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A NARRATIVE LITERATURE REVIEW ON EFFECT OF PULSED ELECTROMAGNETIC FIELD THERAPY IN DIABETES MELLITUS TYPE 2 AND IT'S POSSIBLE MECHANISM OF ACTION

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ABSTRACT

Introduction: Diabetes Mellitus Type 2 (DM2) is one the common conditions prevalent worldwide. Pulsed Electromagnetic Field (PEMF) therapy is a novel advanced electrotherapy modality used by physiotherapy professionals worldwide for a number of conditions including DM2. But, there is a lack of literature on understanding the efficacy and mechanism of action of action of PEMF therapy in individuals with DM2.

Methods: A narrative literature review was conducted. Keyword search included {'PEMF' AND ('DM2' and its related conditions)}. Databases searched include PubMed; Medline; PEDro; Google Scholar and other database resources. Each selected study was described in brief. 97 research articles were identified initially. 90 research articles were later rejected depending on the eligibility criteria. Only seven research articles were finally included in the narrative literature review.

Results: Seven experimental research articles were included in the narrative literature review. PEMF was found having a beneficial effect in management of DM2 and its related conditions.

Discussion: Seven research articles included in the narrative literature review were mainly analysed for the type of study, aim, demographics of participants, intervention protocol, treatment duration/ follow up, parameters assessed and results/findings. It was found that mainly PEMF induces nitric oxide synthesis in the body hence; it helps in normalizing blood glucose levels in individuals with DM2 and its related conditions.

Conclusion: PEMF should be used in management of DM2.

Implications: Up-gradation in Physiotherapy Practice; creating an evidence base for role of PEMF in DM2;

Keywords: PEMF, DM2, Narrative Literature Review

INTRODUCTION

Diabetes Mellitus Type 2 (DM2) accounts for almost 90% of all cases of diabetes. In DM2, the response to insulin is reduced, and this is known as insulin resistance. During this state, insulin is ineffective and is initially countered by an increase in insulin production to maintain glucose homeostasis, but over time, insulin production reduces, resulting in DM2. DM2 is most commonly observed in individuals over 45 years of age. Yet, it is increasingly seen in children, adolescents, and younger adults too due to rising levels of obesity, physical inactivity, and energy-dense diets.[1] As per the projections given by International Diabetes Federation (IDF), globally,numberofDM2patients in 2030 would be approximately 550 million. It is expected to cross 100 million inI ndia, by 2030. [2]

A malfunctioning of the feedback loops between insulin action and insulin secretion results in abnormally high glucose levels in blood is the main underlying pathophysiology in DM2. In the case of β-cell dysfunction, insulin secretion is decreased, limiting the body's capacity to maintain physiological glucose levels whereas on the other hand, insulin resistance contributes to increased glucose production in the liver and reduced glucose uptake both in the muscle, liver and adipose tissue. Even if both processes take place early in the pathogenesis and contribute to the development of the DM2, β-cell dysfunction is usually more severe than insulin resistance. Thus, when both β-cell dysfunction and insulin resistance occurs, hyperglycaemia is amplified leading to the progression of DM2.[3]

Some of the common physiotherapy approaches used for the management of various conditions includes exercise therapy, electrotherapy, and manual therapy techniques such as kinesiology taping.[4-7]

Pulsed electromagnetic field (PEMF) therapy is one of the advanced electrotherapy modalities used currently. It is an invisible and non-invasive therapy which is administered by influencing the individual either generally or locally with a magnetic field packed in impulse bundles. Frequency of PEMF therapy ranges between 0.25 and 50 Hz. Electrical energy is used to conduct a series of magnetic impulses through the particular body tissue. This leads to each magnetic impulse inducing tiny electrical signals that stimulate and provide a virtual message for the particular cells. Mitochondrion also known as the powerhouse of the cell which absorbs PEMF therapy waves, which activates a series of reactions to increase and store more cellular energy in the form of adenosine triphosphate. Thus, stimulates the biological function of cells, tissues and body systems within the individual resulting in raising the overall vital energy of the individual. Following are some of the physiological effects of PEMF therapy: a. Enhances capillary formation; b. Accelerates nerve regeneration; c. Enhances synthesis of proteins; d. Increases permeability of cells; e. Increases availability of nitric oxide; f. Increases removal of waste products. [8]

