



Journal of Medical Sciences

ISSN 1682-4474

science
alert

ANSI*net*
an open access publisher
<http://ansinet.com>



Research Article

Effect of Low Level Laser Therapy on Hand Function Performance of Children with Type I Diabetes Cheiroarthropathy

¹Dina Hamdy Desoky, ²Manal Salah Abd El-Wahab and ³Sahar Mohamed Nour El-Din

¹Department of Physical Therapy for Pediatrics, Banha Teaching Hospital, Banha, Egypt

²Physical Therapy Department for Growth and Developmental Disorders in Children and its Surgery, Faculty of Physical Therapy, Cairo University, Egypt

³Department of Pediatrics and Genetics, Medical Genetic Center, Faculty of Medicine, Ain Shams University, Egypt

Abstract

Background and Objective: Cheiroarthropathy is one of diabetic complications that have greater impact on the hand performance. The purpose of this study was to evaluate the effect of low level laser therapy on hand function performance on type I diabetic children with cheiroarthropathy. **Materials and Methods:** Forty diabetic boys, suffering from cheiroarthropathy, aged between 14-17 years participated in this study; they were selected from Banha Teaching Hospital Egypt. The selected patients were randomly assigned into two groups of equal number, the first group (A) represented the control group that was treated by a conventional physical therapy exercises program directed towards improving hand functions, while the other 20 children represented the study group (B) that was treated by low level laser therapy. Pinch strength, hand function performance and metacarpophalangeal (MCP) joints range of motion were assessed for all children before and after the suggested treatment duration. **Results:** Post treatment results showed a statistically significant difference of all measured variables between both groups in favor to the study group ($p < 0.05$). **Conclusion:** It can be concluded that laser therapy is an effective treatment modality in controlling cheiroarthropathy of children with type I diabetes.

Key words: Juvenile diabetes, cheiroarthropathy, hand function

Citation: Dina Hamdy Desoky, Manal Salah Abd El-Wahab and Sahar Mohamed Nour El-Din, 2019. Effect of low level laser therapy on hand function performance of children with type I diabetes cheiroarthropathy. *J. Med. Sci.*, 19: 56-62.

Corresponding Author: Dina Hamdy Desoky, Department of Physical Therapy for Pediatrics, Banha Teaching Hospital, Banha, Egypt Tel: +201222452509

Copyright: © 2019 Dina Hamdy Desoky *et al.* This is an open access article distributed under the terms of the creative commons attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Hand function is an indicator of overall health and well being, it correlates with an individual's ability to perform meaningful and purposeful activities¹. Hand function encompasses strength, endurance, range of motion and quality of hand movement all of which allow individuals to engage in basic daily routines as well as complex functional activities². Systemic diseases frequently affect function of many organs and systems, diabetes is the classical example of the disease of multi-organ involvement including extremities (foot and the hand)³.

Limited extension of the small joints of the hand in association with tight, waxy overlying skin has been described in up to 30% of juveniles with insulin dependent diabetes. This condition, termed juvenile diabetic cheiroarthropathy, that has been described only infrequently in adults⁴⁻⁶. Cheiroarthropathy results in flexion deformity of the metacarpophalangeal (MCP) and interphalangeal (IP) joints with increased resistance to passive extension of these joints ranging from 8-50%, it initially affects the little finger and over time extending radially to the other fingers or to more proximal joints^{7,8}. Patients with cheiroarthropathy complain of stiffness, weakness of grip, clumsiness and decreased dexterity due to reduced ability to perform fine movements⁹. These features will result in the impairment of joint mobility, especially of the small joints of the hand¹⁰. Limited joint mobility is commoner on insulin dependent, juvenile onset, longer duration and poorly-controlled diabetic patients¹¹. Adolescents who have Diabetes Mellitus (DM) with limited joint mobility are predominantly male¹².

