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REFERRED MUSCLE PAIN, SOME CONSIDERATIONS OF ITS SIGNIFICANCE IN PRACTICE

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Abstract: Muscle pain is a common symptom in many musculoskeletal disorders. When it is local as a result of a muscle injury, correct diagnosis does not appear difficult. Referred muscle pain is a symptom associated with diagnostic and therapeutic challenges. It can be a consequence of an injury that develops elsewhere in the body: a skeletal muscle in another area or joint, or it can often be associated with a visceral injury (in this case we have referred muscle pain or secondary muscle pain). The aim of this article is to make a review of the available literature studying the nature, diagnosis, and treatment of referred pain and its relevance to clinical practice. Materials and Methods: In this review, the available scientific articles concerning the field of reflected pain are reviewed: Google Scholar, Pubmed, Science Direct Web of Science, Scopus, and scientific articles in Cyrillic) databases were reviewed. The search results included keywords that define the current problem: muscle pain, referred muscle pain, nociceptive pain, neuropathic pain, radicular pain, somatic, viscera, visceral pain, hyperalgesia, central sensitization, spinal sensitization, visceral hyperalgesia; viscerosomatic convergence; descending modulation, muscle contraction, muscle hypotrophy. Results: When searching for topical scientific results, not many publications have been found. Some of them were older, in some possible mechanisms of pathogenetic manifestation of referred muscle pain were discussed. One article suggested the existence of another possible mechanism besides the generally described ones. Several hypotheses concerning the occurrence of this secondary pain were found to exist, without giving priority to any theory. Most articles described different localizations of symptoms of referred pain and their relationship to other body structures (muscle or joint in a distant region) or internal organ dysfunction or disease. Most of the authors emphasized on the need of better knowledge of this type of pain and the distinction between local, nociceptive, radicular, and neuropathic pain that has a precise clinical characteristic and evidence of a specific injury to an underlying body structure. Conclusion: Knowledge and diagnosing of referred muscle pain is important for clinical practice. Differentiation from primary skeletal muscle pain is still a challenge, but a good knowledge of the problem can provide solutions, although the pathogenetic mechanisms of its occurrence remain unclear. It is likely that the totality of central-nervous mechanisms, the convergence of information from different somatic areas in the dorsal horn and/or its facilitation in it as well as at the level of the thalamus, and the phenomenon of hyperexcitability are essential, although the notion that referred muscle pain has a peripheral origin should not be ignored. Knowledge and targeted search for referred secondary pain could prevent some diagnostic problems and at the same time treat it with appropriate treatments, including the means of physiotherapy.

Keywords: *muscle pain, referred muscle pain, visceral pain, central sensitization, muscle contraction, physiotherapy.*
Field: Medical sciences and Health

1. INTRODUCTION

Muscle pain is a common symptom in many musculoskeletal disorders. When it is local as a result of a muscle injury, a precise diagnosis is not difficult (Märker-Hermann E., 2020; Giamberardino, M. A. et al., 2004; Yankai, A. et al., 2023). Muscle pain is associated with the activation of nociceptive nerve endings, associated with a decrease in tissue pH and adenosine triphosphate. Activation of these receptors in turn increases the excitability of sensory neurons in the spinal cord and leads to central sensitization. This, in turn, causes increased excitability on spinal cord level and is the cause of the onset of muscle pain, in which motoneurons of the injured muscle are inhibited on a central level. The occurrence of muscle spasm usually has a secondary origin and is due to damage to another muscle or joint. Current understanding of pain assumes that there are different types of pain, which are caused by different mechanisms and need to be treated differently depending on the origin of the pain (Mense S., 2008). Reflected muscle pain is a symptom associated with diagnostic and therapeutic challenges. It can be a consequence of an injury that develops elsewhere in the body: a skeletal muscle in another area or joint, or it can often be associated with a visceral injury (in this case referred muscle pain or secondary muscle pain) (Jin, Q. et al., 2023; Giamberardino, M. A. et al., 2004; Sikandar, S., & Dickenson, A. H., 2012).

Referred muscle pain in pathology of internal organs is a symptom that can be observed in

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myocardial infarction. Before true visceral pain develops, indeterminate pain in the lower sternal and/or epigastric, or interscapular region, accompanied by sweating, nausea, and tremor, is reported in the early stages of the disease. Subsequently, pain is localized to the chest in its anterior or posterior projection and often involves the left upper extremity. These cases are not infrequently accompanied by hyperalgesia of the m. Pectoralis major, inter-scapular space and forearm. In rarer cases, symptomatology may be seen in the area of the m. trapezius and/or m. deltoideus. Similar cases of reflected muscle pain in internal organ disease are seen in kidney colic, where it is found in the area of m. Quadratus lumborum and mm. obliquus, while in biliary colic there is reflected pain in the upper right abdominal quadrant and radiation to the back (Giamberardino, M. A. et al., 2004).

Sometimes symptoms can persist over time and a good knowledge of them can guide the clinician to the internal organ that is suffering. For example, weakness of the muscles on the inner side of the thigh may point to problems with the large intestine, such as colitis and obstipation; with flatfoot, it is necessary to monitor the condition of the muscles of the pelvic floor and female reproductive organs; back pain and shoulder forward bending may be associated with diseases of the stomach; hypertonia of the neck flexor muscles may point to problems in the maxillary sinuses, etc.

Lower back pain can be associated with morphological and functional changes in the hip muscles, such as mm. gluteii, m. piriformis m. psoas major (Pourahmadi, M. et al., 2020).

All these examples draw attention to a secondary pain whose primary cause is located in another body segment, but often due to the prolonged persistence of the primary cause, a long-lasting referred muscle pain develops, accompanied by prolonged spasm and hypotrophy of the secondarily affected muscle (Giamberardino, M. A. et al., 2004).

The aim of this article is to make a review of the available literature studying the nature, diagnosis, and treatment of referred pain and its relevance to clinical practice.

2. MATERIALS AND METHODS

In this review, the available scientific articles concerning the field of reflected pain are reviewed: Google Scholar, Pubmed, Science Direct Web of Science, Scopus, and scientific articles in Cyrillic) databases were reviewed. The search results included keywords that define the current problem: muscle pain, referred muscle pain, nociceptive pain, neuropathic pain, radicular pain, somatic, viscera, visceral pain, hyperalgesia, central sensitization, spinal sensitization, visceral hyperalgesia; viscerosomatic convergence; descending modulation, muscle contraction, muscle hypotrophy.

3. RESULTS

When searching for topical scientific results, not many publications have been found. Some of them were older, in some possible mechanisms of pathogenetic manifestation of referred muscle pain were discussed. One article suggested the existence of another possible mechanism besides the generally described ones. Several hypotheses concerning the occurrence of this secondary pain were found to exist, without giving priority to any theory. Most articles described different localizations of symptoms of referred pain and their relationship to other body structures (muscle or joint in a distant region) or internal organ dysfunction or disease. Most of the authors emphasized on the need of better knowledge of this type of pain and the distinction between local, nociceptive, radicular, and neuropathic pain that has a precise clinical characteristic and evidence of a specific injury to an underlying body structure.

4. DISCUSSIONS

Pain is a symptom that alerts to a problem in a particular body segment and is a common reason for a visit to the doctor. Accurate differentiation of pain and its origin is important for proper treatment (Nedyalkova-Petkova & Mihaylova, 2023; Bekir et al., 2022). Often, the diagnostic process is not complicated and with the help of a physical examination and instrumental or other laboratory testing, the source of pain is identified. At the same time, there are cases in which the diagnosis requires checking for the presence of secondary or referred muscle pain. Sometimes this type of pain may precede the clinical manifestation of the underlying disease, and the correct interpretation of this symptom may very early direct the clinician to the actual pathologic process.

For example, in low back pain (Nicol et al., 2023) according to literature data only in 20% of patients with low back pain a precise etiological cause can be found. In about 5% of patients, two or more causes may be found to be present simultaneously (Todorov, 2014). Low back pain is most

commonly caused by damage or degeneration of the intervertebral discs and intervertebral joints, which is characterized by vertebral and radicular syndrome, and in both syndromes the pain has different origins and characteristics. Radicular pain in this case is due to irritation of the dorsal root or their ganglia, or compression of various natures of the dorsal root ganglia (Bogduk, 2009; Vulfsons et al., 2017; Jin, Q. et al., 2023). In cases in which no morphological substrate is found in these structures, low back pain may be caused by thoracolumbar fascia and/or compartment syndrome, paravertebral muscles (mm. iliocostalis and longissimus dorsi) or by m. psoas and/or m. quadratus lumborum, ligaments and insertions in the form of enthesopathy, ligaments, (facet) joints, sacroiliac joints, in osteoporosis of vertebral bodies (Todorov, 2014; Becker et al., 2021) morphological and/or functional changes in the hip muscles, such as mm. gluteii, m. piriformis m. psoas major (Pourahmadi et al., 2020) and others. In other cases, pain in the area of the m. Quadratus lumborum and mm. obliquus may be associated with renal pathology in asymptomatic renal calculi (Giamberardino et al., 2004). Therefore, differentiating primary, local pain from secondary referred pain is an important issue.

There are several scientific theories that attempt to explain the presence of referred muscle pain. According to some, the dorsal horn nociceptors and brainstem neurons receive information from different tissues, which converging results in the inability of higher brain centers to differentiate the actual source of pain (Arendt-Nielsen & Svensson, 2001; Yam M. F. et al., 2018). Referred muscle pain is likely determined by the distribution along the sclerotomes (muscle, fascia, and bone) and more rarely has a dermatomal representation (Whitman, Launico, & Adigun, 2023; Arendt-Nielsen & Svensson, 2001).

According to Mense S. (1993), muscle pain is more often associated with distant areas from the primary focus than skin pain. This is explained by the Convergence-Projection Theory, which postulates that the fusion of afferent information from internal organs at the spinal cord level with somatic afferent information leads to an increase in the activity of neurons in the dorsal horn due to its being read as originating from the same dermatome (Mense S., 1993). This is why it is important to know the connections at the level of the nervous system between the different cortical segments, including between somatic and visceral structures and organs (Gadet, 2019). Other plausible theories that explain referred muscle pain may be: Convergence-facilitation theory. The processing of the resultant subthreshold sensory afferents from skin receptors and from the sinuvertebral nerve is realized by the same spinothalamic structures, therefore these structures cannot localize the exact location of pain. (Simmons et al., 1993).

According to Arendt-Nielsen & Svensson, 2001) Axon-reflex theory (Yaprak, 2008) is a less likely explanation for referred muscle pain. According to them referred muscle pain is probably due to the activation of central-nervous mechanisms because it is possible to induce referred muscle pain in limbs with sensory loss. However, it should be considered that the absence of peripheral afferent for pain reduces the appearance of referred muscle pain, but it can be induced without the presence of peripheral input (Arendt-Nielsen & Svensson, 2001).

