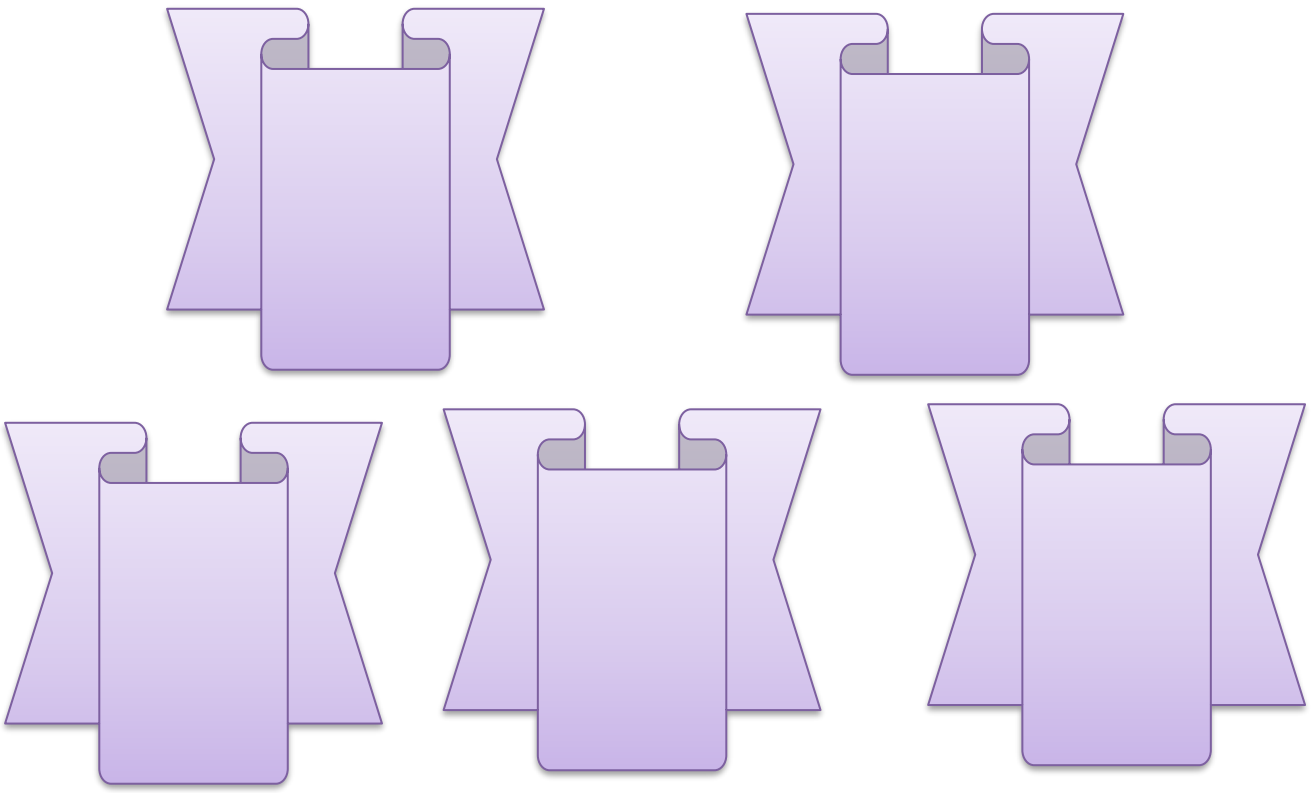
International Journal of Medical Arts

Volume 5, Issue 5, May 2023

https://ijma.journals.ekb.eg/



Print ISSN: 2636-4174

Online ISSN: 2682-3780

Available online at Journal Website
https://ijma.journals.ekb.eg/
Main Subject [Parasitology]

Case Report

The Effects of Nitric Oxide Production and Lymphedema Treatment on A Pregnant Female with A History of Recurrent Abortion: A Case Report

Mohammed Youssef Shakra *

Department of Medical Parasitology, Damietta Faculty of Medicine, Al-Azhar University, Damietta, Egypt

Article information

Received: 10-06-2023

Accepted: 07-07-2023

DOI: 10.21608/IJMA.2023.216724.1698.