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PEMF therapy is one such treatment approach which is supported by very promising results. Recently, researchers have demonstrated improvements in patients with DM2 after using PEMF therapy.[9]
However, at present, there is a dearth of literature on availability of narrative literaure reviews in regard to the effect of PEMF therapy in individuals with DM2. Also, it is very important to understand the mechanism of action of PEMF therapy in individuals with DM2. The aim of this study is to conduct a narrative literature review of research articles on the efficacy of PEMF therapy in individuals with DM2 and to understand the mechanism of action of PEMF therapy in individuals with DM2

MATERIALS AND METHODS

SEARCH STRATEGY

A comprehensive database search was conducted using PubMed, Scopus, Cochrane Library, MedLine, PEDro, Google Scholar and also searched for any available relevant studies in grey literature that assessed the efficacy of the PEMF therapy on diabetes mellitus and its related complications. The search was performed by using the following key words **"'Pulsed Electromagnetic Field Therapy' And ('Diabetes Mellitus' Or 'its related complications')".** The reference lists of most relevant studies were scanned for studies to be included in the narrative literature review. Bias was avoided as two different authors are reviewing the articles independently and wherever a question of dispute arose a third author intervened. All research articles till 19thOctober, 2020, were included in the search. Two independent investigators (NG and TP) conducted the search. Wherever a disagreement arose, it was settled by the intervention of a third author (NW) to resolve the dispute. All disagreements were resolved after a consensus was reached between the three authors. Therefore, bias was aptly avoided, as two author reviewers were involved, and if required, a third author reviewer also intervened whenever necessary.

STUDY SELECTION

All relevant research article titles and abstracts were screened from the relevant databases. After retrieving the potentially relevant studies, full texts were read to apply the eligibility according to the following inclusion criteria: (1) Use of pulsed electromagnetic field therapy, (2) Prospective Study Design, (3) English language, (4) Diabetes Mellitus or its related complications, (5) Published / Black Literature, (6) Unpublished / Grey Literature. Exclusion criteria was determined by (1) Animal studies, (2) Complete study not available, (3) Associated with other ailments, (4) PEMF therapy applied along with surgical intervention, (5) Pregnant females[10]

DATA COLLECTION AND EXTRACTION

Two independent investigators (NG and TP) retrieved all the information and matched for consensus. The main outcome of interest was reviewing the effect of pulsed electromagnetic field therapy in diabetes mellitus and its related complications. Thus, after the application of the eligibility criteria, studies were analyzed based on aim of the study, duration/ follow up, intervention protocol, outcome measures or parameters assessed, and most significant results. In addition, the description of the PEMF devices used in the various studies for the treatment of diabetes mellitus type 2 and its related conditions was also analyzed, along with the additional information reported of the device used.

RESULTS

STUDY SELECTION

A total of 97 articles were initially selected through database searching based on title and abstract. Only seven research articles were found to be relevant to the search strategy incorporated which were analyzed in detail. The exclusion of articles from the narrative literature review was mainly due to the full text being not available; surgical procedure used to apply PEMF; duplicates of research article; research articles in non-English language or other languages, or it was associated with other physical ailments along with diabetes mellitus type 2 and other related conditions. A total of 90 articles were excluded from the narrative literature review. Finally, only seven articles were selected in the narrative literature review.

DESCRIPTION OF STUDIES

Table one presents the characteristics of the seven included original research studies. Overall, the studies included a total of 219 participants. All the included participants reported complaints of either DM2 or its related conditions; however, with different aetiologies like: DM2 and DM2 complications like diabetic polyneuropathy or neuropathy, peripheral blood circulation and diabetic foot ulcers.[9, 11-17]
The inclusion criteria varied across all the research articles included in the narrative literature review. Nonetheless, across the included research articles, a few similarities were found among the research articles. All the research studies were done in an adult population above 18 years of age, with clinically evaluated DM2 and its related conditions. Pregnancy or planned pregnancy and presence of cardiac pacemaker or other electronic implants was a common exclusion criterion among most of the included studies reviewed. The other exclusion criteria were study specific exclusion criteria in the respective research articles.