Hyperexcitability theory - the development of a central hyperexcitability mechanism may modify and modulate referred muscle pain, and substance P may possibly play a role in this regard (Arendt-Nielsen & Svensson, 2001; Polgár et al., 2020). According to Lidbeck J. (2002), dysfunctionality in central nervous information processing may explain the causes of different types of musculoskeletal pain, which in turn will allow, depending on the different pathophysiological mechanisms of pain induction, to differentiate different rehabilitation programs for pain management (Lidbeck, 2002; Martins et al., 2022, Krenn et al., 2020).

According to the Thalamic convergence theory, referred pain is not a consequence of information processing at the spinal cord level, but results from the accumulation of information in brain neurons after information from referred pain and from the damaged anatomical structure is aggregated. Computer simulations have been described that show that there may be communication between different cortical and subcortical structures (Arendt-Nielsen & Svensson, 2001; Lee & Winer, J. A. 2011).

Other authors assume that referred muscle pain has a predominantly peripheral origin. Farasyn, A. (2007) proposes the “barrier-dam” theory (Farasyn, 2007). According to this theory, if injured muscle structures (hard and/or soft myofibrosis), symptomatic and/or asymptomatic trigger points are located along the path of peripheral afferent sensory nerves in skeletal muscle, these structures can disrupt conduction along the nerve, compressing it and causing referred muscle pain. It has been suggested that these myofibrotic structures are a consequence of incomplete repair of a local inflammatory process in the setting of an impaired immune response in the tissue. This theory, for example, explains the burning pain in Meralgia paresthetica (tingling and burning pain in the outer thigh due to pinching of the n. cutaneus femoris lateralis, which is compressed at the exit of the pelvis) (Dengler N. F., 2023). By reducing the effect of the “barrier-dam” by means of deep cross-friction massage on rigid fibrosis (for at least 2 weeks), the reduction and disappearance of referred muscle pain in pseudo-sciatica is explained, which is associated

with nonspecific low back pain resulting from compression of the n. clunium superior medialis from muscle stiffening in the upper part of the m. gluteus medius et m. tensor fasciae latae (Konno et al., 2017); as well as in tension headache (in the temporal and/or orbital and/or frontal region of the head) caused by myofibrous points in the muscular body of m. sternocleidomastoideus et pars superior m. trapezius, which compress the nn. auricularis et transversus colli, et n. occipitalis; and also, in radiating tension along the dorsal part of the shoulder and upper limb, which results from squeezing at the level of the rhomboid and infraspinatus muscles of the rr. dorsales nn. thoracis (Farasyn, 2007).

It is likely that a cluster of central-nervous mechanisms, the convergence of information from different somatic areas in the dorsal horn and/or its facilitation in the dorsal horn, as well as at the level of the thalamus, the phenomenon of hyperexcitability and/or damage to peripheral muscle areas are essential for the occurrence of the referred muscle pain phenomenon.

Referred muscle pain may also be due to damage to various structures in the spine (Kurosawa, Murakami & Aizawa, 2015), such as the intervertebral discs, facet joints and sacroiliac joints (Jin et al., 2023). In these cases, it is very important to differentiate, true radicular pain (radicular-type pain, weakened or absent tendon and periosteal reflexes, muscle weakness and/or hypotrophy, and paresthesia along the course of the corresponding dermatome innervated by the peripheral nerve) and/or neuropathic pain (allodynia with hyperalgesia, spreading along the dermatomal type in the area innervated by the corresponding peripheral nerve) from referred muscle pain, because there may often be overlap of the areas of manifestation, but referred muscle pain does not spread along the dermatomal or radicular type (Farasyn, 2007); Jin et al., 2023). The pain is often dull, is described as an expanding pressure and spreads over a wide area, and sometimes has the character of hyperalgesia. Occasionally, muscle hypotrophy and hyperalgesia may also be observed in the area of reflected pain. There is no neurological symptomatology including numbness and paresthesia, as this type of pain is not caused by pathological compression on nerve roots. The shoulder and neck region are the most common areas in which secondary pain is seen when the cervical facet joints are affected, whereas dysfunction of the thoracic facet joints results in pain in the back and iliac crest region. Damage to the lumbar facet joints results in referred muscle pain in the area between the hip and thigh (reflected pain in the hip region, hip joint, and lateral thigh for the upper lumbar facet joints and in the posterior thigh region for the lower lumbar facet joints) (van Kleef et al., 2010; Manchikanti et al., 2020; Jin et al., 2023).

Referred muscle pain occurring in the lower back, buttock, groin, and thigh, even the foot, which is not radicular in origin, may be due to involvement of the sacroiliac joints (van der Wurff et al., 2006; Jin et al., 2023).

Recognition and targeted searching of the reflected secondary pain could prevent some diagnostic problems and at the same time treat it with appropriate treatments, including the means of Physical and Rehabilitation Medicine.

Due to the mentioned heterogeneity of the Referred muscle pain, a multimodal approach for its treatment is recommended, which incorporates pharmacological treatment, invasive therapy with local anesthetic blockages or intra-articular administration of corticosteroids, radiofrequency coagulation of articular nerves, methods from Physical Medicine, regular performance of therapeutic exercises and psychological support of patients (van Kleef et al., 2010; Jin et al., 2023; Li. et al., 2023).

Acupuncture, Manual medicine techniques, Trigger point injections, Laser therapy, Superficial dry needling in combination with muscle stretching, Massage, Application of heat or ice, TENS (Transcutaneous electrical nerve stimulation), Ethyl chloride spray and stretch technique, Ultrasound, Exercise may come into consideration in the treatment of referred muscle pain (Lidbeck, 2002; Yildirim, Öneş & Gökşenoğlu, 2018; Harada et al., 2019; Gibson et al., 2019; Ali et al., 2020; Chang et al., 2021; Martins et al., 2022; Krenn et al., 2020; Yankai, A. et al., 2023; Portilla et al., 2023).

5. CONCLUSIONS

Knowledge and diagnosing of referred muscle pain is important for clinical practice. Differentiation from primary skeletal muscle pain is still a challenge, but a good knowledge of the problem can provide solutions, although the pathogenetic mechanisms of its occurrence remain unclear. It is likely that the totality of central-nervous mechanisms, the convergence of information from different somatic areas in the dorsal horn and/or its facilitation in it as well as at the level of the thalamus, and the phenomenon of hyperexcitability are essential, although the notion that referred muscle pain has a peripheral origin should not be ignored. Knowledge and targeted search for referred secondary pain could prevent some diagnostic problems and at the same time treat it with appropriate treatments, including the means of physiotherapy.

REFERENCES

Ali, H. A., Elzohiery A. K., Arafa, M. M., Elkadery, N. A. (2020). Dry needling versus ultrasonic in treating cervical myofascial pain syndrome, QJM: An International Journal of Medicine, 113(1), hcaa064.005, https://doi.org/10.1093/qjmed/hcaa064.005

Arendt-Nielsen, L., & Svensson, P. (2001). Referred muscle pain: basic and clinical findings. The Clinical journal of pain, 17(1), 11–19. https://doi.org/10.1097/00002508-200103000-00003

Becker, L., Ziegeler, K., Diekhoff, T., Palmowski, Y., Pumberger, M., & Schömig, F. (2021). Musculature adaption in patients with lumbosacral transitional vertebrae: a matched-pair analysis of 46 patients. Skeletal radiology, 50(8), 1697–1704. https://doi.org/10.1007/s00256-021-03722-x

Bekir, N., Valeva, S., Mollova, K., & Uzunova, A. (2022). Study of the effectiveness of mulligan manual mobilization in tennis elbow. KNOWLEDGE - International Journal, 51(4), 595–599.

Bogduk N. (2009). On the definitions and physiology of back pain, referred pain, and radicular pain. Pain, 147(1-3), 17–19. https://doi.org/10.1016/j.pain.2009.08.020

Chang, W. H., Tu, L. W., Pei, Y. C., Chen, C. K., Wang, S. H., & Wong, A. M. (2021). Comparison of the effects between lasers applied to myofascial trigger points and to classical acupoints for patients with cervical myofascial pain syndrome. Biomedical journal, 44(6), 739–747. https://doi.org/10.1016/j.bj.2020.05.020

Dengler N. F. (2023). Treatment of idiopathic meralgia paresthetica - is there reliable evidence yet?. Neurological research, 45(5), 429–434. https://doi.org/10.1080/01616412.2022.2151115

Farasyn A. (2007). Referred muscle pain is primarily peripheral in origin: the “barrier-dam” theory. Medical hypotheses, 68(1), 144–150. https://doi.org/10.1016/j.mehy.2006.05.063

Farasyn, A. (2007). Referred muscle pain is primarily peripheral in origin: The “barrier-dam” theory, Medical Hypotheses, 68(1), 144-150. (https://www.sciencedirect.com/science/article/pii/S0306987706004488)

Gadet P. Segmental innervation: a graphic synthesis of correspondence between dermatomes, myotomes, sclerotomes and viscerotomes. Systematic review of existing works and publications about dermatomes, myotomes, sclerotomes and viscerotomes aimed to design a graphic synthesis of somato-visceral correspondences. Russian Osteopathic Journal. 2019;(3-4):150-163. (In Russ.) https://doi.org/10.32885/2220-0975-2019-3-4-150-163

Giamberardino, M. A., Affaitati, G., Lerza, R., Vecchiet, L. (2004) Referred Muscle Pain and Hyperalgesia from Viscera: Clinical and Pathophysiological Aspects. Basic and Applied Myology, 14(1): 23-28.

Gibson, W., Wand, B. M., Meads, C., Catley, M. J., & O’Connell, N. E. (2019). Transcutaneous electrical nerve stimulation (TENS) for chronic pain - an overview of Cochrane Reviews. The Cochrane database of systematic reviews, 4(4), CD011890. https://doi.org/10.1002/14651858.CD011890.pub3

Harada, T., Miyagi, M., Izukura, H., Endou, G., Ushigome, N., Tsuruoka, H., Mizutani, A., Ohshiro, T., & Ebihara, S. (2019). The effect of low level laser therapy for pain in major muscles controlling two joints. Laser therapy, 28(2), 111–115. https://doi.org/10.5978/islsm.19-OR-07

Jin, Q., Chang, Y., Lu, C., Chen, L., & Wang, Y. (2023). Referred pain: characteristics, possible mechanisms, and clinical management. Frontiers in neurology, 14, 1104817. https://doi.org/10.3389/fneur.2023.1104817

Konno, T., Aota, Y., Kuniya, H., Saito, T., Qu, N., Hayashi, S., Kawata, S., & Itoh, M. (2017). Anatomical etiology of “pseudo-sciatica” from superior cluneal nerve entrapment: a laboratory investigation. Journal of pain research, 10, 2539–2545. https://doi.org/10.2147/JPR.S142115

Krenn C, Horvath K, Jeitler K, Zipp C, Siebenhofer-Kroitzsch A, Semlitsch T. Management of non-specific low back pain in primary care – A systematic overview of recommendations from international evidence-based guidelines. Primary Health Care Research & Development. 2020;21:e64. doi:10.1017/S1463423620000626

Kurosawa, D., Murakami, E., & Aizawa, T. (2015). Referred pain location depends on the affected section of the sacroiliac joint. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society, 24(3), 521–527. https://doi.org/10.1007/s00586-014-3604-4

Lee, C. C., & Winer, J. A. (2011). Convergence of thalamic and cortical pathways in cat auditory cortex. Hearing research, 274(1-2), 85–94. https://doi.org/10.1016/j.heares.2010.05.008

Li, S. J., Zhang, S. L., & Feng, D. (2023). A comparison of pulsed radiofrequency and radiofrequency denervation for lumbar facet joint pain. Journal of orthopaedic surgery and research, 18(1), 331. https://doi.org/10.1186/s13018-023-03814-5

Lidbeck J. (2002). Central hyperexcitability in chronic musculoskeletal pain: a conceptual breakthrough with multiple clinical implications. Pain research & management, 7(2), 81–92. https://doi.org/10.1155/2002/310974

Manchikanti, L., Kosanovic, R., Cash, K. A., Pampati, V., Soin, A., Kaye, A. D., & Hirsch, J. A. (2020). Assessment of Prevalence of Cervical Facet Joint Pain with Diagnostic Cervical Medial Branch Blocks: Analysis Based on Chronic Pain Model. Pain physician, 23(6), 531–540.