Low-level laser therapy (LLLT) is efficient on bioenergetics muscle activation and these effects may influence performance during physical activities. The LLLT is a way to improve muscle performance as it induces photochemical effects on cells by light absorption at photoreceptors phenomenon described as photo biomodulation. Phototherapy has been widely used in research of different tissues, such as tendons, peripheral nerve, skin tissue, bones and muscle¹³. So the purpose of this study was to evaluate the effect of low level laser therapy in treating cheiroarthropathy of diabetic children.

MATERIALS AND METHODS

Study design: This study was a randomized controlled clinical trial that was performed at the Physical Therapy Department of Banha Teaching Hospital Cairo-Egypt from May, 2017 till April, 2018.

Subjects: Forty diabetic boys with cheiroarthropathy, aged between 14-17 years participated in this study, they were selected according to the following inclusion criteria: (1) All of them diagnosed as type 1 diabetes mellitus for more than 5 years and are suffering from cheiroarthropathy at least 6 months ago (2) Have flexion deformity of MCP and IP joints of both hands, (3) Positive prayer sign (incomplete approximation of one or more of the digits when the child attempted to approximate the palmar surfaces of the proximal and distal interphalangeal joints when palms pressed together and the fingers abducted) and (4) Positive table top sign (child not able to completely lay his palms flat on a horizontal surface). Exclusive criteria: (1) Recent hand operations, (2) Fracture or dislocation in upper limbs and (3) Children who had history of hand injury, rheumatoid arthritis and dupuytren contracture.

Procedures: The study was conducted after the approval of the ethical committee of the Faculty of Physical Therapy, Cairo University. All parents signed a consent form to participate in this study. Outcome measures were detected for all participants at baseline and 3 months following treatment application.

Evaluation procedures

Detecting pinch strength: Baseline pneumatic bulb hand dynamometer with a maximum pressure indicator was used to measure the participants pinch strength. Following the recommendation of the American Society of Hand Therapists¹⁴ from sitting on an armchair with forearm support, feet flat on the floor, shoulder adducted to side, elbow flexed 90° and forearm in neutral, the smallest bulb of the dynamometer was placed in the participant's fingers with the seam resting between thumb and lateral surface of the index, the participant was asked to squeeze the bulb with his fingers with maximum force. Each participant completed one set of three pinch strength trials for the dominant hand, with 15 sec rest period between each measurement and the mean of the three trials was calculated.

Detecting hand function performance: Sollerman hand function scale was used to assess hand function performance, it provide a true picture of grip function in activities of daily living and reflect the most common main grips used in daily life. The test consists of 20 subtests, each task considered to be an activity of daily living¹⁵. The test equipment box was

mounted on the wall in front of the patient so that the test could be applied quickly and easily. All test items were done uni-manually except subtests 11, 14 and 15 which require bilateral hand use. The subtests are timed and level of difficulty displayed and the quality of performance using the correct pinch or grip position then the participant was scored on a 5-point scale.

Detecting range of motion: Baseline 6-inch finger goniometer was used to assess MCP Joints range of motion. The active extension was measured for each joint individually¹⁶.

Treatment Intervention

For control group (A): Children in this group were treated by conventional physical therapy program aiming to improve limited upper limb joint mobility. Hot packs were wrapped around dorsal and palmer surfaces of both hands for 15 min, joint mobilization, manual passive stretching and self-stretch, strengthening exercises for extrinsic muscles of hand and strengthening exercises for intrinsic muscles of hand.

For the study group (B): Children in this group were treated by (Helium-Neon-Infra red laser therapy) He-Ne continuous with wavelength 633 nm and IR pulsed with wavelength 905 nm laser was applied from sitting with MCP and IP joints were supported in slightly flexed position to open up joint space. The laser applicator was placed perpendicular and fixed at 30 cm away from treatment area. Small joints of both hands were exposed to laser therapy for 10 min through a sweeping computerized scanning.

