

ROLE OF HYPERLIPIDEMIA IN DIABETIC NEUROPATHIC PAIN

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ABSTRACT

This article focuses on the role of hyperlipidemia in Diabetic Neuropathic Pain. It gives idea about the complex relationship between Hyperlipidemia and Diabetic neuropathic pain, exploring the potential mechanism and clinical implications. Diabetic neuropathic pain is an enfeebling complication of diabetes. According to the International Diabetic Federation, about 425 million people worldwide are affected by diabetes. More than 90% of the Diabetic subjects are affected by Distal Symmetrical Polyneuropathy. Neuropathic pain affects the somatosensory nervous system through lesions or disease resulting in the peripheral or central system. Diabetic neuropathic pain generally occurs in type 2 diabetic patients. It also gives idea about types of neuropathic pain such as Nociceptive (stimulation of peripheral nociceptors in the skin, joint, and muscle) and Neuropathic (pain generated by damage to the nervous system). In this review classification according to site of inflammation with types of Neuropathic pain is also discussed. While Hyperlipidemia (a disorder of high lipid levels in the blood) is a rooted risk factor for Diabetes, its specific contribution to Diabetic Neuropathic Pain remains unclear. Hyperlipidemia imparts Neuropathic pain through oxidative stress, endothelial dysfunction, inflammation and

altered lipid metabolism. We have described methods for inducing hyperlipidemia in animals and in humans. Triton is the drug used for inducing hyperlipidemia in animals. Many drugs such as poloxamer, cholic acid, lithium chloride may be used to induce hyperlipidemia in animals. The review also gives idea about experimental procedures which is needed for inducing hyperlipidemia, the types of subject required, and serum analysis. This review emphasizes that Hyperlipidemia can be managed by lifestyle modification; pharmaceutical mediation may help in reducing Neuropathic pain.

Keywords: Hyperlipidemia, Neuropathic Pain, Diabetic Neuropathic Pain

1. INTRODUCTION:

1.1 Neuropathic Pain:

Neuropathic pain usually occur in lesion or disease which damage the somato sensory system, it consist of central neurons and peripheral fibers of A β , A δ and C fibers, and have an effect on 7–10% of the common population [1]. Regardless of many challenges, the process of understanding the pathophysiology of neuropathic pain is increasing the expansion of personalized interventions methods and new diagnostic procedures, which accentuate the approach for the management of neuropathic pain [1]. Neuropathic pain affects the somato sensory nervous system by lesions or disease result in periphery or centrally. Some of the neuropathic pain consists of post-stroke pain, postherpetic neuralgia, trigeminal neuralgia,

and painful polyneuropathy [2]. The neuropathic pain is primarily can be diagnosed by clinical findings [3]. The main distinguishing feature in all neuropathic pain is the paradoxical coupling of sensory loss and pain, it can be with or without sensory hypersensitivity event in the painful location [4].

Neuropathic pain display Painful Diabetes Neuropathy, painful radiculopathy, Postherpetic Neuralgia, causalgia, and central pain syndrome. In presence of neuropathic pain does not prevent the occurrence of other form of pain mechanism. For example a patient with PDN may have a foot ulcer, where the predominant component of pain is inflammatory, in addition to the continuing burning neuropathic pain [5].