Märker-Hermann E. (2020). Muskelschmerzen und Muskelschwäche – eine interdisziplinäre Herausforderung [Muscle pain and muscle weakness - an interdisciplinary challenge]. Deutsche medizinische Wochenschrift (1946), 145(13), 871. https://doi.org/10.1055/a-0952-9661

Martins, C., Sayegh, S., Faundez, A., Fourchet, F., & Bothorel, H. (2022). Effectiveness of a Group-Based Rehabilitation Program Combining Education with Multimodal Exercises in the Treatment of Patients with Nonspecific Chronic Low Back Pain: A Retrospective Uncontrolled Study. Biology, 11(10), 1508. https://doi.org/10.3390/biology11101508

Mense S. (1993). Neurobiologische Mechanismen der Ubertragung von Muskelschmerz [Neurobiological mechanisms of muscle pain referral.]. Schmerz (Berlin, Germany), 7(4), 241–249. https://doi.org/10.1007/BF02529860

Mense S. (2008). Muscle pain: mechanisms and clinical significance. Deutsches Arzteblatt international, 105(12), 214–219. https://doi.org/10.3238/artzebl.2008.0214

Nedyalkova-Petkova, D., & Mihaylova, M. (2023). The effect of early physical factors on the recovery of an acute ankle sprain: initial results. KNOWLEDGE - International Journal, 60(4), 707–712.

Nicol, V., Verdaguer, C., Daste, C., Bisseriex, H., Lapeyre, É., Lefèvre-Colau, M. M., Rannou, F., Rören, A., Facione, J., & Nguyen, C. (2023). Chronic Low Back Pain: A Narrative Review of Recent International Guidelines for Diagnosis and Conservative Treatment. Journal of clinical medicine, 12(4), 1685. https://doi.org/10.3390/jcm12041685

Polgár, E., Bell, A. M., Gutierrez-Mecinas, M., Dickie, A. C., Akar, O., Costreie, M., Watanabe, M., & Todd, A. J. (2020). Substance P-expressing Neurons in the Superficial Dorsal Horn of the Mouse Spinal Cord: Insights into Their Functions and their Roles in Synaptic Circuits. Neuroscience, 450, 113–125. https://doi.org/10.1016/j.neuroscience.2020.06.038

Portilla G, Montero de Espinosa F. Device for Dual Ultrasound and Dry Needling Trigger Points Treatment. Sensors. 2023; 23(2):580. https://doi.org/10.3390/s23020580

Pourahmadi, M., Asadi, M., Dommerholt, J., & Yeganeh, A. (2020). Changes in the macroscopic morphology of hip muscles in low back pain. Journal of anatomy, 236(1), 3–20. https://doi.org/10.1111/joa.13086

Sikandar, S., & Dickenson, A. H. (2012). Visceral pain: the ins and outs, the ups and downs. Current opinion in supportive and palliative care, 6(1), 17–26. https://doi.org/10.1097/SPC.0b013e32834f6ec9

Simmons, J. W., Jr, Ricketson, R., & McMillin, J. N. (1993). Painful lumbosacral sensory distribution patterns: embryogenesis to adulthood. Orthopaedic review, 22(10), 1110–1118.

Todorov P. (2014). Chronic low back pain – a clinical-anatomical review. Тодоров П. (2014). Хронична болка в кръста – клинико-анатомичен преглед. GP News, 12; available on https://gpnews.bg/

van der Wurff, P., Buijs, E. J., & Groen, G. J. (2006). Intensity mapping of pain referral areas in sacroiliac joint pain patients. Journal of manipulative and physiological therapeutics, 29(3), 190–195. https://doi.org/10.1016/j.jmpt.2006.01.007

van Kleef, M., Vanelderen, P., Cohen, S. P., Lataster, A., Van Zundert, J., & Mekhail, N. (2010). 12. Pain originating from the lumbar facet joints. Pain practice : the official journal of World Institute of Pain, 10(5), 459–469. https://doi.org/10.1111/j.1533-2500.2010.00393.x

Vulfsons, S., Bar, N., & Eisenberg, E. (2017). Back Pain with Leg Pain. Current pain and headache reports, 21(7), 32. https://doi.org/10.1007/s11916-017-0632-x.

Whitman, P. A., Launico, M. V., & Adigun, O. O. (2023). Anatomy, Skin, Dermatomes. In StatPearls. StatPearls Publishing.

Yam, M. F., Loh, Y. C., Tan, C. S., Khadijah Adam, S., Abdul Manan, N., & Basir, R. (2018). General Pathways of Pain Sensation and the Major Neurotransmitters Involved in Pain Regulation. International journal of molecular sciences, 19(8), 2164. https://doi.org/10.3390/ijms19082164

Yankai, A., Leelarungrayub, J., & Laskin, J. J. (2023). Preliminary Study: Short-term Beneficial Effects of Thai Tok Sen Massage on Pain, Pressure Pain Threshold, and Upper Trapezius Muscle Thickness Among People with Shoulder Pain. International journal of therapeutic massage & bodywork, 16(1), 3–12. https://doi.org/10.3822/ijtmb.v16i1.779

Yaprak, M. (2008). The axon reflex. Neuroanatomy, 7: 17–19

Yildirim, M. A., Öneş, K., & Gökşenoğlu, G. (2018). Effectiveness of Ultrasound Therapy on Myofascial Pain Syndrome of the Upper Trapezius: Randomized, Single-Blind, Placebo-Controlled Study. Archives of rheumatology, 33(4), 418–423. https://doi.org/10.5606/ArchRheumatol.2018.6538

Lekić, L., & Pavlović, B. (2024). Transdermal application of vitamin d and its effects on psoriasis, *MEDIS - Medical Science and Research, 3*(1), 7-11. doi: 10.35120/medisij030107l
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TRANSDERMAL APPLICATION OF VITAMIN D AND ITS EFFECTS ON PSORIASIS

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Abstract: Psoriasis represents a disorder of skin hypoproliferation, where vitamin D is frequently utilized in its treatment. Ultraviolet (UV) radiation stimulates the synthesis of vitamin D3 (cholecalciferol) in the epidermis. This compound undergoes further conversion into active metabolites, specifically 25-hydroxycholecalciferol and 1,25-hydroxycholecalciferol, which play crucial roles in skin health. However, in conditions like psoriasis, disruptions in skin functioning impede the cutaneous production of vitamin D, initiating a detrimental cycle. This disruption leads to a gradual reduction in vitamin D levels throughout the body, consequently destabilizing skin homeostasis. Topical application of vitamin D enables a substantial reduction in psoriasis on target areas of the body such as the scalp, joints, hands and lumbar region. The research records reductions of 100%, 80%, and 50% in the mentioned regions.

Keywords: vitamin D, psoriasis, participants, scalp, joints, lumbal region, hands
Field: Pharmacoeconomics, Pharmacy

1. INTRODUCTION

Vitamin D, along with its metabolites and analogs, constitutes a group of compounds with various functions in the body. It possesses the ability to dissolve in fat, akin to secosteroids and prohormones. Additionally, vitamin D is found in two primary forms: Vitamin D2, also known as ergocalciferol, and vitamin D3, referred to as cholecalciferol (Bocheva et al., 2021). One of its most crucial roles is synthesis within the body, particularly in the skin, where it is synthesized from endogenous cholesterol (7-dehydrocholesterol) under the influence of UV B (290-315 nm) radiation (Pitukweerakul et al., 2019). This synthesis converts vitamin D from its prohormone form into its active form. Subsequently, it undergoes metabolism in the liver, converting into 25-hydroxyvitamin D (25-OH D), with further transformations occurring in the kidneys, resulting in the active form known as calcitriol (1.25 (OH)2 vitamin D). A deficiency in vitamin D can lead to a disease called psoriasis, a chronic immune-mediated inflammatory skin disorder with a prevalence of 2-3% in the general population (Bhat et al., 2022). It commonly manifests on the skin, although inflammatory processes can occur in other organs. Psoriasis is now recognized as a systemic pathology, encompassing other conditions, ranging from psoriatic arthritis to obesity and metabolic disorders (Brozyana et al., 2022). Dermatological conditions associated with psoriasis are characterized by hyperproliferation of keratinocytes, impaired epidermal barrier function at skin lesion sites, and infiltration of activated inflammatory cells into the skin (Raharja et al., 2021). Various factors contribute to its development, including autoimmune, genetic, hormonal, and psychosomatic factors. Moreover, vitamin D plays a critical role in regulating calcium and phosphorus homeostasis, thereby maintaining the integrity of the skeletal system. The potential efficacy of vitamin D supplementation as an adjunctive treatment option in psoriatic patients remains intriguing yet conservative.

1.2. VITAMIN D CREAM

Vitamin D Cream represents a product by brend „Dr. Pasha“ from Sarajevo. The cream has the following details of patent claim:

- Cholecalciferol, Vitamin D3: Ph Eur,BP,USP;
- CAS-br. 67-97-0;
- Molecular formula: $C_{27}H_{44}O$ (Hill) (Figure 1);
- EZ-number 200-673-2;

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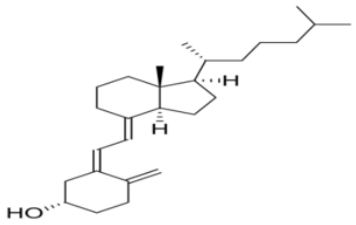
Figure 1. Composition of the general formula of Vitamin D3



(Bouillon et al., 2020)

The well-known structure of vitamin D3 is integrated into the cream base, which, due to its composition delivers active substances to the application site. These included: Shea butter, Almond oil and Hydrolyzed oat protein in the form of potassium salts and Xanthan gum, whose composition includes: Agua, Prunus Amygdalus Ducis Oil, Glycerin, Cetearyl Alcohol, Glyceryl Oleate, Butyrospermum Parkii Butter, Glyceryl Stearate, Dehydroacetic Acid, Benzyl Alcohol, Xanthan Gum, Cholecalciferol, Potassium Olivoyl Hydrolyzed Oat Protein, Tocopherol.This cream is intended as dermal support in conditions where there is a need to replenish a deficiency of vitamin D, and it is applied with approximately 1200 IU of vitamin D. It is to be applied to the treated skin twice a day, in the morning and evening, with the aim of delivering an adequate dose of vitamin D to the treated area much faster and more efficiently than would be achieved through oral supplementation.