Data analysis: All statistics were calculated by using the statistical package of social sciences (SPSS) version 25. Descriptive statistics (mean and standard deviation) were computed for pinch strength and MCP joints range of motion using unpaired t-test was applied for age, pinch strength and MCP joints range of motion between both groups. Mann-whitney U-test was used for hand performance between both groups.

RESULTS

Regarding the age in both groups, the results of the present study revealed a statistically insignificant difference between the two groups as the mean values of age were 14.55 ± 1.27 years and 14.75 ± 1.44 years for group A and B, respectively with $p > 0.05$ (Table 1).

A statistically insignificant difference ($p > 0.05$) regarding pinch strength was recorded as mean values for the study and control groups pre-treatment were 5.23 ± 1.42 and 5.37 ± 1.65 for pinch strength. Comparing mean values after treatment application between the study and control groups showed a statistically significant difference as mean values of pinch strength were 7.02 ± 1.35 and 5.78 ± 1.72 , respectively ($p < 0.05$) (Table 2).

Pre-treatment median values of hand function performance detected by sollerman scale between group B and group A were 57.50 and 57.50, respectively show insignificant difference ($p > 0.05$). Median values of hand function performance post-treatment between the study and control groups showed a statistically significant difference as median values were 62.50 and 60.00, respectively ($p < 0.05$) (Table 3).

A statistically insignificant difference ($p > 0.05$) regarding metacarpophalangeal joints range of motion was recorded as mean values for the study and control groups pre-treatment were 138.00 ± 11.27 and 135.25 ± 11.80 for the thumb finger, 135.50 ± 10.50 and 132.11 ± 9.50 for the index finger, 138.00 ± 10.42 and 135.71 ± 7.80 for the middle finger, 138.25 ± 9.63 and 134.21 ± 8.90 for the ring finger and 135.75 ± 7.93 and 134.55 ± 8.50 for the little finger, respectively ($p > 0.05$). Comparing mean values of metacarpophalangeal joints range of motion after treatment application between the study and control groups showed a statistically significant difference as mean values were 145.50 ± 13.00 and 140.70 ± 12.20 for the

Table 1: Age mean values for both control and study groups

Parameters	Mean \pm SD		t-value	p-value
	Study group	Control group		
Age	14.75 ± 1.44	14.55 ± 1.27	0.464	0.64

Table 2: Mean values of pinch strength for the dominant hand for both groups

Parameters	Mean \pm SD		t-value	p-value
	Study group	Control group		
Dominant hand				
Pre-treatment	5.23 ± 1.42	5.37 ± 1.65	0.307	0.760
Post-treatment	7.02 ± 1.35	5.78 ± 1.72	2.548	0.015

Table 3: Hand function performance for the study and control group

Parameters	Median		z-value	p-value
	Study group	control group		
Dominant hand				
Pre-treatment	57.50	57.50	0.312	0.758
Post-treatment	62.50	60.00	2.515	0.011

Table 4: Mean values of MCP joints range of motion for the study and control group pre and post treatment

Parameters	Mean ± SD		t-value	p-value
	Study group	Control group		
Thumb				
Pre	138.00 ± 11.27	135.25 ± 11.80	1.503	0.141
Post	145.50 ± 13.00	140.70 ± 12.20	1.949	0.043
Index				
Pre	135.50 ± 10.50	132.11 ± 9.50	1.105	0.276
Post	143.50 ± 10.14	136.50 ± 10.01	2.196	0.034
Middle				
Pre	138.00 ± 10.42	135.71 ± 7.80	0.934	0.356
Post	145.75 ± 10.65	139.50 ± 9.01	2.028	0.04
Ring				
Pre	138.25 ± 9.63	134.21 ± 8.90	1.020	0.314
Post	145.75 ± 10.03	139.00 ± 9.52	2.293	0.027
Little				
Pre	135.75 ± 7.93	134.55 ± 8.50	0.085	0.933
Post	144.50 ± 9.49	138.75 ± 9.10	2.203	0.034

thumb finger, 143.50 ± 10.14 and 136.50 ± 10.01 for the index finger, 145.75 ± 10.65 and 139.50 ± 9.01 for the middle finger, 145.75 ± 10.03 and 139.00 ± 9.52 for the ring finger and 144.50 ± 9.49 and 138.75 ± 9.10 for the little finger, respectively (p<0.05) (Table 4).

