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Muscle cramps — a mini review of possible causes and treatment options available with a special emphasis on diabetics — a narrative review

ABSTRACT

Muscle cramps are characterized by sudden, painful involuntary contraction of the muscles. The cramps sometimes become disabling and the prevalence is more in the elderly. The etiology of the cramps are diverse and some time the cramps are idiopathic. There are many underlying pathophysiological disorders like hypocalcemia, hypomagnesemia, hypothyroidism, and hepatorenal dysfunction which causes muscle cramps. Similarly, diabetes mellitus results in muscle cramps due to electrolytic imbalance, hypoglycemia, peripheral arterial insufficiency, and neuropathies. Persistent muscle pain in diabetic patients degrades the quality of life of those patients. Although the pathophysiology and etiology of the muscle cramps are understood to some extent, the same is less explored from diabetes mellitus perspective. Hence the objective of this review is to explore the underlying factors responsible for muscle cramps in diabetes so that proper strategy for pharmacotherapy can be made to manage this condition. (Clin Diabetol 2019; 8, 6: 310–317)

Key words: muscle cramps, diabetes mellitus, hypocalcemia, hypomagnesemia

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Introduction

Muscle cramps are generally painful involuntary contraction of muscles caused due to ectopic discharge from nerve terminals or nerves [1]. These muscle cramps differ from benign to sometime disabling. Hence, a detailed history and neurological examination is indispensable to identify diverse etiology of the muscle cramps [2]. According to a cross sectional study on 365 older outpatients in UK, 50% of them reported frequent muscle cramps [3]. In another review 56% out of 515 old patients reported to have muscle cramps at least once in a week [4]. However, a very limited epidemiological data is available on the prevalence of muscle cramps in patients with diabetes and in general population [5]. A demographic study conducted on diabetic patient in Toronto revealed, a 75.5% of type 2 diabetic and 57.5% of type 1 diabetic patients encountered muscle cramps [6]. In the above study, diabetic neuropathy was found to be the most important independent risk factor for muscle cramps. Bharucha et al. in their door-to-door survey analysis in a parsi community found diabetes to be the most common cause for non-compressive neuropathy [7]. The high rate in Parsis is probably related to aging population, and in urban slum, it may be due to nutritional and adverse environmental factors and needs further study. Saha et al. in his study showed an increase in age and sex specific prevalence of neurological disorders in both sexes although there was a minor dip in female population in their fourth and fifth decades [8]. A population-based survey by Gouri-Devi et al. showed a two times high rate of neurological disorders as compared to urban parts but the reasons could not be determined [9].

In diabetes mellitus, muscle cramps are a common symptom which may occur due to electrolytic imbalance, hypoglycemia, peripheral arterial insufficiency and neuropathies. These cramps generally occur in the lower extremities and the patients mostly experience it during night. The symptoms range from cramping muscle pain to burning sensation. Muscle infarction is a rare cause of acute muscle pain in diabetic patients [10]. The cramp-fasciculation and peripheral neuropathies are closely associated with muscle cramps [2]. Besides, hypocalcemia, hypomagnesemia, hypothyroidism, and hepatorenal dysfunction may also contribute to muscle cramps. Sometime these muscle cramps are idiopathic which vary in presentation from subject to subject. There are only few studies available which completely address the issue of muscle cramps in relation with diabetes. Hence, the objective of this review is to discuss completely on the pathology, cause and possible treatment modalities of muscle cramps with special attention on diabetes.

Pathophysiology and etiology of muscle cramps

Various theories have been postulated to explain the pathophysiology of muscle cramps [11].

General pathophysiology of cramps

1. Old theories

Psychosomatic theory

The psychosomatic disorder causing muscle cramps is one among the major theories postulated by olden French and German neurologist. As per Féré, muscle cramps result due to heavy exercise, nervousness, neurasthenia, hysteria or epilepsy [12].

Vascular theory

In the 1920s, vascular insufficiency during muscle contraction was believed to be the major cause of muscle cramps. Accumulation of lactic acid was believed to cause persistent involuntary contraction and muscle cramps [13]. Vascular theories were believed until the mid-1980s in central Europe. However, these theories are rejected by Santler, based on clinical common sense [14, 15].

Deformity theory

Static origin of muscle cramps is one among the theories postulated in the past responsible for muscle cramps. Muscle cramps in feet and calves' muscle are believed to be due to static deformities of the back, the pelvis, legs and feet [16, 17]. As rest removes the sources of irritation, this theory supports the argument of healing effect of the rest on exercise induced muscle cramps [18].