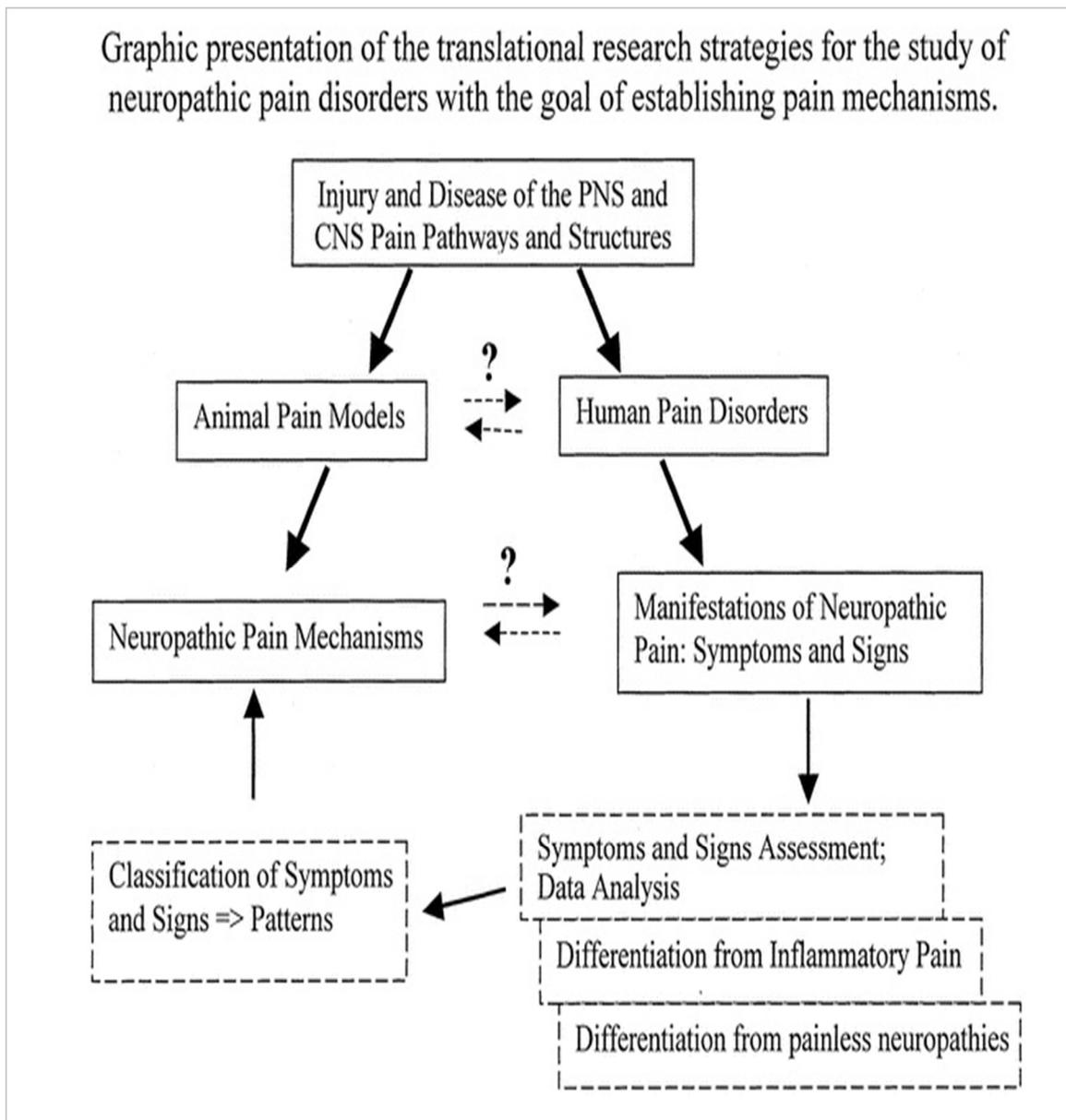


Figure 1: Thick arrows indicate established relationships between diseases of the nervous system and pain symptoms and signs, thinner arrows represent proposed and evolving relationships and processes, while dashed arrows indicate uncertain relationships. Solid line boxes represent established and published types of information, and dashed boxes represent steps that would further define pain mechanisms and complement the information from basic science regarding mechanisms