*Corresponding author

Email: dr.mohammed_youssef@yahoo.com

Citation: Shakra MY. The Effects of Nitric Oxide Production and Lymphedema Treatment on A Pregnant Female with A History of Recurrent Abortion: A Case Report. IJMA 2023 May; 5 [5]: 3291-3296. doi: 10.21608/IJMA.2023.216724.1698.

ABSTRACT

Background: The association between lymphedema and recurrent abortion is not fully clarified. In the present case, I report the occurrence of acute dermatolymphangio-adenitis [previously: cellulitis] about three days before each abortion and the effect of non-surgical treatment of lymphedema on pregnancy.

Case presentation: A 30-years old nulliparous pregnant female complains of right lower limb lymphedema with a history of recurrent abortion. Measurement of Lymphedema circumference and serum nitric oxide assay were done before, during, and after treatment. She was treated by intermittent pneumatic compression to produce wall shear stress on blood and lymphatic vessels, chemical compression by a zinc oxide paste bandage, and, a special elastic stocking. There was a statistically significant increase in serum nitric oxide concentration [F-test=75.814, p<0.001] together with a statistically significant decrease in lymphedema circumference [F-test=24.564, p=0.005]. After treatment there were no acute dermatolymphangioadenitis attacks, the lymphedema subsided and she delivered a full-term healthy infant.

Conclusions: This study aimed to report the safety and efficacy of conservative treatment of lymphedema in a pregnant female with a history of recurrent abortion.

Keywords: Lymphedema; Abortion; Nitric Oxide; Pregnancy; cellulitis

INTRODUCTION

Lymphedema is a chronic disfiguring disease characterized by tissue swelling due to the accumulation of protein-rich fluid that's usually drained through the body's lymphatic system. It affects up to 250 million people worldwide [1].

Lymphedema may be primary or secondary. Secondary lymphedema is more common and developed secondary to either direct or indirect injury to the lymphatic system. The most common cause of secondary lymphedema worldwide is lymphatic filariasis [2].

Recurrent attacks of Acute dermatolymph-angioadenitis [ADLA previously "cellulitis] complicate the clinical course of lymphedema. The affected limb becomes swollen, red, hot, and tender with inflammation of the draining lymph nodes due to secondary bacterial infection [3].

Multi-drug-resistant methicillin-resistant Staphylococcus aureus [MRSA], cephalosporin-resistant Escherichia coli and carbapenem-resistant Pseudomonas aeruginosa were isolated from Lymphatic Filariasis patients [4].

Recurrent abortion is defined as two or more abortions before the 20th gestational week of gestation. Many risk factors are associated with recurrent abortion e.g., endocrine disorders, immunologic, metabolic, genetic, male-related factors, and infectious diseases [5].

There is a significant association between healthcare-associated infection of women and miscarriage. The main causative agents of healthcare-associated infection of women are Escherichia coli, Enterobacter spp., Klebsiella pneumoniae, Enterococcus faecalis, Staphylo-coccus aureus and Pseudomonas aeruginosa [6].

Multiple mechanisms can be used by pathogens to cross the placental barrier. The presence of pathogenic organisms in the placenta induces a maternal immune response to infection that could result in miscarriage [7].

Intermittent pneumatic compression devices assist in lymphedema management by decreasing limb volume [8]. Both intermittent pneumatic compression and compression stockings induce haemodynamic transient shear stress on blood vessels which promote endothelial cells to release nitric oxide [9]. The ultralow molecular weight of nitric oxide enables it to freely diffuse into biological membranes to exert its antibacterial action [10].

This study aimed to report the effects of conservative treatment of lymphedema in a pregnant female with a history of recurrent abortion.

Case presentation

A 30-years -old nulliparous female patient presented with right lower limb lymphedema. It is a filarial lymphedema due to the earlier detection of Wuchereria bancrofti micro-filaremia. She had a history of recurrent abortions. Three consecutive abortions occurred two years after the lymphedema developed at 12,16 and 9 weeks of pregnancy. To specify the cause of the abortion, a blood hormonal profile, TORCH screen, and chromosomal study were done. The laboratory investigations revealed no obvious cause. An interesting finding in the present case is the occurrence of acute dermatolymphangioadenitis in the lymphede-matous limb about three days before each abortion.

