omega-3 fatty acids in patients with active rheumatoid arthritis receiving DMARDs therapy: double-blind randomized controlled trial. Global Journal of Health Science 8(7):18.
Ramsden CE, Faurot KR, Zamora D, Suchindran CM, MacIntosh BA, Gaylord S, Ringel A, Hibbeln JR, Feldstein AE, Mori TA, Barden A (2013). Targeted alteration of dietary n-3 and n-6 fatty acids for the treatment of chronic headaches: a randomized trial. PAIN® 154(11):2441-2451.
Richter CK, Bowen KJ, Mozaffarian D, Kris-Etherton PM, Skulas-Ray AC (2017). Total long-chain n-3 fatty acid intake and food sources in the United States compared to recommended intakes: NHANES 2003-2008. Lipids 52(11):917-927.
Rowland JW, Hawryluk GW, Kwon B, Fehlings MG (2008). Current status of acute spinal cord injury pathophysiology and emerging therapies: promise on the horizon. Neurosurgical Focus 25(5):E2.
Rubio-Rodríguez N, Beltrán S, Jaime I, de Diego SM, Sanz MT, Carballido JR (2010). Production of omega-3 polyunsaturated fatty acid concentrates: A review. Innovative Food Science and Emerging Technologies 11(1):1-12. 10.16965/IJPR.2019.109
Sabour H, Norouzi JA, Latifi S, Shidfar F, Heshmat R, Emami RSH, Larijani B (2015). Omega-3 fatty acids' effect on leptin and adiponectin concentrations in patients with spinal cord injury: A double-blinded randomized clinical trial. The Journal of Spinal Cord Medicine 38(5):599-606.
Samieri C, Maillard P, Crivello O (2012). Plasma long-chain omega-3 fatty acids and atrophy of the medial temporal lobe. Neurology 79:642-650. 10.1038/s41586-020-2527-y
Schwab JM, Zhang C (2014). The paradox of chronic neuroinflammation, systemic immune suppression, autoimmunity after traumatic chronic spinal cord injury. Experimental Neurology 258:121-129. 10.1016/j.expneurol.2014.04.023.
Shahidi F, Shahidi F, Ambigaipalan P (2018). Omega-3 polyunsaturated fatty acids and their health benefits. Annual Review of Food Science and Technology 9(1):345:381. 10.1146/annurev-food-111317-095850
Shavelle RM, Paculdo DR, Tran LM, Strauss DJ, Brooks JC, DeVivo MJ (2015). Mobility, continence, and life expectancy in persons with ASIA impairment scale grade D spinal cord injuries. American Journal of Physical Medicine and Rehabilitation 94(3):180-191. 10.1097/PHM.0000000000000140
Shehab R, Saleh M, Al-Hamati K (2021). Role of Omega-3 Fatty Acid in Childbearing Age Women with Vitamin D Deficiency in Sana'a City. International Journal of Pharmaceutical Investigation 31:118-22. 10.5530/ijpi.2021.1.22
Silva NA, Sousa N, Reis RL, Salgado AJ (2014). Reis: From basics to clinical: a comprehensive review on spinal cord injury. Progress in Neurobiology 114:25-57.
Sridharan N, Uvaraj N, Dhanagopal M (2015). Epidemiologic evidence of spinal cord injury in Tamil Nadu, India. International Journal of Research in Medical Sciences 3:220-223. 10.5455/2320-6012.ijrms20150139
Stein DM, Pineda JA, Roddy VT, Knight WA (2015). Emergency neurological life support: traumatic spine injury. Neurocritical Care 23:155-164. 10.1007/s12028-015-0169-y
Tan A, Sullenbarger B, Prakash R, McDaniel JC (2018). Supplementation with eicosapentaenoic acid and docosahexaenoic acid reduces high levels of circulating proinflammatory cytokines in aging adults: A randomized, controlled study. Prostaglandins, Leukotrienes and Essential Fatty Acids 132:23-29.