DISCUSSION

The pre-treatment results of the current study showed a reduced pinch grip strength which may be explained by Willey and Singh¹⁷ who reported that reduced muscular strength could be due to structural and metabolic changes including increased fat infiltration and changed proportions of muscle fiber types, consequently, glucose is transported and utilized less efficiently during exercise. Also it could be explained by the effects of DM I on the skeletal muscle that were analyzed by clinical observations and showed a clear association between DM I and their pathological effects in skeletal muscle. It was found that alterations in the absence of actin and myosin molecules responsible for muscle contraction, changes in muscle fiber type I (slow-twitch fibers) and muscle fibers type II (fast twitch fibers)¹⁸.

Reduced pinch strength can also be explained by the fact that hyperglycaemia cause a reduction in the number of mitochondria in the muscle cells, a decrease in glycogen synthesis and an increase in the amount of circulating systemic inflammatory cytokines, all of which have a detrimental effect on the skeletal muscles¹⁹.

Decrease in mean values of pinch strength pre-treatment comes in agreements with Balducci *et al.*²⁰ and Gerrits *et al.*²¹ who reported that isometric force was found to be associated

with micro and macro-vascular complications, this correlation of muscle strength with these complications explained by an inadequate blood supply to muscles.

Pre-treatment results showed reduced fingers ROM which matches the findings of Arkkila and Gautier²² who reported that one consequence of prolonged hyperglycemia is non-enzymatic glycosylation of collagen this glycosylation results in abnormally cross-linked collagens, which are unusually resistant to mechanical and enzymatic degradation. The accumulation of glycosylated collagen may be responsible for the periarticular and skin thickening seen in limited joint mobility.

Decrease fingers ROM is also supported by Ismail *et al.*²³ who reported that the ultrasound findings of diabetic cheiroarthropathy are the thickening of the flexor tendon sheaths and subcutaneous tissues. Khanna and Ferguson²⁴ also reported that MRI shows thickening of the flexor digitorum tendons bilaterally with edema and enhancement of the tendon sheaths. Hypertrophy of the retinacular sheath progressively restricts the motion of the flexor tendon which affects force production and efficiency of motion²⁵.

Decreased hand function performance detected by Sollerman test can be explained by Franco *et al.*²⁶ who reported that intracellular hyperglycemia cause high levels of oxidative stress and the formation of advanced glycation endproducts (AGEs). The AGEs are damaging glycosylation products. In such an unfavourable environment, increased production of reactive oxygen species induced that can initiate the inflammatory cascade leading to the production of several cytokines and growth factors causing the hyperglycemia-induced cellular damage.

Reduction of hand function performance pre-treatment can also be explained by Park *et al.*²⁷ who reported that subjects with diabetes were shown to have reduced muscle quality which is associated with longer diabetes duration and poorer glycemic control. The results of the current study can also be explained by fact that limited joint mobility associated with higher glycosylated hemoglobin levels as reduced hand strength has been shown to be related to higher glycosylated hemoglobin levels^{28,29}.

Significant increase in post-treatment mean values of pinch strength in favor to the study group may explained by the work of Xu *et al.*³⁰ who found that low level laser therapy seems to improve muscle performance via the energy metabolism in cells by stimulating photochemical events and enhancing mitochondrial function in muscle cells. Manteifel *et al.*³¹ reported that the structural changes in the mitochondria size promoted by low level laser therapy lead to

an improvement in cell respiration and the formation of adenosine triphosphate (ATP), which provides energy to the cells.