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Table two shows one review, six randomised controlled trials and one pre- post design included in this narrative review. The best level of evidence was 1b for six articles and 2b for the pre-post design study.
Table three shows the PEDro score rating of each of the research articles included in the narrative review. The worst PEDro score was for a study with a score of 3. The best PEDro score was 8 for four of the research articles in the narrative review.
Seven experimental design studies were included in the narrative literature review. The PEMF therapy was often compared with sham treatment or pharmacotherapy or other electrotherapy modality or exercise therapy regimen. Moreover, the studies showed heterogeneity concerning the PEMF therapy protocols, where the duration of application varied from 12 days to 60 days, and the frequency of application from twice a day for 60 days to a single time intervention. [9, 11-17]

The parameters assessed includedWound healing (Wound Surface Area); Neuropathy; Blood Glucose Control (HbA1c);Blood Flow (Blood flow velocity and diameter of the small vein by ultrasound biomicroscopy, Microcirculation at skin over base of first metatarsal bone and distal first phalanx, Microvascular red blood cell (RBC) perfusion, Volume concentration of moving RBCs, RBC speed, Temperature in the Plantar skin measured by laser Doppler flowmetry); Inflammation; Oxidative Stress; Motor Nerve Conduction Velocity (distal latency, amplitude, nerve conduction velocity); Pain - (SFMPQ-VAS); Sleep – MOS Sleep Scale; Quality of Life (EuroQoL EQ-5D); Skin Biopsy; Patient reported outcomes (Perception of pain, Concomitant medication use, Adverse events). [9, 11-17]

DISCUSSION

The main finding of this narrative literature review is that PEMF therapy seems to have a therapeutic effect in DM2 and its related conditions. PEMF therapy has found to be effective in the management of DM2 and its related conditions. It has found to be a safe and reliable tool for the treatment of DM2 and its related conditions.
The findings from the research articles included in the narrative literature review was that PEMF therapy has a positive attributes towards wound healing, chronic pain and neuropathy.[9]
PEMF was caused a reduction in pain and statistically significant improvement in distal latency and nerve conduction velocity.[9, 12, 14] PEMF could modulate neuropathic pain and nerve impulse due to decrease in endoneural hypoxia, perineural edema, ischemia of peripheral nerves and improved microcirculation.[9, 12] A significant improvement in microvascular red blood cell perfusion, volume concentration of moving RBCs (V), RBC speed (U) and temperature (T) in the plantar skin.[9,13] It was also found to reduce the wound surface area.[9,16]

It is commonly found in individuals with DM2, a reduced synthesis of Nitric Oxide which happens to be a key underlying pathophysiology in DM2.[18] PEMF therapy plays a very important role in boosting the synthesis of Nitric oxide in the human body.[9] Therefore, the key mechanism of action for the efficacy of PEMF therapy in individuals with DM2 is that PEMF helps in the synthesis of Nitric Oxide which helps in normalizing the diseased state in DM2. Also, PEMF therapy enhances capillary formation; accelerates nerve regeneration; enhances synthesis of proteins; increases permeability of cells; and increases removal of waste products. Thus, aids in the treatment of DM2 and its related complications. [9] Therefore, PEMF therapy can be included in the management of DM2 and its related conditions as an alternative or as an adjunct to pharmacotherapy. But, there is a need for more extensive research to be carried out to study the effects of PEMF therapy in individuals with DM2 and its related conditions. More case series, clinical trials and systematic reviews ought to be conducted to study the efficacy of PEMF therapy in individuals with DM2 to create more evidence based practice.