2. MATERIALS AND METHODS

The transdermal application of vitamin D in subjects with psoriasis lasted for 3 months. The cream was applied twice daily: 1x in the morning and 2x in the evening before bedtime. The total number of participants was 18, with 7 male participants and 11 female participants. Regions affected by psoriasis included the scalp, joints, hands, and lumbar region. All participants (18) had a vitamin D deficiency in their blood, as confirmed by blood test results. he study was conducted using an online survey tool (Google Forms) The survey was conducted anonymously and with strict confidentiality, collecting data on the patients health status and their medical history. Transdermal vitamin D application therapy did not interfere with the routine patient treatment documentation and was carried out with their informed consent. The research complied with the Convention on Human Rights and relevant local regulations concerning patient rights, such as the Law on Rights, Obligations, and Responsibilities of Patients in the Federation of Bosnia and Herzegovina, the Law on Personal Data Protection in Bosnia and Herzegovina, and the Regulation on Health Records in the Federation of Bosnia and Herzegovina.

3. RESULTS

Table 1. displays results for male and female participants with psoriasis, encompassing individuals aged 15 to 45. In the male cohort (N=7), the predominant age range was 15 to 35, with an equal distribution of 3 participants in each subgroup, while only 1 participant fell into the 36-45 category. Among females (N=11), the majority (6) fell within the 26-35 age range, with 5 participants in the 15-25 category. The smallest subset, mirroring the male group, consisted of 2 participants aged 36-45.

Table 1. Application of vitamin D for managing psoriasis in both males and females

The age group of participants	***The gender group of the participants***			
	Male (N=7)	(%)	Female (N=11)	(%)
from 15-25 age	3	42.85	5	45.45
from 26-35 age	3	42.8	6	54.54
from 36-45 age	1	14.28	2	28.54

(Lekić i Pavlović, 2024)

Within Table 2, the results for predominant regions affected by psoriasis are presented, encompassing the scalp, joints, hands, and lumbar region in both male and female populations. In the male cohort (N=7), the region where psoriasis was most prevalent was joints, observed in 3 participants (42.85%). Additionally, psoriasis was recorded on the hands in 2 participants (28.54%) and in 1 participant each on the scalp and lumbar region (14.25% each). Conversely, among the female population (N=11), a higher number of participants were observed. Psoriasis was predominantly present on the joints in 5 participants (45.45%), making it the most dominant region in this population. Additionally, psoriasis was noted on the scalp, hands, and lumbar region in 2 participants each (18.18%).

Table 2. Regions affected by psoriasis in the male and female populations

Regions affected by psoriasis	***The gender of participants***			
	Male		*Female*	
	N=7	*%*	*N=11*	*%*
Scalp	1	14.25	2	18.18
Joints	3	42.85	5	45.45
Hands	2	28.54	2	18.18
Lumbar region	1	14.28	2	18.18

(Lekić i Pavlović, 2024)

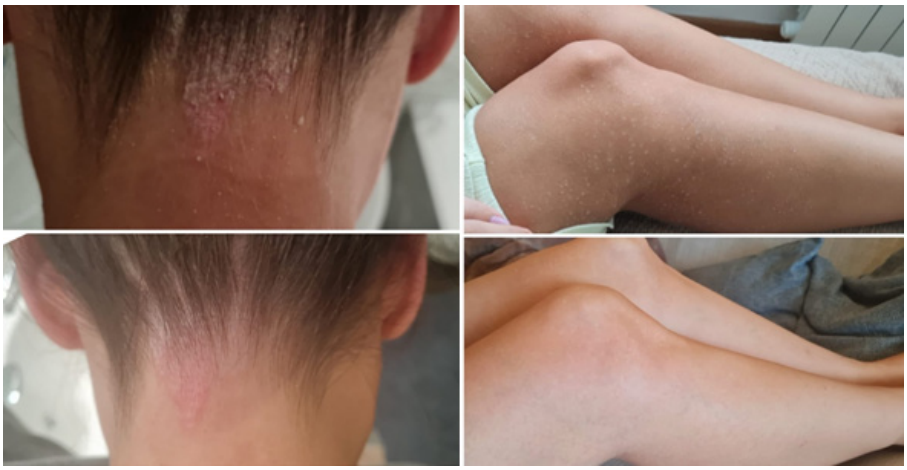
Table 3. presents the outcomes for male and female participants with psoriasis across the scalp, joints, hands, and lumbar regions. The table covers a three-month period of vitamin D cream application, documenting the results. In the male cohort (N=7), for the scalp region (1 participant), an 80% reduction in psoriasis was observed (14.25%). Within the joint region (3 participants), psoriasis reduction was noted as 100% in 2 participants and 80% in 1 participant. The hands region exhibited reductions of 100% and 80% in psoriasis for 1 participant each, while the lumbar region recorded a 100% reduction in psoriasis for 1 participant. In the female population (N=11), for the scalp region, an 80% reduction was observed in 2 participants. Within the joints region, reductions were noted as 100% in 2 participants, 80% in 2 participants, and 50% in 1 participant. Results for the hands region indicated reductions in 2 participants, with a 100% reduction in 1 participant and 80% in the other. Lumbar region results documented reductions of 80% in 2 participants.

Table 3. Application of vitamin D cream in male and female participants in the presence of psoriasis

Reduction of inflammatory acne after 3 month of vitamin D application	***Gender of participants***			
	Male		*Female*	
	N=7	%	N=11	%
SCALP REGION				
100% reduction	0	/	/	/
80% reduction	1	14.25	2	18.18
50% reduction	0	/	/	/
30% reduction	0	/	/	/
10% reduction	0	/	/	/
No improvement observed	0	/	/	/
JOINTS REGION				
100% reduction	2	28.54	2	18.18c
80% reduction	1	14.25	2	18.18
50% reduction	0	/	1	9.09
30% reduction	0	/	/	/
10% reduction	0	/	/	/
No improvement observed	0	/	/	/
HANDS REGION				
100% reduction	1	14.25	1	9.09
80% reduction	1	14.25	1	9.09
50% reduction	0	/	/	
30% reduction	0	/	/	/
10% reduction	0	/	/	/
No improvement observed	0	/	/	/
LUMBAL REGION				
100% reduction	1	14.25%	/	/
80% reduction	/	/	2	18.18
50% reduction	/	/	/	
30% reduction	/	/	/	
10% reduction	/	/	/	
No improvement observed	/	/	/	

(Lekić i Pavlović, 2024)

Figure 2. demonstrates the impact of vitamin D cream on psoriasis-affected areas of the scalp and joints. The findings reveal an 80% decrease in scalp psoriasis and a complete elimination (100%) of psoriasis in the joints region.



(Lekić i Pavlović, 2024)

4. DISCUSION

Psoriasis is presently recognized as a systemic inflammatory disorder characterized by a comprehensive spectrum of comorbidities, spanning from respiratory disease to cardiovascular diseases. The occurrence of psoriasis ranges from 2-3%, exhibiting noteworthy disparities among diverse ethnic cohorts. The pathogenesis of psoriasis remains a focal point of investigation, with evidence pointing towards susceptible genes, identified triggers, and nutritional data predominantly suggestive of a multifactorial pathogenesis wherein a genetically predisposed susceptibility is activated by a predisposing environmental milieu (Formisano et al., 2023). Literary data indicate a significant prevalence and correlation between psoriasis vitamin D, with the research by Al-Tajer et al. (2022) reporting a decreased level of 25-hydroxy vitamin D in 46 psoriatic cases was 30.5 ± 9.3 vs. 38.3 ± 9.6 ng/ml, where the P was < 0.0001. Guillet et al. (2022) approximate that psoriasis typically begins at approximately 33 years of age on average. Yet, in younger individuals, psoriasis appears to be more prevalent in males than in females. In females, psoriasis most commonly manifests between the ages of 16 and 22 or between 55 and 60 years. Psoriasis tends to be more prevalent in males aged 30 to 39 and 60 to 79. Studies, such as that by Blegvad et al. (2017), indicate a higher occurrence of psoriasis in females compared to males, particularly among those with autoimmune disorders. However, there is limited literature on the use of vitamin D cream applied to the skin as a primary method for managing and preventing psoriasis, underscoring our pioneering role in this research field. Section 3 of our study presents compelling evidence of the significant effectiveness of vitamin D cream in treating psoriasis. These findings could establish a solid foundation for future investigations into the transdermal application of vitamin D cream for psoriasis management.

REFERENCES

Al Tajer, N. F., Al-Rawi, J. R., Sahib, S. A. (2022). Vitamin D Levels in Psoriatic Patients. Iraqi Medical Journal, 68(2), 83-89.
Bhat, G. H., Guldin, S., Khan, M. S., Yasir, M., Prasad, G. (2022). Vitamin D status in Psoriasis: impact and clinical correlations. BMC nutrition, 8(1), 115.
Blegvad, C., Egeberg, A., Nielsen, T. E. T., Gislason, G. H., Zachariae, C., Andersen, A. M. N., Skov, L. (2017). Autoimmune disease in children and adolescents with psoriasis: a cross-sectional study in Denmark. Acta Dermato-Venereologica, 97(10), 1225-1229.
Bocheva, G., Slominski, R. M., Slominski, A. T. (2021). The impact of vitamin D on skin aging. International Journal of Molecular Sciences, 22(16), 9097.
Bouillon, R., Schuit, F., Antonio, L., Rastinejad, F. (2020). Vitamin D binding protein: a historic overview. Frontiers in endocrinology, 10, 910.
Brożyna, A. A., Slominski, R. M., Nedoszytko, B., Zmijewski, M. A., Slominski, A. T. (2022). Vitamin D signaling in psoriasis: Pathogenesis and therapy. International Journal of Molecular Sciences, 23(15), 8575.
Formisano, E., Proietti, E., Borgarelli, C., Pisciotta, L. (2023). Psoriasis and Vitamin D: A Systematic Review and Meta-Analysis. Nutrients, 15(15), 3387.
Guillet, C., Seeli, C., Nina, M., Maul, L. V., Maul, J. T. (2022). The impact of gender and sex in psoriasis: What to be aware of when treating women with psoriasis. International Journal of Women's Dermatology, 8(2), e010.