Myogenic theory

Another theory is postulated by Strümpell [19] who said that muscle cramps have a myogenic origin, like myotonia. He postulated that the contraction of the sarcoplasma in the muscle fibrils cause muscle cramps. Hence this pain resembles violent colics. This view was opposed by Grund, 1971 [20].

ATP deficiency theory

It is a well-known fact that muscle cramps occur due to lack of relaxation of skeletal muscles. Upon relaxation of skeletal muscles, myosin fibers get dissociated from actin. For this process to take place ATP must get attached to myosin. A paucity of ATP produces insufficient dissociation of myosin from actin [21]. In one recent study, L-carnitine proved to improve the prognosis cirrhotic cramps [22].

2. New theory

Neural origin theory

Very recent theory on muscle cramps was neural origin of cramps. A strong clinical association exists between muscle cramps and lower motor neuron diseases like amyotrophic lateral sclerosis, neuropathy and radiculopathy. These are not associated with upper motor neuron or muscular disease. Spinal reflex produced due irritation of intramuscular sensory nerve endings by toxins like arsenic, alcohol, diabetes mellitus and cholera. This leads to prolonged irritation of anterior horn nerve cells there by result in muscle cramps [23]. In another study, Klimke reported sympathetic stimulation of skeletal muscle by creatine or neurovegetative irritation is a major factor of muscle cramps [24]. The loss of motor neurons with increased age leads to muscle cramps in older people [2]. This result is espoused by a case-control study where older subjects with nocturnal cramps found to have lesser lower limb muscle-strength compared to their counter parts without nocturnal cramps [25]. Tendon shortening in advanced aged individuals due to long immobility leads to excitation of nerve terminals which in turn leads to the development of cramps.

Site of origin

The site of origin of the muscle cramps plays pivotal role in pathophysiology of muscle cramps. Many studies have suggested that muscle cramps result from a rapid penetrative firing of motor unit action potential which are set at a rate much higher than those needed for involuntary contractions. This is due to spontaneous discharges of motor nerve ending rather than a central or muscular origin [2]. The factors which contribute to muscle cramps include excitability of anterior horn cells or the intramuscular motor nerve endings.

Etiology of muscle cramps

Table 1 is a crisp presentation of etiology of muscle cramps. Table 1 summarises few of the huge number of etiologies of muscle cramps in a diabetic population and it has been found that most of them are either due to idiopathic reason or due to underlying peripheral neuropathy [6, 31]. A study of outpatient veterans reported leg cramps in 75% of those with peripheral vascular disease, 63% of those with hypokalemia, and 62% of those with coronary artery disease [5].

There is a famous case report of a 56 year old poorly controlled type 2 diabetes who experienced severely painful muscle cramps of bilateral upper and lower extremity shortly after analogue insulin injection the cause of which had been attributed to a 16% drop in potassium due to insulin injection from baseline on top of an already existing neuropathy in that patient [26]. A similar finding was observed long back in Duke University Medical Centre way back in 1992 [32].

Diabetic neuropathy and nephropathy were reported to have been associated with high incidence of muscle cramps but neuropathy seems to be an independent risk factor as well as the type of diabetes like type 2 > type 1 [6]. Towards the end of hemodialysis one third of the patients experience muscle cramps [33] which gets subsided by volume expansion with hypertonic dextrose or saline solution. Intentionally changing the sodium concentration of the dialysis fluid during the dialysis is sometimes used to preserve the plasma volume towards the end of the dialysis. This process reduces the incidence of muscle cramps in some cases [34, 35]. It is also known that any acute extra cellular fluid volume contraction cause muscle cramps. This occurs during excessive vomiting, diarrhoea or excessive sweating or diuretic therapy. About 60 percent of patients with cirrhosis reportedly have leg cramps, most of whom are older patients with advanced disease [29]. Chronic venous insufficiency also results in cramps but strangely enough the treatment has not lead to the slowing down of the course of muscle cramps [11]. Nerve damage from cancer treatment may be a cause of legs cramps, with a small study demonstrating that leg cramps were present in 82 percent of patients with cancer [30].

Muscle cramps caused due to adverse event of number of drugs, however, very few drugs reported to have caused leg cramps. The medication with intravenous iron source, raloxifene (Evista), naproxen (Naprosyn), conjugated estrogens, and teriparatide (Forteo) produced very low incidence of leg cramps [31]. Besides, clonazepam (klonopin), celecoxib (Celebrex), and gabapentin (Neurontin) also produce leg cramps, although they are prescribed for treatment of muscle cramps. It is also believed that diuretics like hydrochlorothiazide cause leg cramps [36].

