

Effect of Docosahexaenoic Acid (DHA) on Spinal Cord Injury

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Abstract Spinal cord injury (SCI) has become one of the most leading concerns in the past decade. Preclinical and research studies are now ongoing trying to understand the molecular mechanisms and develop treatment strategies for this neurodegenerative condition. In the last decade, researchers have deciphered few of the leading players that play a major role in worsening the condition. But till date none of these have been applied to the clinical treatment of patients with SCI. Here in this chapter I discuss about one of the dietary requirements that could ameliorate the condition of these patients.

Keywords Spinal cord injury • DHA • Neurodegeneration • Neurotrauma • Treatment



Introduction

Spinal cord injury (SCI) has become one of the most leading concerns in the past decade. Preclinical and research studies are now ongoing trying to understand the molecular mechanisms and develop treatment strategies for this neurodegenerative condition. In the last decade, researchers have deciphered few of the leading players that play a major role in worsening the condition. But till date none of these have been applied to the clinical treatment of patients with SCI. Here in this chapter I discuss about one of the dietary requirements that could ameliorate the condition of these patients.

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The Spinal Cord

The spinal cord together with the brain forms the central nervous system (CNS). It is the most important component connecting the brain with the rest of the body. It is an extension of the brain stem into the vertebral column through the foramen magnum. The spinal cord is a cylindrical bundle of nerve fibers extending from the medulla oblongata and is well protected inside the vertebral column. The spinal cord can be divided into four different regions: cervical, thoracic, lumbar, and sacral, which are in turn divided into several segments. A pair of nerve exits from each segment. There are 31 pairs of spinal nerves corresponding to the different segments of the spinal cord. Each spinal nerve carries both sensory and motor information. This information controls not just the movement of different parts of the body, but also regulates several of the physiological processes. Many of these commands come directly from the brain, and some are regulated from within the spinal cord. In either way, the proper functioning of the spinal nerves is important in maintaining the essential bodily functions (Fig. 1).

Spinal Cord Injury (SCI)

There are about six million people living with paralysis currently that is approximately 1 in every 50 people. And one of the primary causes of paralysis is spinal cord injury (SCI). SCI currently affects about 300,000 individuals in the USA. It has become an increased cause of concern given that there is no direct cure for SCI. SCI usually results from motor vehicle accidents, falls, athletics and gymnastics, diving into shallow water and to some extent from physical violence. The number of males with spinal injuries is far more than the number of women (Fig. 2).

What Is Spinal Cord Injury (SCI)?

SCI is usually a sudden blow to the spine, that disrupts the vertebral column, and can be accompanied by fracture of bones, tear in the muscles and ligaments, and also damage to the spinal tissue. The spinal cord generally is not completely severed, but the axonal connections, nerve fibers and tracts which carry signals to and from the brain are usually affected. This is among the primary injuries which immediately result from such accidents. However, there are a series of secondary damages at the vascular, biochemical, and neuronal aspects of the functioning of the spinal cord. These secondary injuries include inflammation, hypoxia, ischemia, release of free radicals, increased apoptosis, and glial scarring. Thus, in addition to the immediate damage or disruption of the spinal cord, the following secondary injuries make the process of recovery and regeneration of the damaged neurons even more difficult. The higher the region (in the anatomy of the spinal cord), the greater is the damage. Injuries to the upper part of the spinal cord (in the cervical region) can lead to the most