Diabetes is a disease of altered glucose homeostasis and persistent hyperglycemia leads to advanced glycation end products which are primarily responsible for the damage of cells which have a slow turnover³². Low level laser therapy has the ability to stimulate increased cell turnover and proliferation. These effects may be partially attributable to the stimulation of the oxidative metabolic pathways and a resulting increase in overall cell metabolism³³.

Post-treatment improvement of fingers ROM and hand function performance agrees with the findings of Makela³⁴ who reported that diabetes has been identified with excessive oxidative activity and toxins. To help counter this, irradiation of light also stimulates macrophages that remove molecules that have accumulated advanced glycation end products over time and by initiating steps that lead to new protein synthesis and tissue remodeling. The activity of cytochrome enzyme that breaks down toxins and many other substrates are regulated, enabling the control of glucose and the breakdown of glycation end products to prevent the development of complications that arise out of diabetes.

Papana and Maltezos³⁵ reported that microvascular abnormalities associated with cheiroarthropathy lead to tissue hypoxia which contribute to tendon damage. Shoji *et al.*³⁶ reported that reduced neovascularization is consistent with decreased levels of vascular endothelial growth factor as well as reduced angiogenesis in diabetic conditions. Low intensity laser irradiations have been reported to be of beneficial influence on processes of impaired microcirculation. The increase in skin microcirculation achieved after laser irradiation was found as early after initiating light exposure and persisted up to 15 min after stopping it. Low power lasers have an effect of on the proliferation of endothelial cells during angiogenesis and responsible for the opening of preexisting capillaries due to release of transmitter substances³⁷.

Range of motion improvement can be explained by the fact that poor blood flow limits movement and flexibility in the fingers³⁵. Laser therapy improve cutaneous blood flow through increased activity of some cells such as leukocytes and phagocytes stimulating redox activity in the cellular respiratory chain resulting in cell activation, stimulation of production of adenosine triphosphate which enhances the cells' mitotic activity and relaxation of the vessel walls produces vasodilatation³⁸.

CONCLUSION

The finding of this study suggests that low level laser therapy helps in treatment of children with cheiroarthropathy as it improves strength and hand functions abilities.

SIGNIFICANCE STATEMENT

This study confirmed that laser therapy is effective in treatment of children with type I diabetes cheiroarthropathy. This study increases awareness of this complication of diabetes which is a forgotten diabetic hand complication.

ACKNOWLEDGMENT

Authors express appreciation to all children who participated in this study.

REFERENCES

1. Lawrence, E.L., S. Dayanidhi, I. Fassola, P. Requejo, C. Leclercq, C.J. Winstein and F.J. Valero-Cuevas, 2015. Outcome measures for hand function naturally reveal three latent domains in older adults: Strength, coordinated upper extremity function and sensorimotor processing. *Front. Aging Neurosci.*, Vol. 7. 10.3389/fnagi.2015.00108.
2. Reuter, S.E., N. Massy-Westropp and A.M. Evans, 2011. Reliability and validity of indices of hand grip strength and endurance. *Aust. Occup. Ther. J.*, 58: 82-87.
3. Zyluk, A. and P. Puchalski, 2015. Hand disorders associated with diabetes: A review. *Acta Orthop. Belg.*, 81: 191-196.
4. Rosenbloom, A.L., J.H. Silverstein, D.C. Lezotte, K. Richardson and M. McCallum, 1981. Limited joint mobility in childhood diabetes mellitus indicates increased risk for microvascular disease. *N. Engl. J. Med.*, 305: 191-194.
5. Grigic, A., A.L. Rosenbloom, F.T. Weber, B. Giordano, J.I. Malone and J.J. Shuster, 1976. Joint contracture-common manifestation of childhood diabetes mellitus. *J. Pediatr.*, 88: 584-588.
6. Buckingham, B.A., J. Uitto, C. Sandborg, T. Keens, F. Kaufman and B. Landing, 1981. 1103 scleroderma-like syndrome and the non-enzymatic glycosylation of collagen in children with poorly controlled insulin dependent diabetes (IDDM). *Pediatr. Res.*, Vol. 15. 10.1203/00006450-198104001-01129.
7. Smith, L.L., S.P. Burnet and J.D. McNeil, 2003. Musculoskeletal manifestations of diabetes mellitus. *Br. J. Sports Med.*, 37: 30-35.