The patient's physical examination revealed right lower limb lymphedema with early manifestation of acute dermatolymphangio-adenitis. The laboratory investigations revealed a leukocytosis [WBC count was 15,000/ml], a negative blood film for microfilaria, and negative filarial antigenemia. Human chorionic gonado-tropin was assayed, and fortunately, she was pregnant [three weeks gestational age]. Serum Nitric oxide was assayed [ELISA, Elabscience, USA] before treatment and at the end of every week during the first month of pregnancy [during treatment] and then every month till delivery [after treatment]. The mean [average] lymphedema circumference [Fig. 1] was estimated at different levels at the same time as in the nitric oxide assay [11].

She was treated by intermittent pneumatic compression three sessions per week for four weeks by using the lymphedema compression device [Care-med Ltd] according to the manufacturer's instructions. The pneumatic compression device consists of a pump that applies pressure [80–100 mmHg] to multiple individual chambers inside the garment. The chambers inflate in sequence from distal to proximal, hold briefly, and then deflate for a brief intermission before resuming the distal-to-proximal cycle. The duration of the session was

30 minutes followed by chemical compression by a zinc oxide-impregnated paste bandage applied over the lymphedematous limb then wrapped by a cotton layer and bandage and wearing a special elastic stocking till the next session.

RESULTS

After four weeks of treatment, the mean [average] lymphedema circumference decreased, without acute dermatolymphangioadenitis attacks. The serum level of nitric oxide concentration was increased during and after treatment within the range of physiological level [Fig. 2 and table 1]. The reference value for serum nitric oxide concentration is 11.5 to 76.4 µmol/L in women. The increase in serum nitric oxide level was statistically significant [F-test=75.814, p<0.001]. Wearing the special elastic stocking which is formed of an inner cotton layer and outer tuff elastic layer extended during and after pregnancy to prevent the recurrence of lymphedema. The decrease in lymphedema circumference was statistically significant [F-test=24.564, p=0.005]. She delivered a healthy full-term infant.

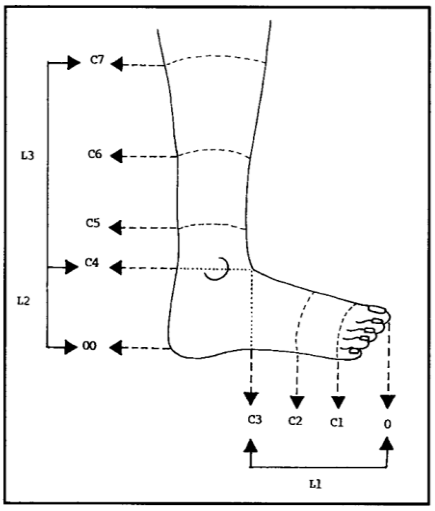


Fig. 1. Measurements at different levels of lower limb: 00 - level of ground; 0 - tip of great toe; C1 - base of metatarso-phalangeal joints; C2 - 10 cms from 0; C3 - mid-tarsal line through most proximal part of dorsum of foot; C4 - line through midpoint of lateral malleolus; C5 - 12 cms from 00; C6 - 20 cms from 00; C7 - 30 cms from 00. L1 - length from 0 to C3; L2 - length from 00 to C4; and L3 - length from C4 to C7.

Fig.2. lymphedematous limb (A) before treatment (B)after treatment

Table [1]: Relation between serum nitric acid concentration and the main lymphedema circumference before, during and after treatment

	Before treatment	During treatment				After treatment							
		1st month				2nd M	3rd M	4th M	5th M	6th M	7th M	8th M	9th M
		1st w	2nd w	3rd w	4th w								
Serum nitric oxide concentration [µmol/L] *	12.1	34.5	43.7	47.9	53.1	41.4	38.9	35.2	33.9	32.6	30.8	31.6	30.1
F-test=75.814, p<0.001													
The mean [average] Lymphedema circumference [cm]	85	62	54	46	41	44	47	43	48	40.5	41	42	45
F-test=24.564, p=0.005													

*Micromole per liter [µmol/L] / week [w] /month [m].