Table 1. Etiology of muscle cramps (decreasing frequency in terms of association to diabetes) [11, 26–30]

Sl. No	Cause
1	Idiopathic
2	Peripheral neuropathy
3	Peripheral vascular diseases
4	Cardiovascular disorders
5	End stage renal disease on maintenance hemodialysis and acute electrolyte changes
6	Insulin induced acute drop in serum potassium levels
7	Cirrhosis of liver
8	Venous insufficiency
9	Cancer chemotherapy
10	Drug induced — intravenous iron sucrose, raloxifene, conjugated estrogens, naproxen, teriparatide, daclizumab, levosalbutamol, etc.
11	Neurological disorders like amyotropic lateral sclerosis, parkinsonism, etc.
12	Lumbar canal stenosis

Muscle cramps are associated with various diseases which cause damage to lower motor neurons including amyotrophic lateral sclerosis (ALS) [37], peripheral nerve injury [38], and polyneuropathies [39]. Cramps are more common in the above diseases compared to other lower motor neuron ailments although the cause is not very clear till date.

Due to metabolic changes during pregnancy 30% of women in their third trimester of pregnancy experience muscle cramps [40].

Pathophysiology of muscle cramps in diabetes

Data is sparse on explaining the pathophysiology of muscle cramps in diabetics and more specifically why it actually happens mostly in early morning hours. In a rodent model study on C57BL/6 male mice, it was seen that mice quadriceps centralized nuclei and caspase 3 protein increased significantly reflected by a p value of < 0.05 in both cases [41]. The data suggested that diabetes induced muscle damage by promoting a profibrotic profile. In another human study on muscle biopsy it was found that rate of ADP depletion with rest ($p = 0.008$) and oxidative phosphorylation ($p = 0.046$) in type 2 diabetic gastrocnemius muscle was impaired as evidenced by ^{31}phosphorus magnetic reso-

nance spectroscopy [42]. L-carnitine deficiency might also play an important role in diabetic mitochondrial dysfunction which has been frequently associated with muscle cramps as the deficiency has been linked to insulin resistance [43].

Mitochondrial dysfunction is another key player in causing muscle cramps in diabetics [44]. One study revealed that almost two thirds of diabetic patients suffer from muscle cramps and often they seem to harbour diabetic neuropathy [6]. Another important aspect is a high prevalence of dyslipidemia in diabetic patients for which statins have to be used and this statin cause a reduction of coenzyme Q10 which is often responsible for the muscle cramps [45, 46]. The other suggested etiologies for muscle cramps in diabetics are hypoglycemia, peripheral arterial disease, neuropathy or electrolyte imbalances [47]. In an epidemiological study it was seen that neuropathy and not nephropathy as well as type of diabetes (type 2 > type 1) were important independent predictors of muscle cramps [6].

Characteristic changes of muscles at molecular level in diabetes

Muscle related pathologies in diabetics have multiple reasons and these are summarized below.

Genetics

Gene expression alterations have been reported with type 2 diabetes. In a study, skeletal muscle biopsies taken from male subjects with type 2 diabetes, their first-degree relatives, and healthy controls were investigated at the gene expression level using the microarray technology [48]. An important finding in another study was the substantial increase in expression of genes that are involved in insulin signaling in skeletal muscle from first degree relatives of type 2 diabetics, and the significant downregulation of the same pathway in samples of type 2 diabetic skeletal muscles (Table 2) [49].

Microangiopathy

Small vessels are often abnormal in the tissues of diabetic patients. In recent years, the center of attention has been focused on the capillary basement lamina, which is a layer of amorphous material chemically resembling collagen coating the exterior of the endothelial cells. There has been widening of the capillary basement lamina in the skeletal muscle biopsies from diabetic patients. The endothelial cells appear unremarkable, but the basement lamina seems greatly widened and is often redundant and laminated with various materials in-between the lamina. In more recent years, attention has been directed to the capillary basement lamina, a layer of amorphous material chemically resembling collagen that coats the exterior of the endothelial cells. This layer is located between the blood carrying oxygen and nutrients and the tissues. Widening of the capillary basement lamina in skeletal muscle biopsies from diabetic patients. In any event, the abnormal production of basement lamina appears to be widespread in the capillary bed of patients suffering from diabetes mellitus and these capillary abnormalities have important consequences with respect to many of the lesions that occur in this disease [50].