Fig. 1 Illustration of the different parts of the spinal cord

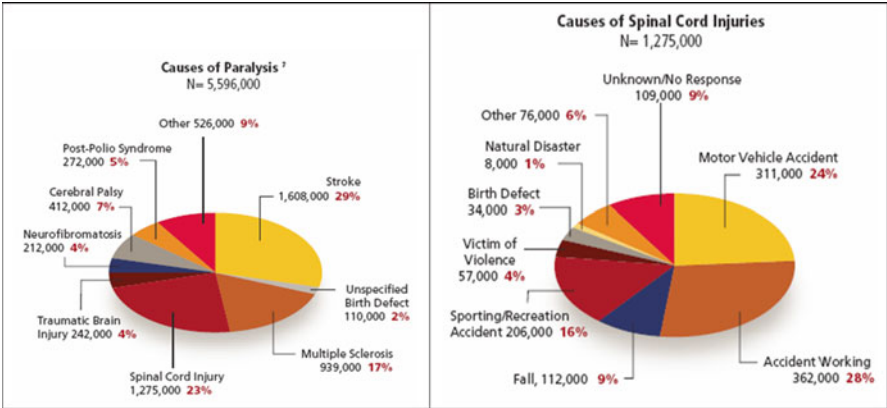
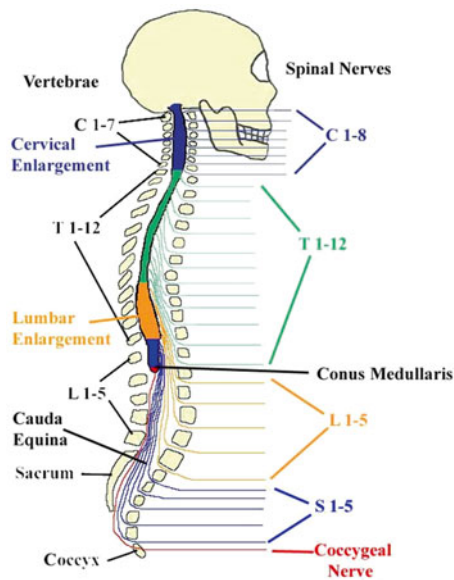


Fig. 2 Pie charts showing the causes of paralysis in general and the different causes of Spinal cord Injury (SCI)

serious injuries, amounting to total loss of movement, paralysis of arms, hands, trunk, and legs (which is also termed as tetraplegia or quadriplegia), complete dependence for everyday life activities, 24 h assistance, impairment of bladder and sexual functions. Injuries to the lower half of the spinal cord (thoracic and lumbar regions) can lead to paralysis of trunk and legs (condition termed paraplegia), partial dependence on aid, movement on a wheelchair depending on the severity of the injury. The injury can be complete or incomplete. In a complete spinal cord injury, the cord is unable to send signals or perform its function below the level of injury, leading to paralysis below the injury level. In the case of incomplete injury, there is still some sensation and function below the injury level for which it does not lead to total paralysis.

A series of damages occur at the molecular level which start after the primary injury and have long-lasting effects on the extent of damage, making it progressively worse and attenuating the recovery process. The processes include inflammation caused by the disruption of the blood–brain barrier followed by an invasion of immune cells in the area of injury, resulting in an inflammatory response killing nearby neurons and oligodendrocytes. This inflammation in turn gives rise to the production of highly reactive form of oxygen molecules called free radicals which are capable of changing the chemical structure of molecules in cells. The very common neurotransmitter in the spinal cord, glutamate is excessively released after injury, overstimulating the nerve cells and destroying them at and beyond the point of injury. Apoptosis is a very common phenomenon that sets in few days after the injury. The still surviving nerve cells which could have helped in regeneration and recovering the severed spinal cord enters the apoptotic pathway. Furthermore, excessive accumulation of astrocytes at the site of injury forms glial scar, which physically obstructs axon growth and disrupts communication with the growth factors. The initial injury which sometimes causes compression of the spinal cord blocks the blood flow, causing swelling and leaking and thus blocking nutrients and oxygen reaching the injury site. All these molecular events slow down the recovery process and sometimes make the injury progressively worse.

Treatments Currently Available

In the case of an SCI, initial medical help is very crucial to avoid further long-term injuries. At any point in time it is very important to keep the head, neck, and the body of the individual aligned till the time medical help arrives. The individual should not move unless it is necessary. Once the individual reaches the emergency room, sometimes they undergo surgery to get rid of extra fluids, fix torn tissues and other physical damages to the body. But there is literally no way to reverse the damage done to the spinal cord. Other treatments include braces or traction to immobilize the spine in order to avoid further injury, also some initial medications like methylprednisolone which if administered within the first 8 h of injury is assumed to decrease the further nerve loss and reduce inflammation. Initial treatments are critical in the sense that they definitely do not change the damage that has already been done, but does help in decreasing any further injuries or help reduce the extent of secondary injuries that will shortly follow after 1–3 days. Medical tests to diagnose the position of the spinal cord and the extent of injury include magnetic resonance imaging (MRI), neurological computerized tomography (CT), and plain X-Rays. These tests help us to know the position of the chest and the skull, exact regions of the injury, inflammation, bone fractures, bleeding, compression of the spinal cord and to know if any injury has occurred to any spinal ligaments (http://www.ninds.nih.gov/disorders/sci/detail_sci.htm).