DISCUSSION

The risk of abortion and/or postnatal deaths is higher in lymphatic filariasis-infected females, especially in endemic areas [12]. lymphatic filariasis is the probable cause of the failure of two cycles of In vitro fertilization [IVF] with good-quality embryos [13]. In an extended study for identifying the lymphatic filariasis morbidity in Ghana, the authors reported that lymphedema may cause infertility and miscarriages. The lymphedema progress either during or after the acute dermatolymphangioadenitis attacks [14].

Pneumatic compression therapy [PCT] is one of the guidelines for lymphedema management. PCT decrease the infection rate and hospital admissions of lymphedema patients [15]. Pneumatic compression delivers the retained fluid to functional lymphatics and decreases the lymphatic load, increase lymphatic reabsorption, and improves trophic changes of skin elasticity. It improves clinical symptoms such as heaviness, itching, pain, and quality of life [16].

Lymphoscintigraphy has shown lymph movement in response to pneumatic compression with 50 – 125 mmHg. The assessment of lymph flow during intermittent pneumatic compression has demonstrated that the optimal pressure for optimal flow was 80 mmHg [17]. The pneumatic compression increases intravascular flow, shear, and compressive strain on the vascular endothelium with the resulting release of nitric oxide [Fig. 3] [18].

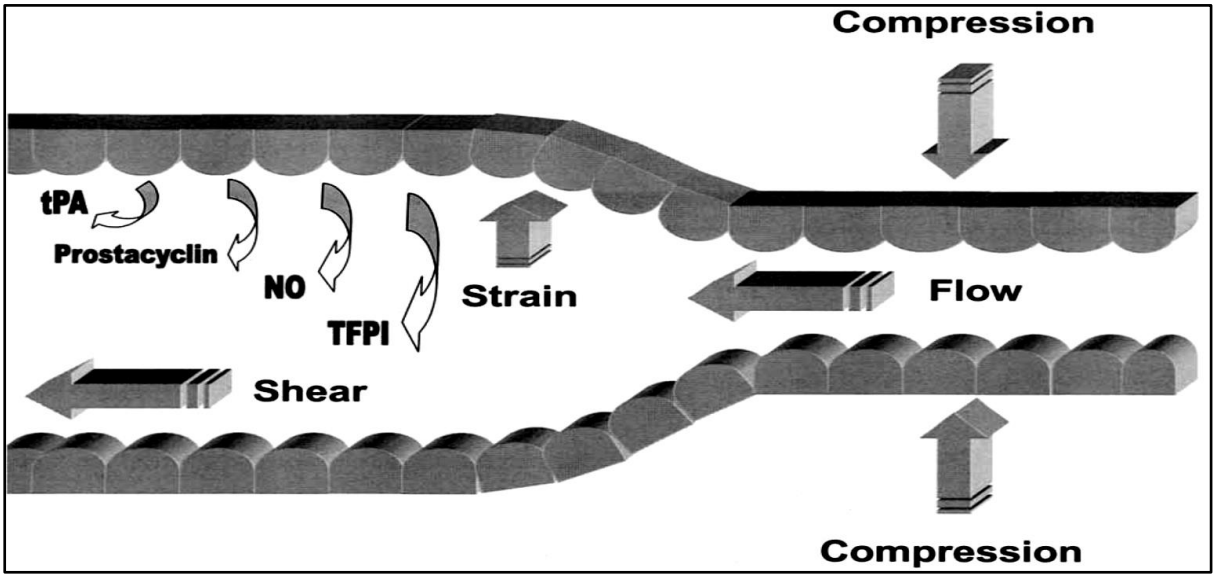


Fig. [3]: Mechanical effects of pneumatic compression on a vein or artery. The pneumatic compression increases intravascular flow, shear, and compressive strain on endothelial cells with the resulting release of biochemical mediators. tPA: tissue plasminogen activator; NO: nitric oxide; TFPI: tissue factor pathway inhibitor [18].