Table 2. Significant genetic changes in pathways/functions

Gene pathway/function	p-value	Remarks
First degree relatives		
Insulin signalling	0.005	Up regulated
TGF-beta signalling	0.068	Up regulated
RNA splicing	0.089	Up regulated
Inorganic anion transport	0.74	Down regulated
Focal adhesion	0.14	Down regulated
Inflammatory response pathway	0.326	Down regulated
Type 2 diabetic patients		
Protein modification	0.979	Up regulated
Cell cycle G1 to S control reactome	0.676	Down regulated
MAPK signalling	0.002	Down regulated
Insulin signalling	0.002	Down regulated
G-protein signalling	0.078	Down regulated
Apoptosis	0.388	Up regulated

Mitochondrial dysfunction

In one recent study, it has been observed that in type 2 diabetic patients the muscle cramps are produced due to impaired bioenergetic capacity of skeletal muscle mitochondria. The study was done by taking the biopsy of vastus lateralis muscle from lean and obese nondiabetic subjects and type 2 diabetic volunteers. The electron microscopy view of the skeletal muscle revealed the presence of smaller mitochondria in type 2 diabetic and obese volunteers compared to their lean counterparts ($p < 0.01$). Similarly, the activity of rotenone-sensitive NADH:O_2 oxidoreductase enzyme was reduced in type 2 diabetic skeletal muscle compared to the healthy subjects. Hence, it was concluded that in the skeletal muscle of diabetic patient the mitochondria lose its bioenergetic capacity.

Table 3. Differential diagnosis of leg cramps

Condition	Clinical features	Diagnosis	Treatment
Claudication	Aching, sometimes cramping, deep pain brought on by exercise; relieved with rest	History Atherosclerotic risk factors Ankle-brachial index Radiographic studies	Risk factor modification Graded exercise Invasive interventions
Exercise-associated muscle cramping	Painful cramps during or immediately after exercise Palpable muscle tightening	History	Graded exercise and stretching
Hypnic myoclonus	Sudden involuntary jerking at the onset of sleep May awaken the patient	History (from bed partner)	Reassurance
Myositis, myalgias	Deep, aching pain unrelated to exertion Weakness and poor exercise tolerance Often occurs in legs, but can affect any muscle	History Elevated creatinine kinase levels (myositis) Statin use Evaluation for polymyositis and dermatomyositis	Treat underlying cause Discontinue statin
Periodic limb movement disorder	Nonpainful, repetitive, rhythmic, slow dorsiflexion of toes, knees, and hips during sleep Daytime fatigue Patient is unaware	History (from bed partner) Polysomnography	Sleep modification, including medications

Skeletal muscle lipid content and oxidative enzyme activity

In type 2 diabetes and obese patients, a reduced oxidative enzyme activity, increased lipid content and increased glycolytic activity was observed in the skeletal muscle. Insulin resistant glucose metabolism is associated with this metabolic characteristic of the muscle [38].

Differential diagnosis and evaluation of muscle cramps

Cramps related to diabetes need to be identified carefully, condition which might mimic the diabetic cramps needs to be excluded by performing relevant test or checking the medical history of the patient. Upon exclusion of the etiologies and symptoms mentioned in Table 3, the muscle cramps related to diabetes are confirmed [51].

Treatment of muscle cramps

It is indispensable to detect underlying cause of structural and metabolic disorder leading to muscle cramps in diabetic patients. Different treatment strategies can be followed to treat acute and chronic pain in diabetes. In case of acute pain non-pharmacological strategies are adapted. Stretching or lengthening the cramps muscle stops most of the acute cramps [52, 53].

In the recent past, various clinical trials were conducted to check the safety and efficacy of various drugs and nutraceuticals in diabetes induced muscle cramps. Miller et al., in the year 2001, conducted a phase III clinical trial to study the effect of gabapentin (a glutamate blocking drug) on patients with ALS. It was a double-blind randomized controlled trail on 204 patients with ALS. The result of this trial was compared with the phase II trial of the same drug conducted in smaller population and for a shorter period of time [54, 55]. Despite the positive phase II trial report, the phase III trial failed to prove the therapeutic efficacy of gabapentin in patients with ALS. The encouraging phase II data was believed to be due to by chance. Finally, it was concluded that gabapentin had no therapeutic effect on patients with ALS. In another study, 28 elderly patients were enrolled to check the efficacy of vitamin B complex (including vitamin B_6 30 mg/day) in reducing the nocturnal leg cramps. After three months of treatment (vitamin B complex capsule TID) 86% of patients experienced remission from muscle cramps [56]. The patients were not known to be suffering from any vitamin deficiency compared to placebo group.