8. Abate, M., C. Schiavone, Salini, V. Schiavone and I. Andia, 2013. Management of limited joint mobility in diabetic patients. *Diabetes Metab. Syndr. Obes.*, 7: 197-207.
9. Somai, P. and S. Vogelgesang, 2011. Limited joint mobility in diabetes mellitus: The clinical implications. *J. Musculoskel Med.*, 28: 118-124.
10. Hordon, L., 2016. Limited joint mobility and other musculoskeletal problems in diabetes. *J. Diabetes Nurs.*, 20: 166-170.
11. Ballantyne, J.A. and G. Hooper, 2004. The hand and diabetes. *Curr. Orthopaedics*, 18: 118-125.
12. Duffin, A.C., K.C. Donaghue, M. Potter, A. McInnes and A.K. Chan *et al.*, 1999. Limited joint mobility in the hands and feet of adolescents with Type 1 diabetes mellitus. *Diabetes Med.*, 16: 125-130.
13. Barbosa, R.I., A.M. Marcolino, V. Souza, G. Bertolino, M.D.C.R. Fonseca and R.R. de Jesus Guirro, 2017. Effect of low-level laser therapy and strength training protocol on hand grip by dynamometry. *J. Lasers Med. Sci.*, 8: 112-117.
14. Shechtman, O. and B. Sindhu, 2015. Grip. In: ASHT Clinical Assessment Recommendations, MacDermid, J., G. Solomon and K. Valdes (Eds.), 3rd Edn., American Society of Hand Therapy, Mount Laurel, New Jersey.
15. Sollerman, C. and A. Ejekar, 1995. Sollerman hand function test: A standardised method and its use in tetraplegic patients. *Scand. J. Plast. Reconstr. Hand Surg.*, 29: 167-176.
16. Norkin, C.C. and D.J. White, 2011. Measurement of Joint Motion: A Guide to Goniometry. 4 Edn., Jaypee Brothers Medical Publications, India.
17. Willey, K.A. and M.A. Singh, 2003. Battling insulin resistance in elderly obese people with type 2 diabetes: Bring on the heavy weights. *Diabetes Care*, 26: 1580-1588.
18. Krause, M.P., M.C. Riddell and T.J. Hawke, 2011. Effects of type 1 diabetes mellitus on skeletal muscle: clinical observations and physiological mechanisms. *Pediatr. Diabetes*, 12: 345-364.
19. Helmersson, J., B. Vessby, A. Larsson and S. Basu, 2004. Association of type 2 diabetes with cyclooxygenase-mediated inflammation and oxidative stress in an elderly population. *Circulation*, 109: 1729-1734.
20. Balducci, S., M. Sacchetti, G. Orlando, L. Salvi and L. Pugliese *et al.*, 2014. Correlates of muscle strength in diabetes: The study on the assessment of determinants of muscle and bone strength abnormalities in diabetes (SAMBA). *Nutr. Metab. Cardiovasc. Dis.*, 24: 18-26.
21. Gerrits, E.G., G.W. Landman, L. Nijenhuis-Rosien and H.J. Bilo, 2015. Limited joint mobility syndrome in diabetes mellitus: A minireview. *World J. Diabetes*, 6: 1108-1112.
22. Arkkila, P.E. and J.F. Gautier, 2003. Musculoskeletal disorders in diabetes mellitus: An update. *Best Pract. Res. Clin. Rheumatol.*, 17: 945-970.
23. Ismail, A.A., B. Dasgupta, A.B. Tanqueray and J.J. Hamblin, 1996. Ultrasonographic features of diabetic cheiroarthropathy. *Br. J. Rheumatol.*, 35: 676-679.
24. Khanna, G. and P. Ferguson, 2007. MRI of diabetic cheiroarthropathy. *Am. J. Roentgenol.*, 188: W94-W95.