Shear stress is produced by the mechanical frictional force of blood flow and contraction of the heart. It is a well-known mechanical signal that affects endothelial cells [function, morphology, and gene expression]. Endothelial nitric oxide synthase [eNOS] derived from the endothelium is constitutively expressed and produces nitric oxide in response to shear stress. Shear stress is produced by the compression of the legs using pneumatic cuffs [19].

Shear stress activates endothelial nitric oxide synthase through phosphorylation, thus producing endothelial nitric oxide, which is important for increasing blood flow and an important signaling molecule that improves microvascular dysfunction and down-regulates the inflammatory cascade [20]. The low concentrations of nitric oxide produced by eNOS in the vessel wall mediate anti-inflammatory, antithrombotic, and vasodilation effects [21].

Nitric oxide is an endogenously produced gaseous molecule involved in multiple physiological processes. In the body, nitric oxide is produced enzymatically from L-arginine by one of three nitric oxide synthase [NOS] isoforms: endothelial [eNOS], neuronal [nNOS], and inducible [iNOS]. NO has antibacterial and anti-biofilm activity through its physicochemical properties [22]. Nitric oxide is a broad-spectrum antibacterial agent including both Gram-positive

and Gram-negative organisms, making it an attractive alternative to traditional antibiotics for treating infections [23].

Nitric oxide has an important defense against several pathogens by cytotoxic mechanism. Nitric oxide can react with superoxide that is endogenously derived from the respiration process of bacteria to generate reactive oxygen/nitrogen species, including the powerful oxidant NO radical [NO•], peroxynitrite [ONOO -], and dinitrogen trioxide [N2O3], which exhibit antibacterial effects on various bacteria by causing the oxidative or nitrosative stress such as DNA deamination and lipid peroxidation [10].

Howlin *et al.* demonstrated that sub-micromolar nitric oxide concentrations effectively treated Pseudomonas aeruginosa [P. aeruginosa] infection in cystic fibrosis [24]. Numerous studies have reported that nitric oxide displays potent antibacterial effects in vitro and in skin infection models when used at proper concentrations. Nitric oxide produced endogenously by endothelial cells stimulates cell proliferation, cell migration, and differentiation of stem cells leading to enhanced vascularization, collagen synthesis, rapid wound healing and skin regeneration [25].

Nitric oxide-based antimicrobials have become popular due to their significant role in the immune system and researchers' need for new antibiotics since typical antibiotics develop resistance within 2 years [26].

Compression elastic stockings have been identified to raise the wall shear stress [WSS] in the superficial veins and lymphatic vessels of the leg in humans. Wearing knee-high compression stockings significantly raises the leg pump lymph pressure and promotes nitric oxide [NO] production by endothelial nitric oxide synthase [27].

Chemical compression by wrapping the limb with zinc oxide alleviates skin inflammation and promotes wound healing. It is economical and efficient in reducing the incidence of skin infection [28, 29].

Conclusion: This study presented the safety and efficacy of conservative treatment of lymphedema and acute dermatolymphangio-adenitis in a pregnant female with a history of recurrent abortion. There is a significant increase in serum nitric oxide together with a significant decrease in lymphedema circumference after conservative treatment.

Conflict of Interest and Financial Disclosure: None.

REFERENCES

1. Maita K, Garcia JP, Torres RA, Avila FR, Kaplan JL, Lu X, Manrique OJ, Ciudad P, Forte AJ. Imaging biomarkers for diagnosis and treatment response in patients with lymphedema. Biomark Med. 2022 Mar;16[4]:303-316. doi: 10.2217/bmm-2021-0487.

2. Istranov AL, Makarov IG, Makarova NV, Tulina I, Ulasov IV, Isakova YI. Combination of conservative and surgical methods in the treatment of giant lymphedema of the scrotum: A case report. Front Surg. 2023 Apr 12;10:1048159. doi: 10.3389/ fsurg.2023.1048159.

3. Olszewski WL, Zaleska MT. Long-Term Benzathine Penicillin Prophylaxis Lasting for Years Effectively Prevents Recurrence of Dermato-Lymphangio-Adenitis [Cellulitis] in Limb Lymphedema. Lymphat Res Biol. 2021 Dec;19[6]: 545-552. doi: 10.1089/lrb.2020.0051.