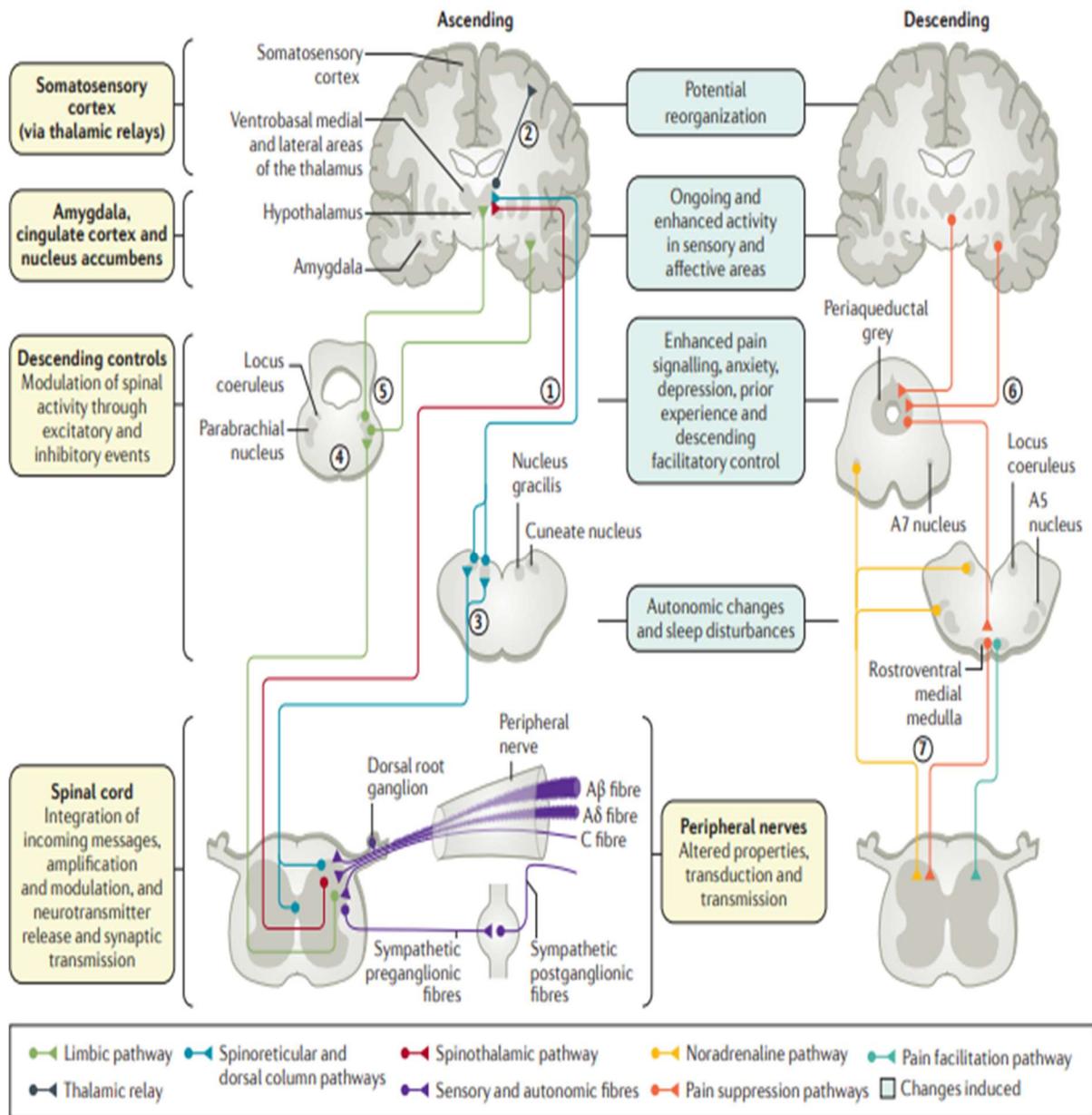


Figure 2: The peripheral and central changes induced by nerve injury or peripheral neuropathy [6]

1.2 Types of Neuropathic Pain:

Neuropathic pain broadly divided into two categories:

1) Nociceptive –It is stimulation of peripheral nociceptors in the skin, joint, and muscle.

2) Neuropathic-It may be defined as pain generated by damage to the nervous system.

In neuropathic pain there is absence of nonstop nociceptive signals whereas nociceptive pain has nonstop signals [7].