STUDY LIMITATIONS

To the best of our knowledge, no other narrative literature review has investigated the therapeutic effects of PEMF specifically on DM2 and its related conditions. Moreover, two independent reviewers were used for screening and critical appraisal, and wherever a disagreement or dispute arose, a third reviewer intervened and resolved the disagreement amicably with consensus. Therefore, bias in the study was reduced.
First, the low number of studies available on the scientific literature investigates that the effectiveness of PEMF on DM2 and its related conditions is scarce. Another limitation is the small size of the sample of the research studies sample included in the narrative literature review, which should be larger to provide power to the conclusion taken from the results. The wide range of devices and the wide range of DM2 and its related conditions precluded the systematization of quantitative data. Therefore, this study could not be converted into a systematic review. The search was restricted to English language research studies; however, previous narrative literature reviews demonstrated that restriction to English language does not provide any additional bias.

CONCLUSION

The evidence within this narrative literature review demonstrates that the PEMF therapy seems to be able to have a therapeutic effect on DM2 and its related conditions. Moreover, when PEMF therapy is added to a standard therapy protocol, it seems to hardly add any harmful effect in DM2 and its related conditions. However, due to the low risk

associated, PEMF therapy can be a potential alternative or adjunct to pharmacological therapy. The lack of studies in this theme warrants further research on PEMF effects on DM2 and its related conditions, with standardized protocols, larger samples, and adjustment for DM2 and its related conditions confounders to achieve stronger conclusions.

Table 1: Characteristics and main results of the included research articles

References	Type of Study	Aim	Duration / Follow-Up	Intervention Protocol	Parameters Assessed	Results
Graak V. et al[11]	Randomised Controlled Trial	To evaluate and compare the effect of low power, low frequency pulsed electromagnetic field of 600 and 800 Hz respectively in management of patients with diabetic polyneuropathy	12 days	N= 30 Group 1 (n1=10) – 600 Hz; Group 2 (n2=10) – 800 Hz; Control Group (n3=10)	• Neuropathy; - Pain - Motor Nerve Conduction parameters (distal latency, amplitude, nerve conduction velocity	• Significant reduction in pain and statistically significant improvement in distal latency and nerve conduction velocity • PEMF can modulate neuropathic pain and nerve impulse due to decrease in endoneural hypoxia, perineural edema, ischemia of peripheral nerves and improved microcirculation • Limitation: Small sample size, Short duration of treatment, non-availability of follow-up data
Sun J. et al[12]	Randomised Controlled Trial	To study whether PEMFs would increase blood flow velocity of the smallest observable vein in people with or without Diabetes Mellitus	One time intervention	N= 43 Group 1 (n1=22) – Diabetes Mellitus; Group 2 (n2=21) – Healthy participants	• Blood circulation - Blood flow velocity and diameter of the small vein by ultrasound biomicroscopy - Microcirculation at skin over base of 1st metatarsal bone and distal 1st phalanx measured by laser Doppler flowmetry	• PEMF increases peripheral blood flow but not general microcirculation in individuals with or without DM
Wrobel M. et al[13]	Randomised, placebo controlled, double blinded	To assess whether a low frequency magnetic field can influence pain intensity, quality of life and sleep , and glycemic control in patients with painful diabetic polyneuropathy	3 weeks, 20 min a day, 5 days a week	N= 61 Group 1 (n1=32) – low frequency magnetic field Group 2 (n2=29) – sham exposure	• Pain - (SFMPQ-VAS) • Sleep – MOS Sleep Scale • Quality of Life (EuroQoL EQ-5D At the beginning and after one, two, three and five weeks • HbA1c - - at baseline and after 5 weeks	• Significant reduction in pain intensity • Extent of pain reduction did not differ significantly between the groups • Both groups had similar improvements in in EuroQoL, MOS and HbA1c values
Sharon T[14]	Grey literature – Pilot Study	To provide an evidentiary basis for using PEMF therapy in a primary care setting to promote microvascular angiogenesis and thereby prevent skin ulceration	10 – 22 treatments with a Diapulse PEMF device	N= 7; individuals between 54 to 65 who have diabetes mellitus type 2 and some level of Diabetic lower extremity ischemia (DLEI)	A laser Doppler flowmeter was used to assess • Microvascular red blood cell (RBC) perfusion • Volume concentration of moving RBCs • RBC speed • Temperature In the Plantar skin	• Significant improvement in microvascular red blood cell perfusion, volume concentration of moving RBCs (V), RBC speed (U) and temperature (T) in the plantar skin, Inclusion of PEMF for treating chronic wounds should be considered
Battecha K. et al[15]	Controlled trial	To investigate the effect of Pulsed Electromagnetic Field on pain and nerve conduction velocity in patients with diabetic peripheral neuropathy	3 times per week for 4 weeks	N= 30; individuals between 40 to 50 who have diabetic neuropathy of both sexes Group A (n=15) PEMF Frequency = 50 Hz, Intensity =20G; Group B (n=15) – Traditional Physical	• Pain – Visual Analogue Scale • Peroneal Nerve Conduction velocity by computerized electromyography	• Significant reduction of pain intensity by visual analogue scale and significant improvement of peroneal nerve conduction velocity in PEMF group • It could be concluded that PEMF combined with traditional physical therapy program has a positive effect on diabetic neuropathy symptoms
Padma K.et al[16]	Pre- Post Study	To evaluate the efficacy of pulsed electromagnetic field therapy as an adjunct therapy in diabetic foot ulcers	45 mins / day for 30 days	N= 30; Diabetes 7.8±1.47 years; mean duration of foot ulcer 4.9±1.2 months with Wagner's grade 1 and 2 were subjected for PEMF therapy	• Wound Surface Area	• Significant reduction in wound surface area observed could be due to PEMF that helped in healing of tissues, improved circulation and reduced inflammation • Thus, PEMF can be an effective and safe adjuvant therapy for treating diabetic foot ulcers