Tang Y, Liu HL, Min LX, Yuan HS, Guo L, Han PB (2019). Serum and cerebrospinal fluid tau protein level as biomarkers for evaluating acute spinal cord injury severity and motor function outcome. Neural Regeneration Research 14:896-902.
Tator CH (1998). Biology of neurological recovery and functional

restoration after spinal cord injury. Neurosurgery 42(4):696-707.
Waliullah S, Sharma V, Srivastava RN, Pradeep Y, Mahdi AA, Kumar S (2014). Prevalence of primary post-menopausal osteoporosis at various sites in Indian females. International Journal of Health Sciences and Research 4(8):113-117.
Ward RE, Huang W, Curran OE, Priestley JV, Michael-Titus AT (2010). Docosahexaenoic acid prevents white matter damage after spinal cord injury. Journal of Neurotrauma 27(10):1769-1780. 10.1089/neu.2010.1348
WHO (2013). WHO | Spinal Cord Injury. WHO, Fact sheet N◦ 384. Available online at. https://www.who.int/news-room/fact-sheets/detail/spinal-cordinjury.
WHO/FAO (1994). Fats and oils in human nutrition. FAO.
Wilson JR, Cadotte DW, Fehlings MG (2012). Clinical predictors of neurological outcome, functional status, and survival after traumatic spinal cord injury: a systematic review. Journal of Neurosurgery: Spine 17(1):11-26. 10.3171/2012.4.AOSPINE1245
Wilson JR, Cronin S, Fehlings MG, Kwon BK, Badhiwala JH, Ginsberg HJ, Jaglal S (2020). Epidemiology and impact of spinal cord injury in the elderly: results of a fifteen-year population-based cohort study. Journal of Neurotrauma 37(15):1740-1751.
Witte TR, Salazar AJ, Ballester OF, Hardman WE. (2010): RBC and WBC fatty acid composition following consumption of an omega 3 supplement: lessons for future clinical trials. Lipids in Health and Disease 9:31. 10.1186/1476-511X-9-31.
Xu ZZ, Berta T, Ji RR (2013). Resolvin E1 inhibits neuropathic pain and spinal cord microglial activation following peripheral nerve injury. Journal of Neuroimmune Pharmacology 8:37-41.
Yezierski RP (2000). Pain following spinal cord injury: Pathophysiology and central mechanisms. Progress in Brain Research 129:429-449.
Yılmaz T, Turan Y, Keleş A (2014). Pathophysiology of the spinal cord injury. Journal of Clinical and Experimental Investigations 5(1). 10.5799/ahinjs.01.2014.01.0378
Yilmaz JL, Lim ZL, Beganovic M, Breazeale S, Andre C, Stymne S, Senger T (2017). Determination of substrate preferences for desaturases and elongases for production of docosahexaenoic acid from oleic acid in engineered canola. Lipids 52(3):207-222.
Yune TY, Chang MJ, Kim SJ, Lee YB, Shin SW, Rhim H, Oh TH (2003). Increased production of tumor necrosis factor-α induces apoptosis after traumatic spinal cord injury in rats. Journal of Neurotrauma 20(2):207-219.
Yusuf AS, Mahmud MR, Alfin DJ, Gana SI, Timothy S, Nwaribe EE, Idris MM (2019). Clinical characteristics and challenges of management of traumatic spinal cord injury in a trauma center of a developing country. Journal of Neurosciences in Rural Practice 10(03):393-399.
Zanarini MC, Frankenburg FR (2003). Omega-3 fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. American Journal of Psychiatry 160:67-169. 10.1176/appi.ajp.160.1.167
Zechner, D, Fujita Y, Hülsken J, Müller T, Walther I, Taketo MM, Birchmeier C (2003). β-Catenin signals regulate cell growth and the balance between progenitor cell expansion and differentiation in the nervous system. Developmental Biology 258(2):406-418.
Zhang L, Terrando N, Xu ZZ (2018). Distinct analgesic actions of DHA and DHA-derived specialized pro-resolving mediators on post-operative pain after bone fracture in mice. Frontiers in Pharmacology 9:412. 10.3389/fphar.2018.00412