1.3 Classification of Neuropathy:

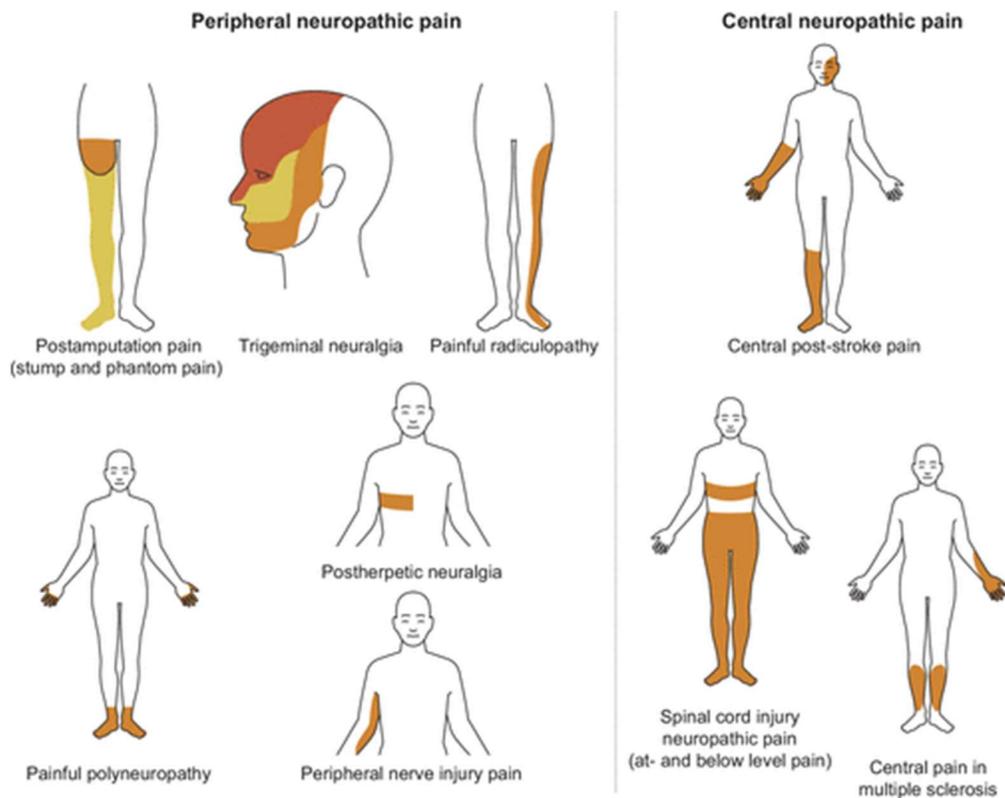


Figure 3: Classification of neuropathic pain along with neuroanatomical distribution of pain and sensory abnormalities with examples [8]

A. Trigeminal Neuralgia:

Trigeminal neuralgia is a type of orofacial pain which affects one or more divisions of the trigeminal nerve. The diagnosis of Trigeminal neuralgia depends on the patient's symptoms like electric shock, pain attacks that are sudden onset and termination, last seconds to less than 2 min, and occur impulsively on innocuous stimuli at trigger zones [8].

B. Neuropathic Pain Following Peripheral Nerve Injury:

This is a miscellaneous group of neuropathic pain occurs during surgery which is caused by

a lesion of a peripheral nerve because of a trauma. The risk of nerve damage gives link, e.g., during surgery, and the risk of developing chronic neuropathic pain but there is no clear connection between severity of injury and type of nerve damage e.g., (transecting, stretching, crushing) and the generation of neuropathic pain [8].

C. Painful Polyneuropathy:

The most common and well-described types of PPN are those due to diabetes, human immunodeficiency virus (HIV), chemotherapy, and leprosy,

etc. Microneurography has documented hyper excitability and spontaneous activity in C-fibers in painful polyneuropathy and particular spontaneous activity and hyperexcitability in mechano-insensitive C-nociceptors seems to be linked to pain, Neuronal hyperexcitability and ongoing activity within sensory neurons in chronic painful polyneuropathy, including altered expression of ion channels and receptors increased expression of reactive metabolites such as methylglyoxal altered neurotransmitter release and inflammatory factors [8].

D. Postherpetic Neuralgia:

PHN is pain that continue for more than 3 months after herpes zoster onset. Mostly occurs in the elderly and 5–20% of patients with herpes zoster. In the cranial nerve Herpes zoster is caused by reactivation of varicella zoster virus, which leads axonal transport causing inflammation and necrosis in the ganglion, nerve root, and thus the development of PHN is dermatomal [8].

F. Central Neuropathic Pain:

Central neuropathic pain occurs in the central somatosensory nervous system is pain caused by a lesion or disease. The patients with brain trauma, brain tumors, and Parkinson's disease may show Central pain [8].

Table 1: Relationship between types of pain and site of inflammation [5]

Types of pains	Inflammation
Physiological pain	Heatpulse ,pinprick
Acute inflammatory pain	Abscess,surgical incision
Chronic inflammatory pain	Rheumatoid Arthritis
Neurogenic pain inflammation	Intradermal capsaicin,complex regional pain syndrome
Inflammatory neuropathic pain	Inflammatory demyelinating polyneuropathy
Neuropathic pain	Phantom pain ,central pain

2. REVIEW FOCUSES ON HYPERLIPIDEMIA IN DIABETIC NEUROPATHIC PAIN:

2.1 Diabetic Neuropathy:

425 million people worldwide have diabetes1 which was estimates by International Diabetes Federation, it is the largest global prevalent of the 21st century [9]. Diabetic neuropathy is a distinctive neurodegenerative disorder of the peripheral nervous system that partially

targets autonomic axons, motor axons and sensory axons [9]. While our assimilation of the complexities of diabetic neuropathy has develops over the past decade, in type 1 and type 2 diabetes the distinct mechanisms underlying neuropathy still remain unknown [9]. Diabetic neuropathy can be defined as “ it is the condition in which pain occurs due to damage to peripheral nerve in people with diabetes after precluding other causes” [10].