Naftidrofuryl, a vasodilator was studies in a cohort of 14 subjects suffering from rest cramps (night cramps). The effect of this drug on cerebrovascular and peripheral vascular disease was well established before. However, Young and Connolly in the year 1993, could establish its significant remedial effect on the rest cramps [57]. Naftidrofuryl could significantly reduce cramps frequency in the patients ($p < 0.004$) in this double-blind placebo-controlled trial. This drug enhances the utilization of glucose and oxygen in peripheral vascular disease and protect brain parenchyma during anoxia.

Diltiazem hydrochloride, a calcium channel blocker, used in hypertension was studied for the management of muscle cramps. In this cross-over double-blind study, 13 patients who experience two or more cramps per week were treated with 30 mg of diltiazem hydrochloride. There was a significant ($p < 0.04$) reduction in the number of cramps in drug treated group compared to placebo [58]. This study proved the therapeutic potential of diltiazem in the management of muscle cramps.

As per recommendation of American Academy of Neurology, vitamin B complex, calcium channel blockers such as diltiazem and naftidrofuryl are effective and can be considered for use in the management of muscle cramps (level C). It has also been recommended to avoid the use of quinine derivatives (level A) owing to their potential toxicity [59]. However, quinines can be used for an individual therapeutic trial upon confirmation on the management of potential adverse effect if any.

Oxidative stress was believed to have an effect on the development of insulin resistance [60] and in some studies treatment with antioxidants seemed to improve glycine control in type 2 diabetic patients by scavenging the reactive oxygen species [61, 62]. In one recent study, high dose of vitamin E supplementation found to improve insulin action by reducing the plasma fasting insulin and glucose levels. There was also substantial decline in cellular oxidant stress and inflammatory activity [63]. Hence, in case of diabetic muscle cramps vitamin E can be used as supplement with the first-line treatment.

The effect of L-carnitine supplementation in the management of cirrhotic muscle cramps is discussed in the previous section. However, in a recent study [64], L-carnitine supplementation (600 mg/day PO for 4 months) was found to improve the quality of life of diabetic patients suffering with muscle cramps. Hence, L-carnitine supplementation can be considered as an ideal strategy to manage muscle cramps in diabetic patients.

Role of ubiquinone

Two forms of Co-enzyme Q10 (CoQ10) namely ubiquinone (oxidized form) and ubiquinol (reduced form occurs naturally in human body [65] and other anaerobic organisms. The production of this enzyme reaches at its highest during mid-twenties and gradually declines with age. The concentration of this enzyme gets reduced to 50% by the time people reach 60 years of age [66]. In the recent past, it was reported that a significant decline in the level of CoQ10 in patients with type 2 diabetes is correlated with an increased plasma glucose level, HbA_{1c} and other oxidative stress markers [67].

The rate limiting enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) is instrumental in the mevalonic acid path way, cholesterol biosynthesis and synthesis of CoQ10.The inhibition of HMGCR, serious muscle injuries (e.g. myopathy, myositis and rhabdomyolysis) are the adverse events of statins (e.g. atorvastatin) used in the treatment of hypercholesterolemia in type 2 diabetes [68, 69]. Hence, CoQ10 supplementation for statin induced muscle symptoms have opened a new avenue in the complementary management of statin-induced myopathy in type 2 diabetic patients [70].

Special focus of muscle cramps in diabetics

The complication of muscle cramps is a very common one in our type 2 diabetic patients and the treatment should be addressed to the underlying cause if possible or else it should be treated as per the above regimen of use of co-enzyme Q10 as part of idiopathic etiology. A summary of treatment in diabetics is shown below in Table 4 as per the major contributing factors towards cramps.

Table 4. Causes and treatments of muscle cramps in diabetics

Cause	Treatment
Peripheral neuropathy	Standard treatment for neuropathy with tricyclic antidepressants, pregabalin, gabapentin
Peripheral vascular diseases and cardiovascular diseases	Stenting if needed, smoking cessation, cilostazol, standard treatment with statins and aspirin and clopidogrel
ESRD on maintenance hemodialysis	Changing the sodium concentration of the dialysis fluid during the dialysis; treating underlying co-existent neuropathy

Conclusion

Muscle cramps in diabetes reduce the quality of life of patients. Diagnosis of muscle cramps in diabetic patients is a common problem in clinical practice. However, the mechanism and underlying cause is less well understood till date. Hence, the diagnosis of muscle cramps should prompt the physician to look for any associated comorbidities like peripheral neuropathies, metabolic disorders, cirrhosis, immune mediated myositis, and ALS etc. Although the availability of treatment is less, the physician should carefully plan the treatment protocol to manage the cramps thereby improve the quality of life of patients living with diabetes.

Ethics policy

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of interest

All the authors have declared to have no conflict of interest.

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