Pitukweerakul, S., Thavaraputta, S., Prachuapthunyachart, S., Karnchanasorn, R. (2019). Hypovitaminosis D is associated with psoriasis: a systematic review and meta-analysis. Kansas Journal of Medicine, 12(4), 103.
Raharja, A., Mahil, S. K., Barker, J. N. (2021). Psoriasis: a brief overview. Clinical Medicine, 21(3), 170.
(https://st4.depositphotos.com/3373927/25478/v/1600/depositphotos_254781182-stock-illustration-vitamin-d-formula-is-ensuring.jpg)

Kulevska-Gonovska, I., Spasov, E., & Янева, P. (2024). Dynamics of mortality from diseases of the circulatory organs in Bulgaria, south central region and Plovdiv province, *MEDIS - Medical Science and Research, 3*(1), 13-18.
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DYNAMICS OF MORTALITY FROM DISEASES OF THE CIRCULATORY ORGANS IN BULGARIA, SOUTH CENTRAL REGION AND PLOVDIV PROVINCE

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Abstract: In the European Union, Bulgaria ranks first in terms of mortality and last in terms of life expectancy. According to Eurostat data for 2018 in Bulgaria, from 2011 until this moment, the coefficients of both preventable mortality with good prevention and mortality preventable with good treatment are higher than the corresponding values for the EU as a whole. There are no prospects for their improvement. The rate of preventable mortality with good prophylaxis reached 226 per 100,000 population, which is significantly higher than the value of the rate in the whole EU (160 per 100,000). On the one hand, weak primary prevention and health promotion, and on the other hand, the need to improve protocols for diagnosis and treatment of the leading causes of death can be pointed out as reasons.

The aim of the present study is to perform a comparative analysis of the dynamics of mortality from diseases of the circulatory organs for Bulgaria, its South Central Region and the Plovdiv province as part of this region.

Materials and methods: documentary analysis - based on data from the National Statistical Institute; inductive and deductive methods; comparative analysis; structural analysis; economical analysis; statistical methods - analysis of the dynamics of phenomena, tabular and graphic analyzes - to visualize the obtained results.

Results: Both for Bulgaria as a whole, as well as for its South Central region and the Plovdiv province, there is a trend of increasing mortality (per 100,000 people of the population) from diseases of the circulatory organs.

Conclusion: From the data of our study, it is clear that, in general, for the observed 10-year period, and more specifically for the last of the years under consideration - 2022, for the entire country, the highest relative share in mortality (per 100,000 population) is occupied by other diseases of the heart. For the South Central region, the mortality rate from ischemic heart disease is the highest. The situation is similar for the Plovdiv province, as part of this region, where the relative share is also the highest - a noticeable 44.0% of the mortality from IHD.

Recommendations: A comprehensive approach and addressing health inequities in all areas aimed at reducing the burden of cardiovascular disease as part of non-communicable chronic diseases is imperative. Of primary importance is the fact that health promotion and disease prevention can lead to a significant reduction in this burden.

Keywords: *mortality, circulatory system diseases, South Central region, Plovdiv province, risk factors*
Field: Medical sciences and Health

1. INTRODUCTION

In the European Union, Bulgaria ranks first in terms of mortality and last in terms of life expectancy.

According to Eurostat data for 2018 in Bulgaria, from 2011 until now, the coefficients of both preventable mortality with good prevention and mortality preventable with good treatment are higher than the corresponding values for the EU as a whole. There are no prospects for their improvement. The rate of preventable mortality with good prophylaxis reached 226 per 100,000 population, which is significantly higher than the value of the rate in the whole EU (160 per 100,000). [4,5]. On the one hand, weak primary prevention and health promotion, and on the other hand, the need to improve protocols for diagnosis and treatment of the leading causes of death can be pointed out as reasons. [4]

Ischemic heart disease (IHD) is the second leading cause of death after cerebrovascular disease. IHD accounted for 11% of all deaths, despite a sharp decline since 2000. Due to the reduction of some behavioral risk factors, and in part to improved early diagnosis and treatment, this decline has been more pronounced among women than among men (such as free annual medical examinations for cardiovascular disease and increased use of hypertension drugs). [3]

The average death rate for the EU, preventable through good treatment - 92 per 100,000 people is twice lower than that in Bulgaria, where it is 188 per 100,000 people. A total of 42% of all deaths due to

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treatable causes were premature deaths from stroke (23%) and ischemic heart disease (19%).[5]

Almost 3 times higher is the standardized mortality rate from diseases of the circulatory organs in Bulgaria - 1,115.8 per 100,000 people, while the average for the EU is 356.6 per 100,000 people. [4,5]

As is known, not only classic cardiovascular risk factors (arterial hypertension, smoking, dyslipidemias, obesity, immobility, genetic predisposition, etc.) are the reason for the development and occurrence of diseases of the circulatory organs. A number of personality problems, psychological balance, the role of the value system, socio-economic conditions and stress also have a significant impact. I.e. the risk of developing these diseases is determined to a significant extent by a number of individual and population characteristics (demographic structure of the population, income, national culture, education, customs, etc.) and the level of health care. [7,8]

The aim of the present study is to perform a comparative analysis of the dynamics of mortality from diseases of the circulatory organs for Bulgaria, its South Central region and the Plovdiv province as part of this region.

Study period - 2013-2022.

2. MATERIALS AND METHODS

For the research we used: documentary analysis - based on data from the National Statistical Institute, inductive and deductive methods, comparative analysis, structural analysis, economic analysis, statistical methods - analysis of the dynamics of phenomena, tabular and graphic analyzes - to visualize the obtained results.

3.RESULTS

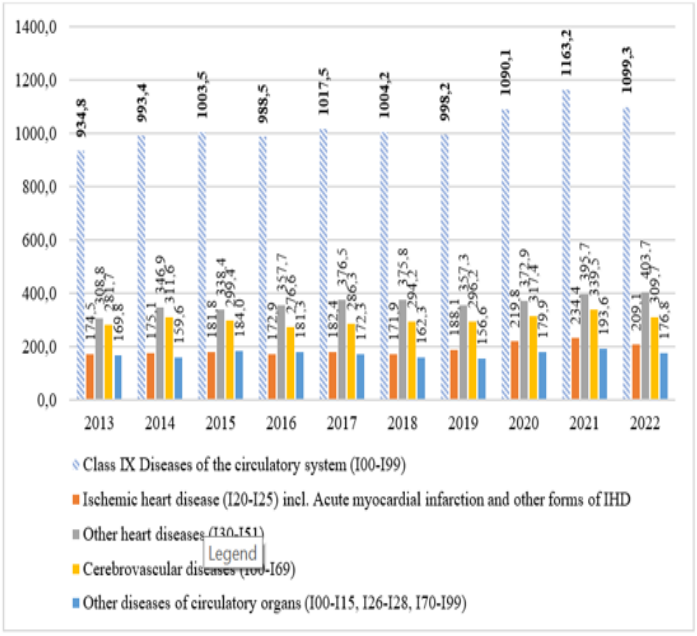

Fig 1. Mortality from diseases of the circulatory organs (per 100,000 people of the population) - total for Bulgaria

Source: National Statistical Institute
Note: Data are from the Harmonized List of 86 Reasons developed by Eurostat, used for international comparisons.

From figure 1, it is clear that the mortality rate from diseases of the circulatory organs (per 100,000 people of the population) for the considered 10-year period in general for Bulgaria shows an increasing trend by 17.6%, with the peak value being in 2021.

The highest increase values (by 30.7 percent) are characteristic of other heart diseases (I30-I51), followed by mortality per 100,000 people from ischemic heart disease (I20-I25), including . acute myocardial infarction and other forms of ischemic heart disease (by 19.8%). The increase in cerebrovascular diseases (I60-I69) was by 10 percent, and the lowest (by 4.1%) was the increase in mortality from other diseases of the circulatory organs (I00-I15, I26-I28, I70-I99).

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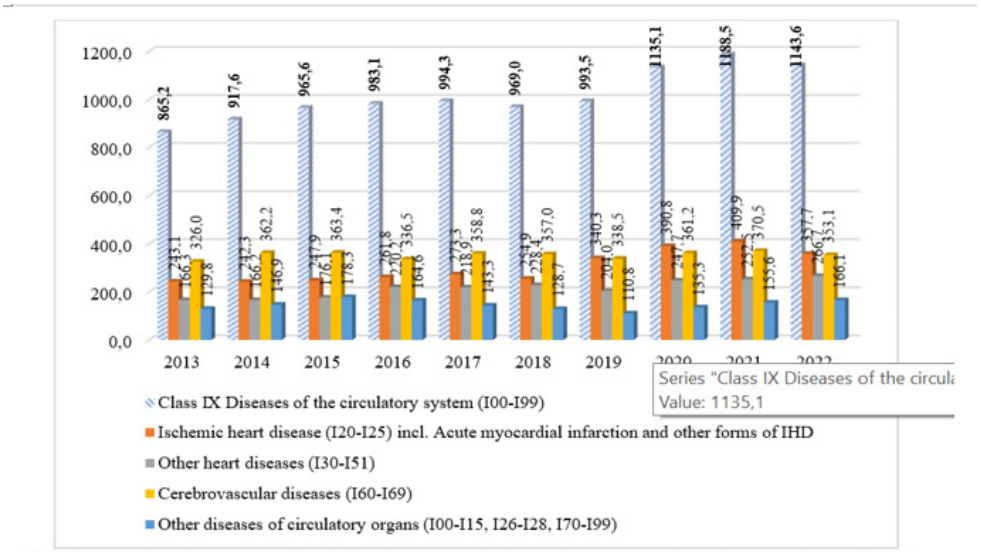

Fig. 2. Mortality from diseases of the circulatory organs (per 100,000 of the population) - South Central Region

The health care system in the South Central region is relatively well developed and covers the health care needs of the population in accordance with the standards of the country. [11] For the region, the dynamics of mortality rates from diseases of the circulatory organs (per 100,000 people of the population) is as follows:

And here the trend is on the rise. In total, for the period 2013-2022, the increase was 31.2%. There was a 60.4 percent increase in deaths per 100,000 people from other heart diseases, followed by a 47.1 percent increase in deaths from ischemic heart disease and a 28 percent increase in deaths from other diseases of the circulatory system.

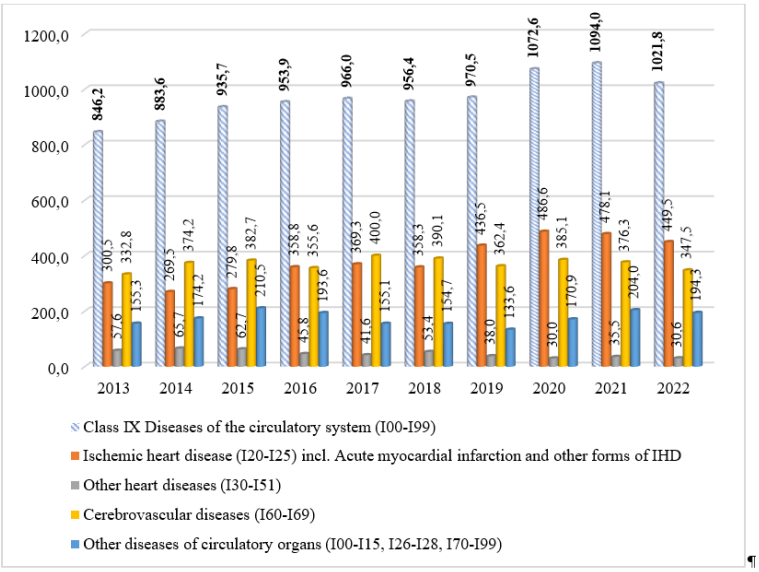

Fig. 3. Mortality from diseases of the circulatory organs (per 100,000 people of the population) - Plovdiv province
Source: National Statistical Institute

Plovdiv is one of the provinces with the largest number of doctors and hospital beds per capita. The index of accessibility to specialist doctors is significantly more favorable than the average for the country. Plovdiv is the province with the highest number of patients undergoing treatment. [2]

Figure 3 shows that in the Plovdiv province the increase was 20.8 percent for the period 2013-2022. With the largest relative share of 49.6% increase in mortality per 100,000 people in 2022 of ischemic heart disease, followed by an increase of 46.9% in other heart diseases. Other diseases of the circulatory system increased by ¼, and cerebrovascular diseases by only 4 percent

Table 1. Structure of mortality from diseases of the circulatory organs (per 100,000 people of the population) for 2022.