Tallis A. et al[17]	Randomised, Sham-Controlled, Double Bilnd Pilot Study	To determine the potential efficacy of and safety of dual energy pulsed electromagnetic field therapy (PEMF) on painful distal symmetric diabetic sensorimotor polyneuropathy (DSPN)	Twice daily for 30 mins for 60 days	N= 18 PEMF – n=11, Sham n=7 subjects with Type 2 Diabetes and painful DSPN	• Objective Measures 1. Skin biopsy 2. NCV study 3. Plantar foot skin perfusion pressure • Patient reported outcomes 1. Perception of pain 2. Concomitant medication use 3. Adverse events	• Improved Dorsal foot Skin perfusion Pressure, Improved velocity, conduction and amplitude of plantar and sural nerve, compliance with device use was noted along with no long term use adverse effects • Limitation: Need for large sample size research studies in order to generalize findings

Table 2 shows the Level of Evidence of the research articles included in the narrative review

References	Type of Study	OXFORD Centre of Evidence Based Medicine	Level of Evidence
Graak V. et al[11]	Randomised Controlled Trial	1b	VII
Sun J. et al[12]	Randomised Controlled Trial	1b	VII
Wrobel M. et al[13]	Randomised, placebo controlled, double blinded	1b	VII
Sharon T[14]	Grey literature – Pilot Study	1b	VII
Battecha K. et al[15]	Controlled trial	1b	VII
Padma K.et al[16]	Pre- Post Study	2b	VIII
Tallis A. et al[17]	Randomised, Sham-Controlled, Double Blind Pilot Study	1b	VII

Table 3 shows the PEDro scale rating for each of the research articles included in the study

References	1	2	3	4	5	6	7	8	9	10	11	Total
Graak V. et al[11]	+	+	-	+	-	-	-	+	+	+	+	7
Sun J. et al[12]	+	+	-	+	-	-	-	+	+	+	+	7
Wrobel M. et al[13]	+	+	+	+	-	-	-	+	+	+	+	8
Sharon T[14]	+	+	-	+	-	-	-	+	+	+	+	7
Battecha K. et al[15]	+	+	+	+	-	-	-	+	+	+	+	8
Padma K.et al[16]	+	-	-	-	-	-	-	+	-	-	+	3
Tallis A. et al[17]	+	+	+	+	-	-	-	+	+	+	+	8