4. Aglomasa BC, Adu-Asiamah CK, Asiedu SO, Kini P, Amewu EKA, Boahen KG, *et al.* Multi-drug resistant bacteria isolates from lymphatic filariasis patients in the Ahanta West District, Ghana. BMC Microbiol. 2022 Oct 11;22[1]:245. doi: 10.1186/ s12866-022-02624-9.

5. Bahia W, Soltani I, Abidi A, Haddad A, Ferchichi S, Menif S, Almawi WY. Identification of genes and miRNA associated with idiopathic recurrent pregnancy loss: an exploratory data mining study. BMC Med Genomics. 2020 Jun 1;13[1]:75. doi: 10.1186/s12920-020-00730-z.

6. Giakoumelou S, Wheelhouse N, Cuschieri K, Entrican G, Howie SE, Horne AW. The role of infection in miscarriage. Hum Reprod Update. 2016;22[1]:116-33. doi: 10.1093/humupd/dmv041.

7. Megli CJ, Coyne CB. Infections at the maternal-fetal interface: an overview of pathogenesis and defence. Nat Rev Microbiol. 2022 Feb;20[2]:67-82. doi: 10.1038/s41579-021-00610-y.

8. Keeley V, Riches K, Ward L, Franks PJ. A Prospective Preliminary Study Examining the Physiological Impact of Pneumatic Compression Dosing in the Treatment of Lower Extremity Lymphedema. Lymphat Res Biol. 2023 May 4. doi: 10.1089/lrb.2022.0087. Online ahead of print.

9. Nickles MA, Ennis WJ, O'Donnell TF Jr, Altman IA. Compression therapy in peripheral artery disease: a literature review. J Wound Care. 2023 May 1;32[Sup5]:S25-S30. doi: 10.12968/jowc. 2023.32.Sup5.S25.

10. Wang TY, Zhu XY, Wu FG. Antibacterial gas therapy: Strategies, advances, and prospects. Bioact Mater. 2022 Nov 11;23:129-155. doi: 10.1016/ j.bioactmat.2022.10.008.

11. Pani SP, Vanamail P, Yuvaraj J. Limb circumference measurement for recording edema volume in patients with filarial lymphedema. Lymphology. 1995 Jun;28[2]:57-63. PMID: 7564492.

12. Campillo JT, Chabot EB, Awaca-Uvon NP, Tambwe JP, Kuyangisa-Simuna G, Boussinesq M, Chesnais CB, Pion SD. Effect of Lymphatic Filariasis and Hookworm Infection on Pregnancy Course and Outcome in Women Living in the Democratic Republic of the Congo. Am J Trop Med Hyg. 2021 May 3;104[6]:2074-2081. doi: 10.4269/ ajtmh.20-1422.

13. Bazi T, Finan R, Zourob D, Sabbagh AS, Nasnas R, Zreik TG. Filariasis infection is a probable cause of implantation failure in in vitro fertilization cycles. Fertil Steril. 2006 Jun;85[6]:1822.e13-5. doi: 10.1016/j.fertnstert.2005.11.067.

14. Stanton MC, Best A, Cliffe M, Kelly-Hope L, Biritwum NK, Batsa L, Debrah A. Situational analysis of lymphatic filariasis morbidity in Ahanta West District of Ghana. Trop Med Int Health. 2016 Feb;21[2]:236-44. doi: 10.1111/tmi.12643.

15. Soran A, Toktas O, Grassi A, Sezgin E. Adding Pneumatic Compression Therapy in Lower Extremity Lymphedema Increases Compliance of Treatment, While Decreasing the Infection Rate. Lymphat Res Biol. 2022 Jun;20[3]:315-318. doi: 10.1089/lrb.2020.0086.

16. Borman P. Lymphedema diagnosis, treatment, and follow-up from the view point of physical medicine and rehabilitation specialists. Turk J Phys Med Rehabil. 2018 Sep 3;64[3]:179-197. doi: 10. 5606/tftrd.2018.3539.

17. Phillips JJ, Gordon SJ. Intermittent Pneumatic Compression Dosage for Adults and Children with Lymphedema: A Systematic Review. Lymphat Res Biol. 2019 Feb;17[1]:2-18. doi: 10.1089/lrb.2018. 0034.