	Bulgaria - total	South Central Region	Plovdiv province
Class IX Diseases of the circulatory system (I00-I99)	**100.0%**	**100.0%**	**100.0%**
Ischemic heart disease (I20-I25) incl. Acute myocardial infarction and other forms of IHD	19.0%	31.3%	44.0%
Other heart diseases (I30-I51)	36.7%	23.3%	3.0%
Cerebrovascular diseases (I60-I69)	28.2%	30.9%	34.0%
Other diseases of circulatory organs (I00-I15, I26-I28, I70-I99)	16.1%	14.5%	19.0%

Source: National Statistical Institute

Table 1 presents the structure of mortality from diseases of the circulatory organs (per 100,000 people of the population) for 2022.

As it becomes clear, for the entire country, the highest relative share (36.7%) in mortality (per 100,000 population) is occupied by other heart diseases (I30-I51), followed by cerebrovascular diseases (28.2%). The arrangement is different in the South Central region, in which ischemic heart disease and cerebrovascular disease account for approximately 31.3 and 30.9 percent, respectively. The situation is similar for the Plovdiv province, where the relative share is also the highest, with a notable 44.0% of mortality from ischemic heart disease. Again, the second place is occupied by the mortality rate (per 100,000 people of the population) from cerebrovascular diseases 34.0%.

In third place (19.0%) for the entire country is the considered type of mortality from ischemic heart disease, for the South Central region (23.3 percent) are other heart diseases (I30-I51), and for the Plovdiv province (19.0%) - other diseases of the organs of blood circulation.

The lowest is the relative share of the observed indicator for Bulgaria and the South Central region of other diseases of the circulatory organs (I00-I15, I26-I28, I70-I99), respectively 16.0% and 14.5%. Against this background, it is impressive that only 3.0% of mortality (per 100,000 people of the population) from other heart diseases (I30-I51) were reported for the Plovdiv province.

4. DISCUSSION

The general conclusion reached by the scientists who carried out scientific studies examining the reasons for the reduction of mortality from cardiovascular diseases (CVD) in the USA and some European countries is that half of the effect is due to limiting the main risk factors - diet, smoking and physical activity. At the same time, the other half is due to the progress of medical science and practice, especially in recent years. Invasive and non-invasive treatment methods (highly effective new drugs and operative interventions) focused on individuals with clinically evident disease are included here. In these countries, the burden shift from CVD and other chronic diseases is at a higher level among older people. It is important to note that the active prevention of negative risk factors mainly among the young population of economic reproductive age is the essence of the effect of reducing cardiovascular mortality.

In contrast to developed countries, where prevention and treatment push the clinical manifestation of CVD to an increasingly advanced age, in developing countries, the age of target organ involvement is increasingly decreasing. Moreover, in developed countries, the social security system bears most of the burden of CVD. In developing countries, institutional social care is often lacking, long-term care is most often provided by another elderly family member. Indicators show that disability is no less a social and economic burden than premature death. CVDs cause at least 1/3 of all disability in the over 60 age group [8]

In our country, the situation is more alarming. Diseases of the circulatory system have been the leading cause of death for decades. Due to the fact that they are mainly carried out by the health system, the measures implemented at the country level at this stage do not give a significant result. Despite the enormous losses - material and human due to this type of disease, public structures and citizens do not actively behave in this direction. The future of the nation and its prosperity depends on dealing with these diseases, which is why health promotion and their prevention should become a national task. [7,8]

According to WHO data, in recent years there has been an increase in the relationship between chronic non-communicable diseases in general and cardiovascular diseases in particular and air pollution,

other environmental factors, psychological, social and economic risks. Therefore, premature mortality from chronic non-communicable diseases (Sustainable Development Goal 3.4) is an appropriate marker of how the region is performing in terms of preventing and addressing unhealthy behaviors and risk factors on the one hand, and the performance of health systems on the other. Central to determining the success of at least nine Sustainable Development Goals (SDGs) will be progress in addressing NCDs problems. [9]

5. CONCLUSIONS

In Bulgaria, diseases of the organs of blood circulation are characterized by a significantly higher level of morbidity and mortality among the population compared to the EU. In addition, they also have emerging unfavorable dynamics over time. On the one hand, a large part of people of active age are affected, and on the other hand, these diseases occupy a high share in the structure of the causes of death among the population. CVDs also occupy a high share in the structure of treatment and rehabilitation costs, they also require the intervention of highly qualified and specialized medical assistance, as well as complex treatment, in which expensive medications are used. This is also the reason why they are popularly known as "socially significant diseases", because of the cruel societal price we pay not only in financial means, but also in lost years of life and life in good health.

From the data of our study it is clear that in general for the observed 10-year period and more specifically for the last of the years under consideration - 2022 for the whole country the highest relative share (36.7%) in mortality (per 100,000 people population) occupy other diseases of the heart (I30-I51), followed by cerebrovascular diseases (28.2%). The arrangement is different in the South Central region, in which ischemic heart disease and cerebrovascular disease have approximate shares of 31.3 and 30.9 percent, respectively. Similar to the region of which it is a part is the situation for the Plovdiv province, where the relative share, with a notable 44.0%, of mortality from ischemic heart disease is also the highest. Here again, the mortality from cerebrovascular diseases ranks second, 34.0%.

6. RECOMMENDATIONS

A comprehensive approach and addressing health inequities in all areas aimed at reducing the burden of cardiovascular disease as part of chronic non-communicable diseases is imperative. Of paramount importance is the fact that health promotion and disease prevention can significantly reduce this burden. [5]

The impact of non-communicable chronic diseases goes beyond ill health and poor well-being, as they also cause huge economic losses. Diseases of the organs of blood circulation, as part of chronic non-infectious diseases, are mainly grouped in people with low socio-economic status and are an important cause of high health care costs. Increased efforts are needed in multiple sectors - effective economic instruments such as price policies and insurance. [9]

REFERENCES

ESC Guidelines on cardiovascular disease prevention in clinical practice, European Heart Journal (2021) 42, 3227–3337, doi:10.1093/eurheartj/ehab484; 15

Institute of Market Economy, (2023). Regional profiles. Development indicators 2023; 79

OECD/European Observatory on Health Systems and Policies (2019), България: Здравен профил на страната 2019 г., State of Health in the EU, OECD Publishing, Paris/European Observatory on Health Systems and Policies, Brussels.; 5

OECD/European Observatory on Health Systems and Policies (2021), България: Здравен профил на страната 2021, State of Health in the EU, OECD Publishing, Paris/European Observatory on Health Systems and Policies, Brussels.; 3-12

Ministry of Health, (2022). Draft National Health Strategy 2030; 11,26,35

National Statistical Institute, https://www.nsi.bg/bg/content/3357

Shipkovenska E. et al., (2015). Cardiovascular diseases. In: World Population Health. Ed. Gorex Press;105-109

Vodenicharov Ts., S. Popova, M. Mutafova, E. Shipkovenska (2013). Social Medicine, Ed. "GorexPress"; 312-316

World Health Organization. Regional Office for Europe, (2021).The European Health Report 2021.Taking stock of the health-related Sustainable Development Goals in the COVID-19 era with a focus on leaving no one behind: 40

Zlatanova T., (2021) Health and Health Inequalities, Forty-Sixth Science and Technology Session, CONTACT 2021, ed. TEMTO; 88-93

https://pd.government.bg/?page_id=1571

Sančanin, B., & Penjišević, A. (2024). Non-communicable diseases in republic of Serbia: Causes and consequences, *MEDIS - Medical Science and Research, 3*(1), 19-25. doi: 10.35120/medisij030119s
UDK: 616.1/.8-036.12-084(497.11)

NON-COMMUNICABLE DISEASES IN REPUBLIC OF SERBIA: CAUSES AND CONSEQUENCES

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Abstract: The growing trend of chronic non-communicable diseases, which affects both developed and developing countries, is linked to changes in diet and lifestyle. Despite numerous epidemiological pieces of evidence and recognized risk factors for the development of chronic non-communicable diseases, there are still worrying indicators of morbidity and premature mortality as a consequence of non-communicable chronic diseases. The goal of the work is to point out the urgent need to create effective and sustainable health policies that would provide answers to growing public health challenges. Additionally, the authors emphasize in the paper the key risk factors and the necessity of transforming patterns of inadequate behavior in order to mitigate, and in the future, to stop the unfavorable trend of newly diagnosed cardiovascular diseases, stroke, diabetes, and cancer, as the leading causes of disability and premature death, as well as to reduce the burden on health funds

Keywords: *non-communicable diseases, cardiovascular diseases, malignant diseases, respiratory diseases, diabetes*
Field: Medical Sciences and Health

1. INTRODUCTION

The established way of life and habits need to be changed, starting with increasing physical activity, improving eating habits, as well as reducing exposure to a large number of external harmful influences. In this sense, primary prevention plays an irreplaceable role, which means preventing the onset of disease by removing harmful effects, that is, by implementing desirable behavior. For example, a large number of malignant diseases can be prevented through primary prevention measures related to the reduction of risk factors such as smoking, inadequate nutrition, the presence of carcinogens in the workplace or living environment. (Republican expert commission for the development and implementation of guidelines in clinical practice, 2005) Although preventable, chronic non-communicable diseases are the leading causes of illness, absenteeism, disability, and premature death in the world. A key fact shows that 41 million people die each year from non-communicable diseases, which is equivalent to 74% of all deaths in the world. Additionally, every year 17 million people die from chronic non-communicable diseases before the age of 70, and even 86% of these premature deaths are recorded in low- and middle-income countries. (WHO, 2023a) The Republic of Serbia has not been spared from these negative trends: the aging of the population and the negative social and economic trends of recent decades have affected the health status of the population. The transition of the state and society led to the fact that the health potential of the nation was exhausted, resulting in negative health indicators whose improvement is slow in the time of socio-economic recovery. (Radevic et al., 2022)

Given that science does not have all the answers to how some diseases arise, significant attention must also be given to secondary prevention, that is, early detection of diseases. Education and mass preventive programs in the early detection of the disease, when the chances of cure are incomparably greater, have no alternative. The decision of the World Health Organization (WHO) to extend the Global Action Plan for the Prevention and Control of Chronic Non-Communicable Diseases 2013-2020 until 2030 should be viewed in this context. The WHO Roadmap supports actions that should accelerate progress in the prevention and control of chronic noncommunicable diseases. The goal is to reduce premature mortality by one-third by 2030. (WHO, 2023a)

Chronic non-communicable diseases have common characteristics (Hovan Somborac, 2022):

- Multicausality: they arise as a result of the unfavorable action of several factors at the same time;
- Irreversibility of tissue and organ or system damage;
- Insidiousness in the development of forms that are more difficult to access for diagnosis;
- Diseases are lifelong, although with continuous and consistent treatment, their development can be stopped or slowed down;

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- The treatment is long-term, and the results depend on the quality of the treatment;
- In the course of the development of the disease, it occasionally worsens;
- Health care must be continuous, comprehensive and long-lasting;
- Preventability, thanks to the ability to act on risk factors.