As a later and long-term therapy comes in the physical therapy and rehabilitation which can help the patient recover slowly from the initial trauma, enabling him/her

to become more and more independent to perform everyday functions and lead a better life. These therapies help in muscle strengthening and mobility, use of assistive devices like leg braces, and wheelchairs, occupational therapy to improve fine motor skills, vocational therapy helping to get back to work, recreational therapy to engage in sports and other social activities, better adjustment of bladder and bowel movements (Tator and Benzel 2000). Controlling diet to control obesity and providing the right nutrient is an essential part of the posttraumatic treatment.

Ongoing Research with SCI

Scientists have been highly involved in studying every aspect of SCI extensively trying to understand the molecular mechanisms which make the recovery process very difficult and target molecules to change events that attenuate the process of regeneration. The challenge lies in the fact that there are multiple molecules and cells involved, each of which have their signaling cascades, making it difficult to treat the disease with just one target. More than one molecule and perhaps mechanisms have to be regulated, at the same time to achieve the goal of combating the condition.

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Currently different SCI models are being used to study the molecular mechanisms which mimic the injury type in humans. The two most commonly used models are contusion or an acute injury to the spinal cord with an electromagnetic impactor or weight-drop technique (Cheriyian et al. 2014) and the compression injury model with a specific force and for a particular duration. Other models include distraction (stretching of the cord), dislocation (mechanical displacement of the vertebrae), transection (partial or complete surgical transection), or chemical injury models (using molecules that play a role in causing the secondary injury) (Cheriyian et al. 2014).

Preclinical research for the treatment of SCI mainly revolves around the efforts of trying to modulate the signaling cascades leading to secondary damage. Several groups have been targeting different molecules which lead to excitotoxicity, oxidative stress, inflammation, blockade of regeneration. Riluzole, a sodium channel blocker, has been shown to successfully reduce excitotoxicity following SCI. This compound has been approved for ALS and is currently in the Phase I/II trial for SCI (Mu et al. 2000; Schwartz and Fehlings 2001; McAdoo et al. 2005). Minocycline, which is a synthetic tetracycline derivative clinically used to treat acne, has been shown to be highly neuroprotective in the recent years. It is known to inhibit caspase-1 and caspase-3, inhibit production of NO, decrease glutamate excitotoxicity and many others. Use of minocycline to treat animals with SCI has proved to result

in improved hindlimb function, reduced lesion size, and superior behavioral recovery when compared to commonly used methylprednisolone (Wells et al. 2003). Cethrin, an antagonist of Rho, is being used in the Phase I/II clinical trial to treat patients with complete cervical and thoracic injury. Rho, a small intracellular family of G-proteins, gets activated by glial cells at the lesion site in SCI. Cethrin, a Rho antagonist, is shown to reduce tissue damage, dampen apoptosis and thus enhance the process of regeneration, leading to improved locomotory functions (Dubreuil et al. 2003). A lot of work is also ongoing in the direction of trying mechanisms to remyelinate the demyelinated axons which have been spared during the injury.

Methylprednisolone, a synthetic corticosteroid, is currently widely used in the clinic in the treatment of SCI, after the results that came from the three trials in the National Acute Spinal Cord Injury Studies (NASCIS). However, this compound has been shown to cause various side effects, urging discovery and development of other potential therapeutic compounds for SCI.

Cellular transplants after SCI have been demonstrated to be successful in animal studies. Mouse ES cells transplanted into rats with spinal cord injury have resulted in better functional recovery (McDonald et al. 1999). The next step would be to try transplanting cells, induced pluripotent cells in human clinical trials (Nakamura and Okano 2013). Neuralstem, Inc. is in the process of Phase I clinical testing of human neural stem cells (NS1-566) in the treatment of SCI to reestablish the broken circuitry of the spinal cord, in collaboration with UC San Diego Health System. This trial is intended for four patients with complete thoracic (T2–T12) SCI and who are within 2-year time window post-injury. Success with the same cell line has been already witnessed with ALS patients.

Omega-3 Fatty Acids

It would be difficult to find an individual in the recent scientific world who is not aware of the benefits of Omega-3 fatty acids. This is just a brief recapitulation of what we already know about this particular type of fatty acid.