Hyperglycemia is main cause for the development of human diabetic neuropathy [10]. Diabetic neuropathy is a descriptive term that encompasses a spectrum of clinical and subclinical syndromes with differing anatomical distributions, clinical courses, and possibly differing underlying pathogenetic mechanism [11]. The pathology of diabetic neuropathy partly responsible for nerve dysfunction and microvascular disease which leads to protein kinase C activation, advanced glycation end products, polyol pathway flux, and oxidative stress [12]. The most basic form of diabetic neuropathy is Diabetic

Sensorimotor Polyneuropathy (DSP) other diagnoses that need to be excluded :paraproteinemia, chronic inflammatory demyelinating polyneuropathy, vitamin B12 deficiency,and polyneuropathy such as familial, toxic, neoplastic, hypothyroid, uremic, and ethanol induced are other types [13]. Generally for Diabetic Neuropathic Pain treatments include antidepressants i. e Duloxetine, anticonvulsant i. e gabapentin or pregabalin and tropical treatment i. e capsaicin apart from this foot care should be kept in mind.

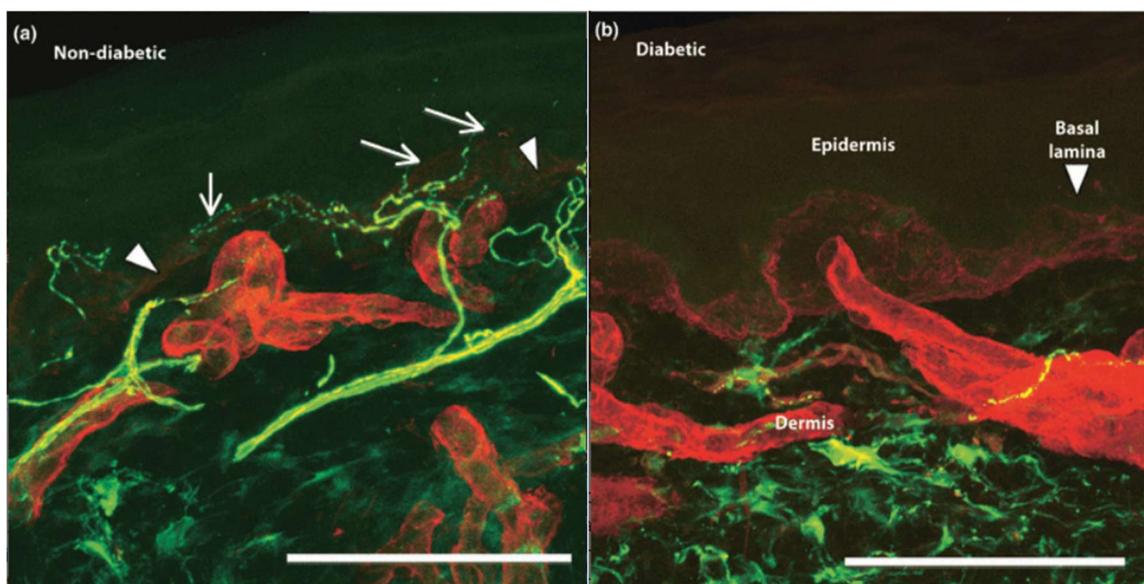


Figure 4: Epidermal innervation in diabetic patients as shown by immunostaining;with PGP9.5 [14]
(a) In a normal patient of 32-year-old man, small branching fibers penetrating to basal lamina obtained from dermis distribute diffusely and end in the surface of the epidermis of skin

(b) In a type2 diabetic patient with symptomatic neuropathy 52-year-old woman with 15 years duration of diabetes, fibers in the epidermis are completely lost. Only a few fibers are barely left in the dermis. Vascular systems also develop in the upper dermis that is red color of tortuous structure