Established unhealthy eating habits, as well as a significant reduction in physical activities, result in an increase in obese people, which represents a significant health risk. Of great importance for public health is the finding that the prevalence of obesity has an exponential trend in almost all regions of the world. Morbidity associated with obesity and its complications reduces life expectancy and results in an unacceptable and unsustainable cost burden for health institutions and society as a whole. (Knežević & Jandrić Kočić, 2023) Physical activity is a fundamental tool in achieving physical and mental health, bringing more health, social, and economic benefits by reducing the risk of developing chronic non-communicable diseases. Regular physical activity in the elderly maintains functional independence, while at all ages it enhances the quality of life. (Petković Košcal et al., 2007)

Chronic non-communicable diseases cause 41 million deaths annually worldwide. Cardiovascular diseases hold the leading position, contributing to a total mortality of 17.9 million, followed by malignant diseases with 9 million deaths, chronic respiratory diseases with 3.9 million, and diabetes mellitus with a participation of 1.6 million deaths. (Lazić et al., 2020) The most common causes of death in 2022 in the Republic of Serbia belong to the following disease groups - ICD-10. (Institute of Public Health of Serbia, 2023):

- Diseases of the circulatory system: 47,3% (men 43,1% and women 51,5%);
- Tumors: 18,5% (men 20,1% and women 16,8%);
- COVID-19: 7,6% (men 8,3% and women 6,9%);
- Diseases of the respiratory system: 6,0% (men 6,8% and women 5,3%);
- Diseases of glands with internal secretion, nutrition and metabolism: 3,0% (men 2,7% and women 3,2%).

From 2013 to 2022, the overall mortality rate in the Republic of Serbia increased by 17.4%. During that period, mortality rates from diabetes increased by 18.9%, heart and blood vessel diseases by 4.6%, while fewer deaths from injuries and poisoning were registered, declining by 15.3%. Deaths from cancer increased by 1.1%, and from obstructive lung diseases by 0.3%.

2. CARDIOVASCULAR DISEASES

Cardiovascular disease is a major contributor to the global burden of disease among noncommunicable diseases. The World Health Organization attributes the majority of global deaths to cardiovascular disease (17.9 million), with the highest mortality in developing and low- and middle-income countries. (WHO, 2023a) Epidemiological research has led to the conclusion that risk factors for the development of cardiovascular diseases can be divided into changeable and non-changeable. Genetic material, sex, and age are immutable risk factors, but they are closely related to modifiable risks that include behavioral factors (diet, physical activity, alcohol and tobacco consumption), biological factors (hypertension, obesity, dyslipidemia, hyperinsulinemia), and finally social factors, which include interactions of socioeconomic, cultural, and environmental parameters. (Lazic et al., 2020)

Table 1. Number of deaths from cardiovascular diseases (Serbia), 2013-2022 (I00-I99)

Diseases and conditions	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Female	28.862	29.302	29.686	28.314	29.306	28.481	28.218	29.688	30.304	27.929
Male	24.505	24.691	24.690	23.788	24.362	24.182	24.112	25.617	26.306	23.696
Total	53.367	53.993	54.376	52.102	53.668	52.663	52.330	55.305	56.610	51.624

Source: Miljus, 2023.

By preventing and controlling diseases of the heart and blood vessels, it is possible to significantly improve health. Control of these diseases can be achieved through prevention at the individual and population levels, reducing inequalities in health, joint action of health and non-health sectors, early detection (screening), preventive interventions, and promotion of protective factors. (Official Gazette of

the Republic of Serbia, 2010)

The cardiovascular benefits of physical activity and exercise are multifactorial and include important systemic effects on skeletal muscles, peripheral vasculature, metabolism, neurohumoral system, as well as changes in the heart muscle itself. Certain epidemiological studies have shown that the effects of physical activity can be achieved with moderate physical activity of about 150 minutes per week, while additional health benefits are obtained with an increase in the volume or intensity of physical activity. (Jakovljević & Djordjević, 2017)

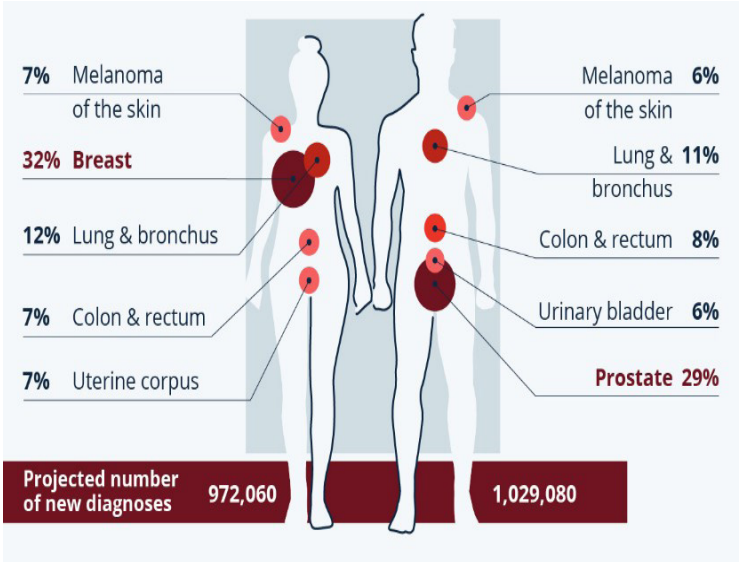
Šarčević et al. (2014) warn that excessive salt intake in the human diet results in a drastic increase in cardiovascular diseases: numerous studies confirm that to maintain metabolic processes, a daily intake of 1.5 grams is sufficient, while the American Heart Association recommends a daily intake of 8-15 grams. In populations that consumed less than 3 grams of salt per day in the 20th century, the absence of hypertension was recorded.

Pointing out that Serbia ranks first in Europe in terms of mortality from cardiovascular disorders (410/100,000 Europe: 504/100,000 Serbia), Bojić (2014) highlights insomnia and sleep disorders as significant, but still insufficiently recognized health and economic burdens and risk factors for cardiovascular and cerebrovascular diseases. The most common types of insomnia that lead to cardiovascular consequences are primary insomnia and insomnia related to breathing disorders. These forms of insomnia are independent risk factors for hypertension, coronary heart disease, and the onset and worsening of heart failure.

3. MALIGNANT DISEASES

Although cardiovascular diseases are still the leading cause of death in the world, in some developed countries cancer mortality is increasing alarmingly. According to the indicators of the World Health Organization, in 2022, 20 million new cases of cancer will be diagnosed in the world and 9.7 million will die. The estimated number of people who would survive within five years of a cancer diagnosis was 53.5 million. Approximately 1 in 5 people will get cancer during their lifetime, and 1 in 9 men and 1 in 12 women will die from the disease. (WHO, 2024) The American Cancer Society estimates that in 2024, the number of new cases in the US will exceed two million for the first time, or 5,500 cancer diagnoses per day. The main types of cancer affecting men and women will remain largely the same as in previous years: the most commonly diagnosed cancers are breast cancer in women and prostate cancer in men. (Buchholz, 2024) This trend is largely influenced by the aging and growth of the population, as well as the increase in diagnoses of six of the 10 most common cancers: breast, prostate, endometrial, pancreatic, kidney and melanoma. In 2024, more than 611,000 cancer deaths are projected in the US, which is 1,600 per day. (Collins, 2024)

Figure 1. The most Common Types of Cancer in the U.S.
Projected share of new cancer diagnoses in the U.S. in 2024, by gender



Source: American Cancer Society, 2024.

Malignant tumors in women in the Republic of Serbia are most often diagnosed in the breast, bronchus and lungs, colon and rectum, while in men the most common cancer is the bronchus and lungs, followed by colon and rectal cancer and prostate cancer. In 2020, 41,419 people suffered from malignant tumors: 22,110 men and 19,309 women. The values of the incidence rate in women were 271.6 per 100,000, and in men 328.2 per 100,000 inhabitants.

In the same year, 20,767 patients died of cancer, 11,611 men and 9,156 women. The mortality rate from cancer in women is 104.1 per 100,000 inhabitants, and in men 156.7 per 100,000 inhabitants (Mortality is the number of deaths).

Mental disorders that come in comorbidity with a tumor greatly reduce the quality of life and have an impact on the success of treatment. Early detection of mental disorders, screening, development and use of appropriate scales in disease diagnosis, as well as the selection of appropriate therapy are prerequisites for improving the quality of life and influencing a favorable prognosis. Special emphasis should be placed on psycho-oncology, a team and multidisciplinary approach that is the only one that can provide timely and quality help to cancer patients. (Vuk Pisk et al., 2017).

Research carried out in Serbia showed that a large part of the population does not recognize the risk factors that are responsible for the occurrence of the most common cancers, while a significant part of the population has two or more risk factors at the same time, such as smoking tobacco, insufficient physical activity, improper diet, obesity or excessive alcohol consumption. (Miljuš, 2021: 96)

Table 2. Number of deaths from malignant neoplasms (Serbia), 2013-2022 (C00-C97)

Diseases and conditions	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Female	8.990	9.205	8.998	9.273	9.388	9.433	9.206	9.156	9.005	8.734
Male	12.101	12.117	12.377	12.253	12.087	12.174	12.134	11.611	10.974	10.616
Total	21.091	21.322	21.375	21.526	21.475	21.607	21.340	20.767	19.979	19.350

Source: Miljus, 2023.

3. CHRONIC RESPIRATORY DISEASES

Chronic respiratory diseases (CRD) affect the airways and other lung structures, with some of the most common being chronic obstructive pulmonary disease (COPD), asthma, occupational lung diseases, and pulmonary hypertension. Risk factors include tobacco smoking, including passive smoking, air pollution in open and closed spaces, occupational exposure to gases and particles, and genetic predispositions. (Institute for Public Health of Montenegro) The World Health Organization (WHO, 2023b) indicates that smoking is still one of the leading causes of chronic obstructive disease, which kills more than three million people every year. An estimated 392 million people live with COPD, and three-quarters of them live in low- and middle-income countries.

Respiratory system diseases in the Republic of Croatia place the greatest burden on general/family medicine. In 2018, 1,719,988 diagnoses were established in general medicine offices, accounting for 17% of the total number of established diseases and conditions. Most diseases are respiratory infections, with obstructive diseases of the respiratory system responsible for 5.8% of diagnoses among respiratory diseases (99,695 visits), and it's noted that the use of primary health care for the 0-6 and 7-19 age groups is declining. (Antoljak, 2021)

Kuhajda et al. (2022) emphasize the importance of respiratory rehabilitation as the basis of non-pharmacological treatment for patients with chronic obstructive disease, citing numerous positive effects on the most significant symptoms of the disease and quality of life. Latincic et al. (2023) highlight the relevance of using pharmacological treatment, including bronchodilators, systemic steroids, and/or antibiotics. As a non-pharmacological strategy for the treatment of acute exacerbations of chronic obstructive pulmonary disease associated with acute respiratory insufficiency, they emphasize the importance of applying respiratory support in the form of oxygen therapy and non-invasive ventilation.