Biochemically, fatty acids are carboxylic acids with a long aliphatic chain which can be either saturated (with no double bonds between carbon atoms) or unsaturated (with one or more double bonds). Essential fatty acids are a class of unsaturated fatty acids which is essential for humans and other animals that cannot be synthesized and thus have to be ingested in the form of food. The most important essential fatty acid for humans is omega-3 fatty acid and omega-6 fatty acid or linoleic acid (LA). The three types of omega-3 polyunsaturated fatty acids are alpha-linolenic acid (ALA, found in plant oils), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA, fish oil). DHA can either be obtained from mother's milk or can be synthesized from omega-3 fatty acid ALA. The foods rich in omega-3 fatty acids are fish, fish oil, walnuts, flaxseed, flaxseed oil, and leafy vegetables. Since our body lacks the desaturase enzyme needed to transform omega-6 fatty acid to omega-3 fatty acids, including the abovementioned foods in regular diet is extremely essential (Fig. 3).

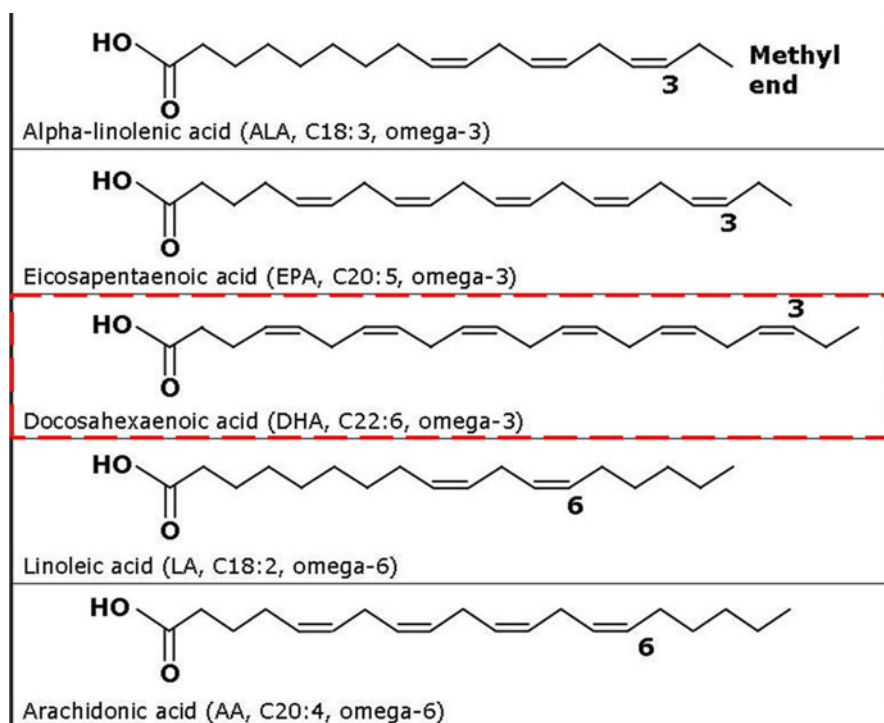


Fig. 3 Different types of essential fatty acids

Why Are Omega-3 Fatty Acids So Important?

At the molecular level omega-3 fatty acids are an integral part of cell membranes, and affect the activity of the cell membrane receptors, binding to their respective substrates, downstream signaling cascade, which will eventually either regulate the expression of various proteases, or regulate gene expression at the nuclear level. DHA is an essential component for brain and central nervous system development in infants. It is also required in adults to maintain proper neurological functioning. DHA is taken up by brain in preference to other fatty acids (Horrocks and Yeo 1999). Deficits in DHA have been associated with numerous physiological disorders like rheumatoid arthritis, diabetes mellitus, and cardiovascular disease; some forms of cancer; neurological disorders like depression, Alzheimer's disease, attention deficit hyperactivity disorder (ADHD), and unipolar disorder. DHA has been shown to help in the growth of nerves by regulating nerve growth factors. In infants, DHA in the brain helps in learning ability, and also helps to maintain neuron functioning in the case of adults (Horrocks and Yeo 1999). The multifaceted function of DHA has been well studied and is known to ameliorate the symptoms of many disorders.

DHA is also known to modulate anti-inflammatory and pro-inflammatory factors. Membrane-bound phospholipase A2 forms free DHA, which ultimately is transformed into docosatriene, a compound that inhibits inflammatory genes and pro-inflammatory factors like NF- κ B, TNF- α , which on the one hand decreases expression of pro-apoptotic proteins like Bax and Bik and on the other hand increases expression of anti-apoptotic proteins like Bcl-2. These factors eventually help in neuroprotection and cell survival (Mukherjee et al. 2004; Bazan 2006). DHA is also known to have an antioxidant effect (Ephraim et al. 2002; Satkunendrarajah and Fehlings 2013). Apart from the neuroprotective role of DHA, it seems to regulate the ion channels like sodium, potassium, and calcium (Vreugdenhil et al. 1996). Since one of the crucial secondary effects of SCI is excitotoxicity resulting from excessive release of the excitatory neurotransmitter glutamate mediated by calcium-mediated exocytosis, regulation of ion channels can provide effective means of controlling deleterious effects of over-excitability. In addition to its structural contribution, DHA seems to regulate signal transduction, gene expression, inflammation, and ion channel function (Satkunendrarajah and Fehlings 2013).