18. Chen AH, Frangos SG, Kilaru S, Sumpio BE. Intermittent pneumatic compression devices -- physiological mechanisms of action. Eur J Vasc Endovasc Surg. 2001 May;21[5]:383-92. doi: 10. 1053/ejvs.2001.1348.

19. Adams JA, Uryash A, Lopez JR. Non-Invasive Pulsatile Shear Stress Modifies Endothelial Activation; A Narrative Review. Biomedicines. 2022 Nov 28;10[12]:3050. doi: 10.3390/bio-medicines10123050.

20. Weaver SRC, Rendeiro C, Lucas RAI, Cable NT, Nightingale TE, McGettrick HM, Lucas SJE. Non-pharmacological interventions for vascular health and the role of the endothelium. Eur J Appl Physiol. 2022 Dec;122[12]:2493-2514. doi: 10.1007/ s00421-022-05041-y.

21. Lee WJ, Tateya S, Cheng AM, Rizzo-DeLeon N, Wang NF, Handa P, *et al.* M2 Macrophage Polarization Mediates Anti-inflammatory Effects of Endothelial Nitric Oxide Signaling. Diabetes. 2015 Aug;64[8]:2836-46. doi: 10.2337/db14-1668.

22. Yang L, Feura ES, Ahonen MJR, Schoenfisch MH. Nitric Oxide-Releasing Macromolecular Scaffolds for Antibacterial Applications. Adv Healthc Mater. 2018 Jul;7[13]:e1800155. doi: 10. 1002/adhm.201800155.

23. Hall JR, Rouillard KR, Suchyta DJ, Brown MD, Ahonen MJR, Schoenfisc MH. Mode of nitric oxide delivery affects antibacterial action. ACS Biomater Sci Eng. 2020 Jan 13;6[1]:433-441. doi: 10.1021/ acsbiomaterials.9b01384.

24. Howlin RP, Cathie K, Hall-Stoodley L, Cornelius V, Duignan C, Allan RN, *et al.* Low-Dose Nitric Oxide as Targeted Anti-biofilm Adjunctive Therapy to Treat Chronic Pseudomonas aeruginosa Infection in Cystic Fibrosis. Mol Ther. 2017 Sep 6;25[9]:2104-2116. doi: 10.1016/j.ymthe.2017.06. 021.

25. Ahmed R, Augustine R, Chaudhry M, Akhtar UA, Zahid AA, Tariq M, *et al.* Nitric oxide-releasing biomaterials for promoting wound healing in impaired diabetic wounds: State of the art and recent trends. Biomed Pharmacother. 2022 May; 149:112707. doi: 10.1016/j.biopha.2022.112707.

26. Carpenter AW, Schoenfisch MH. Nitric oxide release: part II. Therapeutic applications. Chem Soc Rev. 2012 May 21;41[10]:3742-52. doi: 10.1039/ c2cs15273h.

27. Sugisawa R, Unno N, Saito T, Yamamoto N, Inuzuka K, Tanaka H, *et al.* Effects of Compression Stockings on Elevation of Leg Lymph Pumping Pressure and Improvement of Quality of Life in Healthy Female Volunteers: A Randomized Controlled Trial. Lymphat Res Biol. 2016 Jun; 14[2]:95-103. doi: 10.1089/lrb.2015.0045.

28. Hebert AA. A new therapeutic horizon in diaper dermatitis: Novel agents with novel action. Int J Womens Dermatol. 2021 Feb 16;7[4]:466-470. doi: 10.1016/j.ijwd.2021.02.003.

29. Chang AY, Tonui EC, Momanyi D, Mills AR, Wasike P, Karwa R, Maurer TA, Pastakia SD. Development of Low-Cost Locally Sourced Two-Component Compression Bandages in Western Kenya. Dermatol Ther [Heidelb]. 2018 Sep;8[3]: 475-481. doi: 10.1007/s13555-018-0248-z.

International Journal of Medical Arts

https://ijma.journals.ekb.eg/
Print ISSN: 2636-4174
Online ISSN: 2682-3780