25. Kameyama, M., S. Meguro, O. Funae, Y. Atsumi and H.J. Ikegami, 2009. The presence of limited joint mobility is significantly associated with multiple digit involvement by stenosing flexor tenosynovitis in diabetics. *J. Rheumatol.*, 36: 1686-1690.
26. Franco, R., R. Sanchez-Olea, E.M. Reyes-Reyes and M.I. Panayiotidis, 2009. Environmental toxicity, oxidative stress and apoptosis: Menage a trois. *Mutat. Res./Genet. Toxicol. Environ. Mutagen.*, 674: 3-22.
27. Park, S.W., B.H. Goodpaster, E.S. Strotmeyer, N. de Rekeneire and T.B. Harris *et al.*, 2006. Decreased muscle strength and quality in older adults with type 2 diabetes: The health, aging and body composition study. *Diabetes*, 55: 1813-1818.
28. Amin, R., T.K. Bahu, B. Widmer, R.N. Dalton and D.B. Dunder, 2005. Longitudinal relation between limited joint mobility, height, insulin-like growth factor 1 levels and risk of developing microalbuminuria: The Oxford regional prospective study. *Arch. Dis. Child.*, 90: 1039-1044.
29. Cederlund, R.I., N. Thomsen, S. Thrainsdottir, K.F. Eriksson, G. Sundkvist and L.B. Dahlin, 2009. Hand disorders, hand function and activities of daily living in elderly men with type 2 diabetes. *J. Diabetes Complications*, 23: 32-39.
30. Xu, X., X. Zhao, T.C.Y. Liu and H. Pan, 2008. Low-intensity laser irradiation improves the mitochondrial dysfunction of C2C12 induced by electrical stimulation. *Photomed. Laser Surg.*, 26: 197-202.
31. Manteifel, V., L. Bakeeva and T. Karu, 1997. Ultrastructural changes in chondriome of human lymphocytes after irradiation with He-Ne laser: appearance of giant mitochondria. *J. Photochem. Photobiol. B: Biol.*, 38: 25-30.
32. Mishra, M., H. Kumar, R.K. Singh and K. Tripathi, 2008. Diabetes and nanomaterials. *Dig. J. Nanomater. Biostructures*, 3: 109-113.
33. Lubart, R., Y. Wollman, H. Friedmann, S. Rochkind and I. Laulicht, 1992. Effects of visible and near-infrared lasers on cell cultures. *J. Photochem. Photobiol. B: Biol.*, 12: 305-310.

34. Makela, A.M., 2004. Theoretical backgrounds for light application in diabetes. Laser Florence, 2004. <https://drlaser.hu/wp-content/uploads/Diabetes-Theory-of-LLLT-for-diabetes.pdf>
35. Papanas, N. and E. Maltezos, 2010. The diabetic hand: a forgotten complication? J. Diabetes Complications, 24: 154-162.
36. Shoji, T., H. Koyama, T. Morioka, S. Tanaka and A. Kizu *et al*, 2006. Receptor for advanced glycation end products is involved in impaired angiogenic response in diabetes. Diabetes, 55: 2245-2255.
37. Schindl, L., R.V. Baehr, A. Krause, H. Kern, M. Schindl and A. Schindl, 1994. Influence of low-incident-energy laser irradiation on the arthus phenomenon induced on the Rabbit's Cornea: A controlled study. J. Clin. Laser Med. Surg., 12: 31-33.
38. Klebanov, G.I., M.V. Kreinina, E.A. Poltanov, T.V. Khristoforova and Y.A. Vladimirov, 2001. Mechanism of therapeutic effect of low-intensity infrared laser radiation. Bull. Exp. Biol. Med., 131: 239-241.