Role of DHA, an Omega-3 Fatty Acid in Treating SCI

SCI is perhaps the worst of its kind in terms of trauma, long-lasting injuries, progressively worsening conditions, and the posttraumatic challenges faced by the patient pertaining to regular life activities, emotional uncertainties of also the family members who manage extremely delicate situations in which they have to deal with the growing frustration outbursts of the patient and at the same time provide all kinds of support, emotional and physical.

Presently, with treatments for SCI still very scarce, the multifaceted properties of DHA are being applied with the intention to combat the condition from all aspects. Several groups have studied the effects of DHA on SCI, in mostly rodents, rats and mice. Different injury models have been used mimicking the injuries in humans, from commonly used compression to contusion as well as hemisection, transection, and thoracic cervical spondylotic myelopathy (CSM). Treatments include bolus intravenous injection (250–500 nmol/kg), dietary supplementation (750 mg/kg/day to 1.2 g/100 g), and also the use of transgenic mice. Treating with bolus I.V. injection of DHA resulted in improvement in locomotor function (horizontal ladder and beam walk), increase in neurons and oligodendrocytes (white matter), and reduction in the oxidation, apoptosis, and the lesion size of the injury (King et al. 2006). Pretreatment with bolus along with dietary omega-3 fatty acids on T-10 contusion NYU impactor improves bladder function, locomotor function, axonal conduction measured by transcranial magnetic motor evoked potential, survival of neurons and oligodendrocytes (Figueroa et al. 2012, 2013). Dietary supplementation of DHA

alone has shown to increase spinal cord injury learning, ameliorate expression of pro-restorative signaling molecule mRNA like BDNF, CREB, syntaxin-3 (Joseph et al. 2012; Langston et al. 2012). Bolus injection along with dietary supplementation of T-12 compression studies is shown to attenuate inflammation, oxidative stress, size of the lesion cavity, and lipid and protein peroxidation (Huang et al. 2007; Lim et al. 2012). T-12 spinal compression in rats followed by treatment with bolus DHA or along with dietary supplementation revealed reduced neutrophil infiltration and increased neuronal integrity by MAP-2 in immunohistochemistry (Ward et al. 2010; Hall et al. 2012). Treatment with fenretinide, a synthetic retinoid derivative with antioxidant and anti-inflammatory properties widely used in cancer treatments, resulted in reduced oxidative stress and inflammation measured by TNF- α , revealing a potential relationship of fenretinide positively regulating the levels of DHA homeostasis (López-Vales et al. 2010). Elevated endogenous omega-3-polyunsaturated fatty acid levels in transgenic *fat-1* mice lead to improved outcome after spinal cord injury associated with increased neuronal and oligodendrocyte survival and reduced loss of neurofilaments, microglia activation, and expression of pro-inflammatory mediators (Lim et al. 2013).

Mechanism of Action of DHA

DHA, the commonly used omega-3-polyunsaturated fatty acid, has been proved to have beneficial outcome in the treatment of spinal cord injury beyond any reasonable doubt. But the precise mechanism by which this molecule accomplishes this task is not yet well known. Several groups have been studying the mechanism, but still it is not well understood.

DHA is known to regulate transmembrane receptors like G-proteins, thus regulating a plethora of signaling cascade resulting in the receptor activation and inactivation. Also loss of DHA leads to reduced levels of phosphatidylserine (PS), indicating a possible regulation of cell signaling via PS (Salem et al. 2001). Fish oil (High DHA/EPA) increased insulin secretion but had no effect on mice deficient for GPR 120, a polyunsaturated fatty acid receptor (Furutani et al. 2015). Application of DHA for amelioration of depression revealed that the antidepressant effect of DHA is due to the translocation of Gs α from lipid raft and enhancing the actions of adenylate cyclase (Zhu et al. 2015). Neuroprotectin D1 (NPD1), derived from DHA, is shown to downregulate the expression of pro-inflammatory enzyme COX-2, and apoptosis in HNG cells and Alzheimer's disease mouse models. It also shifts the cleavage of β -amyloid precursor protein (β APP) holoenzyme from an amyloidogenic into the non-amyloidogenic pathway, thus rescuing brain cells in the early stages of neurodegeneration (Zhao et al. 2011). All these above studies suggest that the scientific community is trying to delineate the mechanism from all angles, but we are yet to join the dots.