2.2 Hyperlipidemia:

Over the last 20 years, scientific evidence has accumulated that broadly describes a link between atherosclerosis and lipoprotein disorders, and clinical demonstrates myocardial infarction, stroke, and sudden cardiac death [15]. Hyperlipidemia is a prime reason of atherosclerosis and atherosclerosis-associated conditions such as peripheral vascular disease, ischemic cerebrovascular disease, coronary heart disease and pancreatitis [16]. Cardiovascular disease (CVD) is the leading cause of death among adults, and people with hyperlipidemia are at twice the risk of developing CVD as compared to those with normal total cholesterol levels [17]. Hyperlipidemia is a disorder of high lipid level in blood. One of the main reason for hyperlipidemia is defect in lipid metabolism which is caused by the flaw in lipoprotein lipase activity or the absence of the surface Apoprotein C-II. Other causes include various genetic abnormalities and environmental factors [16]. Type IV and type V hyperlipoproteinemia patients neurological occurred as mixed types of sensory and motor peripheral neuropathy and dementia [18]. Hyperlipidemia can be classified as Modifiable and Non-modifiable risk factors hyperlipidemia [19].

Management of hyperlipidemia include medical, nutritional and lifestyle modifications which includes regular exercise, healthy diet (limit saturated fats), weight management and foot care [19]. Strict blood sugar control, lipid management, medicine for pain relief includes tricyclic antidepressants that are amitriptyline can also be helpful in managing hyperlipidemia. If hyperlipidemia is managed it can directly be helpful in managing Diabetic Neuropathic Pain.

3. Induction of Hyperlipidemia In Experimental Animals:

A single parenteral administration of Triton WR-1339 to adult rats produces a hyperlipidemia in which cholesterol, triglycerides and phospholipids increase to a maximum in about 20 hr and decrease. Thereafter evidences suggest that Triton physically alters very low density lipoproteins, rendering them refractive to the action of lipolytic enzymes of blood and tissue. This prevents or delays their removal from blood and secondarily stimulates the synthesis of lipid, enhancing the hyperlipidemia. Garattini and Paoletti performed two tests. In the "first phase" test the drug was given intraperitoneally at the same time as Triton, and a decrease in hyperlipidemia 8 hr later compared to controls

was taken as evidence of activity resulting from an inhibition of increased synthesis of cholesterol and fatty acids. In second phase the drug was given 22-24 hr after triton and decreased blood 8 hour later were compared to controls and were interpreted as drug's ability to accelerate the lipid removal [20].

Hypercholesterolemia increased with Triton dose, reaching maximum levels at about 24, 36 and 48 hr after 250, 350 and 450 mg/kg doses, respectively, and decreased thereafter. In contrast the marked hypertriglyceridemia induced by these Triton doses reached maximum levels by 24 hr and began to decrease almost immediately [20].