Sources of DHA

As already mentioned, since DHA cannot be synthesized in the human body it has to be consumed as a part of the regular diet. A typical American diet contains more of omega-6 than omega-3 fatty acids, and the former tends to add up to the fat content in the system. There are a bunch of food sources that are rich in omega-3 fatty acids and are good sources of DHA like walnuts, sardines, salmon, brussels sprouts, cauliflower, tofu, green leafy vegetables with flaxseed at the top of the list. Below is a detailed table of the various food sources and their DRI/DV (Dietary Reference Intakes/Daily Value) (Fig. 4).

Commercially Available DHA

There are a dozen different types of dietary supplements of DHA, which are commercially available. These supplements are manufactured by various manufacturers and aimed at different age groups; hence, their strengths are different and also they are sometimes available in combination with other vitamins. DHA supplements are consumed by pregnant women or women who are trying to get pregnant (since the first few weeks in pregnancy are very crucial for brain and spinal cord formation) along with prenatal vitamins. Supplementary DHA is also available for lactating mothers, in the form of postnatal DHA. They are usually consumed by growing toddlers and children, who have higher needs for DHA, in order to maintain a developing brain and visual system, and are available as Kids DHA, in different kid-friendly forms, thus making it likable to kids. Also DHA is required for adults, who need to maintain proper brain functioning, retention capability, memory, and also other physiological conditions like cardiovascular function (Fig. 5).

Conclusion

The above review summarizes the challenges involved in the treatment of spinal cord injury, and discusses the potential benefits of the omega-3-polyunsaturated fatty acid, DHA as an emerging therapeutic for the same purpose.

The situation encountered by a patient suffering from SCI is very different from any other type of injury. Unlike injuries in other parts of the body, leaving out the probability of amputation of a limb, or other devastating situations beyond treatment—which sometime involve multiple fractures, lesions, bruises—injury in the spinal cord is a progressively worsening condition and leads to neurodegeneration. Patients with spinal cord injury face multiple secondary damages, which alter their way of living for the rest of their lives. Depending on the extent of injury they may require 24 h physical aid and extreme levels of assistance which cause emotional and depressing side effects, and they may have an inability to work and may

| Food Source | DRI/DV (%) | Healthiest World Ranking |
|------------------|------------|--------------------------|
| Flaxseeds | 133 | excellent |
| Walnut | 113 | excellent |
| Sardines | 61 | Very good |
| Salmon | 55 | Very good |
| Brussels sprouts | 11 | Very good |
| Cauliflower | 9 | Very good |
| Tofu | 28 | Good |
| Broccoli | 8 | Good |
| Cod | 8 | Good |
| Collard greens | 8 | Good |
| Spinach | 7 | Good |
| Kale | 5 | Good |
| Romaine Lettuce | 5 | Good |
| Green beans | 5 | Good |

Fig. 4 Various sources of DHA, ranked according to excellence

Fig. 5 Different types of commercially available DHA, dietary supplements



experience disruption of urinary and sexual functions. The families of the patients also have to undergo a lot of emotional upheavals trying to cope with this traumatic situation. There are several rehabilitation centers which provide not only physiological assistance to these patients but also the emotional support that is required for the patients and their families.

The discovery of an effective treatment for SCI is thus urgent. Since the secondary damage is multidimensional and deteriorates with time, dealing with the condition from one end will not be helpful, or if helpful at all will not be sustainable in a typically hostile condition. Therefore, a treatment which is multifaceted and can simultaneously modulate various functions at the cellular and nuclear level is required. Moreover, given the fragile condition of the patients, a less invasive or maybe noninvasive treatment is the ideal therapy desired. DHA either as injection or in regular diet or as a dietary supplement has huge potential given the improvements reported in rodent studies. Though clinical trials have to be done in human patients and this will require some time, if successful, DHA could prove to be a blessing for thousands of people currently suffering from SCI. Moreover, preclinical studies to lay out the mechanism are underway, to understand the big picture and implement it in clinical treatments.

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