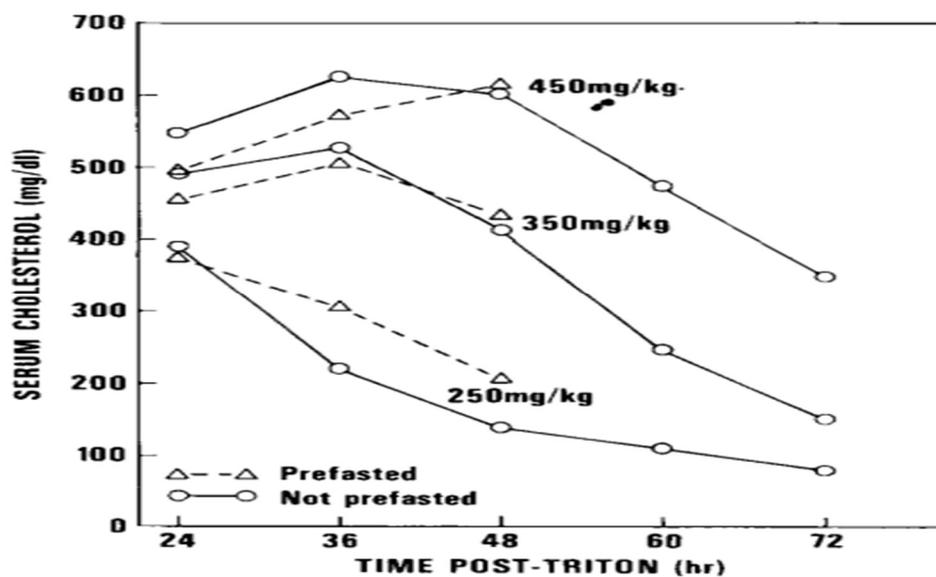


Figure 5: Effects of Triton dose and fasting on serum cholesterol

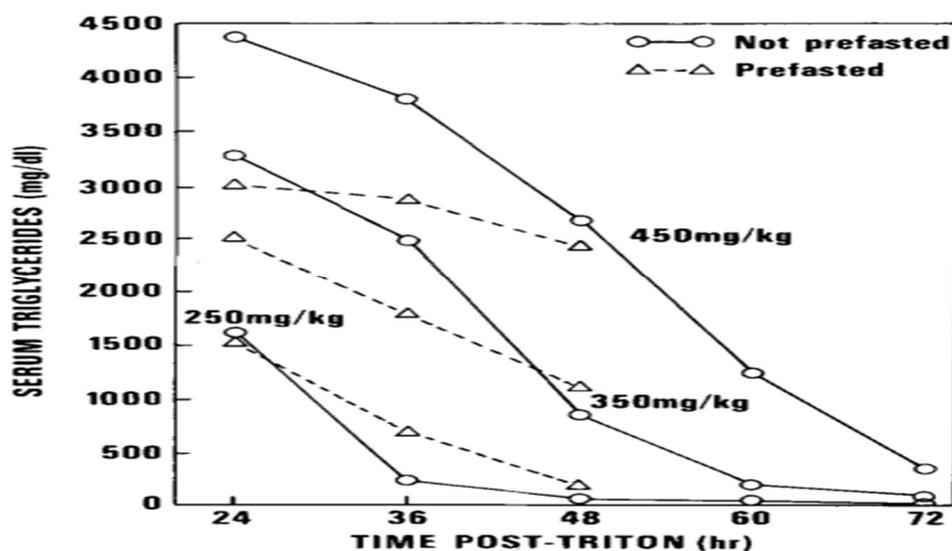


Figure 6: Effects of Triton dose and fasting on serum triglycerides

3.1 EXPERIMENTAL PROCEDURE:

3.1.1 Animals and Diet:

Male albino rats derived from the Sprague Dawley strain obtained and were housed in groups of five animals and allowed free access to food and water for at least 21 days before being distributed by weight into experimental groups. Diet was 10% coconut oil substituted for corn oil, and 18% casein and 0.2% methionine as the protein source [20].

3.1.2 Screening Procedure

Rats of average body weight 270 g (range 240-300 g) were fasted for 24 hr and were injected via a tail vein with 225 mg Triton WR-1339 /kg dissolved in 0.15 M NaCl at a concentration of 62.5 mg/ml. Rats were divided in a group of five animals each in 48 groups. Six groups were given vehicle (0.25% aqueous methyl cellulose) and others were given test sample. The total screening dose was 30 mg/kg for a 270 g rat in 4 ml. Each rat received two 2 ml doses by gastric intubation at an interval of 20 hours. Fasting was continued during the post-Triton period. After 48 hr blood was drawn. Triton administration from the abdominal aorta under sodium cyclopal anesthesia allowed clotting and serum was obtained by centrifugation [20].

3.1.3 Serum Analysis:

Serum cholesterol was determined from 1: 10 isopropanol extracts of individual samples using ferric chloride-sulfuric acid reagent in the AutoAnalyzer. Triton levels were determined by measuring absorption at 278 mp in 1:10 isopropanol extracts [20].

4. CONCLUSION:

Hyperlipidemia is a disorder of high lipid level in blood. One of the main reason for hyperlipidemia is defect in lipid metabolism. Diabetic neuropathy is a distinctive neurodegenerative disorder of the peripheral nervous system that partially targets autonomic axons, motor axons and sensory axons. Hyperlipidemia can be managed by nutritional and a lifestyle modification which includes regular exercise, healthy diet (limit saturated fats), weight management and foot care which directly reduces the diabetic neuropathic pain. Hyperlipidemia or high levels of lipids in the blood can damage nerve fiber, this leads to neuropathic pain which is high risk in diabetic patients. Therefore control lipid level can reduce Diabetic neuropathic pain. This conclusion summarizes the significance of hyperlipidemia in Diabetic neuropathic pain and suggests potential for clinical research.

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