Table 3. Number of deaths from leading non-communicable diseases by sex (Serbia), 2013-2022 (J40-J47)
Chron. Opstr. Lung disease

Diseases and conditions	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Female	997	982	1.065	1.066	1.188	1.117	1.118	1.084	976	1.023
Male	1.590	1.517	1.658	1.603	1.731	1.591	1.603	1.483	1.382	1.366
Total	2.577	2.499	2.723	2.669	2.919	2.708	2.721	2.567	2.358	2.389

Source: Institute of Public Health of Serbia, 2023.

4. DIABETES

Diabetes mellitus, or sugar disease, is a set of metabolic disorders manifested by hyperglycemia, which occurs due to disorders in the secretion and/or action of insulin. It is a progressive, chronic disease that affected 463 million people worldwide in 2019, with an estimated number of sufferers reaching 700 million in 2045. The number of people with type 2 diabetes (T2DM) is significantly higher, with an estimate that almost half of the sufferers are over 65 years old. (Stantić Romić et al., 2023) It is estimated that around 10% of the population suffers from diabetes, with a tendency for the number of sufferers to increase, both younger and older. Such a trend is associated with obesity, less physical activity, and lifestyle. There are arguments that cigarette smoking and alcohol influence the occurrence of circulatory and inflammatory changes. (Vučetić, 2023: 35) Previous research into risk factors for type 2 diabetes mellitus indicates the possibility of preventing this disease by correcting lifestyle. Knowledge about diabetes and its complications, knowledge of risk factors for the onset of the disease, and a good personal perception of one's own risk for diabetes seem to be crucial for behavior change. (Pajić et al., 2022)

In 2019, 7.8% of the population over the age of 15 suffered from diabetes in Serbia (7.5% of men and 8.0% of women). In the age group 65+, 18.6% of the population of Serbia had diabetes, significantly more in urban areas than in rural areas. Based on the standardized mortality rate of 14.8 per 100,000 inhabitants, Serbia belongs to the group of European countries with high rates of dying from this disease. (Institute of Public Health Pančevo, 2023) Diabetes is the fifth leading cause of death in the world, and the third in Serbia, among all causes of death. Annually, approximately 3,000 people die from this disease in Serbia. An increase in deaths has been observed in the last ten years: the mortality rate from diabetes has increased from 39.1 in 2013 to 46.5 per 100,000 inhabitants in 2022. (Institute of Public Health of Serbia, 2023: 79)

Table 4. Mortality rates (per 100.000) from the most common non-communicable diseases by sex (Serbia)

Diseases and conditions	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Female	41,5	38,73	46,4	49,9	53,5	48,6	47,8	52,7	53,74	48,7
Male	36,6	31,6	38,7	39,3	45,7	42,3	40,2	45,5	44,2	44,2
Total	39,1	35,2	42,7	44,8	49,7	45,5	44,1	49,2	49,1	46,5

Source: Institute of Public Health of Serbia, 2023.

Type 1 diabetes is one of the most common diseases in children and young people. The annual incidence in children aged 0-14 years in Europe has a wide range, from 3.2/100,000 in Macedonia, 14.8/100,000 in Serbia to 64.2/100,000 in Finland. In many countries around the world, the annual increase in the frequency of this disease in childhood amounts to 3 to 5%. The disease is equally prevalent in both sexes, and its frequency increases with age, with the highest incidence registered during puberty. (Ministry of Health of Serbia, 2013:59)

Numerous studies have confirmed the positive correlation between aging and the incidence of diabetes: the frequency is particularly pronounced in the age cohort of 60 to 74 years (17.6%). Also, the micro and macrovascular level of complications of diabetes is of concern: patients with this diagnosis live 5 to 10 years shorter than the healthy generation, with cardiovascular and amputation risks that are many times higher. (Vrdoljak & Pavlov, 2014)

5. CONCLUSION

Chronic non-communicable health disorders represent a key public health problem worldwide, with clearly differentiated risk factors: hypertension, hypercholesterolemia, smoking, alcohol consumption, improper diet, obesity, and insufficient physical activity. Therefore, it is necessary to continuously ensure quality data on the leading non-communicable health disorders, modern and safe IT support with a feedback system of information, as well as more meaningful education of health workers, with a focus on primary health care programs. Respecting evidence-based medicine, the authors suggest the standardization of diagnostic-therapeutic procedures with the latest global achievements. In this sense, it is desirable to create a list of knowledge and skills necessary for activities that could contribute to strengthening public health care, as well as the creation of effective and cost-effective programs for continuous monitoring, prevention, and control of leading non-communicable health disorders. It is necessary to persevere in the establishment and full implementation of a unique protocol for diagnosing, treating, and monitoring chronic non-communicable diseases, along with continuous patient education. However, it should be noted that reducing the number of premature deaths and significantly reducing the burden, morbidity, and disability is not possible without a broader multisectoral approach to creating a new socio-economic and ecological paradigm that will catalyze the complete elimination and reduction of people's exposure to risk factors for the development of chronic non-communicable diseases.

REFERENCE

Antoljak, N. (2021). Epidemiology Asthma and Chronic Obstructive Pulmonary Disease. Medicus, 30(2): 139-144
Bojić, T. (2014). Nesanica kao faktor rizika za kardiovaskularne bolesti. Engrami, 36(1-2): 31-36. https://doi.org/10.5937/engrami1402031B
Buchholz, K. (2024). The Most Common Types of Cancer in the U.S. Statista. Available at:
https://www.statista.com/chart/20692/most-common-types-of-cancer-us/ (Accessed date: January 31, 2024)
Collins, S. (2024). 2024 – first Year the US Expects More than 2M New Cases of Cancer. American Cancer Society. Available at: https://www.cancer.org/research/acs-research-news/facts-and-figures-2024.html (Accessed date: January 17, 2024)
Hovan Somborac, J. (2002). Model praćenja faktora rizika hroničnih masovnih nezaraznih bolesti. Medicinski pregled, 55(11-12): 470-474
Institute of Public Health of Serbia. (2023). Health Statistical Yearbook of the Republic of Serbia 2022. Belgrade. https://www.batut.org.rs/download/publikacije/pub2022v1.pdf
Institut za javno zdravlje Crne Gore (NN). Hronične plućne bolesti. Available at: https://www.ijzcg.me/me/hronicne-plucne-bolesti (Accessed date: February 11, 2024)
Jakovljević, V. & Djordjević, D. (2017). Physical activity for the prevention of cardiovascular diseases. Serbian Journal of Experimental and Clinical Research, 18(2): 99-109. https://doi.org/10.1515/SJECR-2016-0049
Knežević, S., & Jandrić Kočić, M. (2023). Gojaznost – pandemija našeg vremena od posebnog značaja. Medicinski glasnik Specijalne bolnice za bolesti štitaste žlezde i bolesti metabolizma „Zlatibor", 28(89): 56-75. https://doi.org/10.5937/mgiszm2389056K
Kuhajda, D., Kuhajda, I., Ilić, M., Maksimović, S., Crnobrnja, J., Lalić, N., & Bojović, M. (2022). Risk factors as outcome predictors of pulmonary rehabilitation in patients with chronic obstructive pulmonary disease. Srpski arhiv za celokupno lekarstvo, 150(1-2): 35-40. https://doi.org/10.2298/SARH210724088K
Latinčić, M., Vlačić, T., Depčinski, D., Kalem, M. & Ćorić, T. (2023). Treatment of severe exacerbations of chronic obstructive pulmonary disease in hospital setting. Respiratio, 13(1-2): 117-121.
https://doi.org/10.26601/rsp.aprs.23.10
Lazić, V., Mijović, B., & Maksimović, M. (2020). Ishrana kao faktor rizika za nastanak hroničnih nezaraznih bolesti. Biomedicinska istraživanja, 11(1): 44-53. https://doi.org/10.5937/BII2001044L
Miljus, D. (2023). Health Statistical Yearbook of Republic of Serbia 2022 – Non-communicable Diseases. Belgrade: Institute of Public Health of Serbia "Dr Milan Jovanovic Batut".
Miljuš, D. (2021). Incidence and mortality of malignant tumours in Serbia: a comparative analysis. Glasnik javnog zdravlja, 95(1): 85-98. https://doi.org/10.5937/gjz2101085M
Ministarstvo zdravlja Srbije. (2013). Nacionalni vodič dobre kliničke prakse – Diabetes mellitus. Beograd.
Official Gazette of the Republic of Serbia No. 11 of March 5, 2010. National program of prevention treatment and control of cardiovascular diseases in the republic of Serbia until 2020.
Pajić, D., Antić, G., Dimoski, Z., Terzić Marković, D., & Majstorović, B. (2022). Identifikacija faktora rizika u prevenciji dijabetes melitusa tip 2 kod zdravstvenih radnika. Sestrinska vizija, 6(10): 22-27. https://doi.org/10.5937/SESTRVIZ2210022P
Petković Košcal, M., Damjanov, V., Jevtović, I., Jovanović, M., & Pantović, V. (2007). Physical Activity and Lifestyle Modification in Prevention of Diabetes Mellitus. Zdravstvena zaštita, 36(2), 35-51. https://doi.org/10.5938/ZZ0702035P
Radević, S., Kocić, S., Simić Vukomanović, I., Radovanović, S., Kocić, M., Radovanović, J., Selaković, V. &
Andrić, D. (2022). Faktori rizika povezani sa hroničnim nezaraznim bolestima u populaciji žena centralne Srbije. Glasnik javnog zdravlja, 96(2): 136-151. https://doi.org/10.5937/serbjph2202136R
Republička stručna komisija za izradu i implementaciju vodiča u kliničkoj praksi. (2005). Prevencija malignih bolesti – Nacionalni vodič za lekare u primarnoj zdravstvenoj zaštiti. Beograd.
Stantić Romić, D., Požar, H., & Šumonja, S. (2023). Efekat zdravstveno vaspitne intervencije u formi savetovanja na promene antropometrijskih i biohemijskih parametara obolelih od dijabetes melitusa tip 2. Sestrinska reč, 26(86): 17-23.

Šarčević, D., Lilić, S. & Vranić, D. (2014). Redukcija soli u ishrani ljudi – globalna strategija u 21. veku. Tehnologija mesa, 55(2): 162-168. https://doi.org/10.5937/tehmesa1402162S

Vrdoljač, D., & Pavlov, R. (2014). Diabetes in Elderly. Collegium antropologicum, 38(2): 243-246

Vučetić, Č. (2023). Dijabetesno stopalo i hirurško lečenje. Galenika Madical Journal, 2(8): 35-42. https://doi.org/10.5937/Galed2308035V

Vuk Pisk, S., Filipčić, I., Bogović, A., Milovac, Ž., Todorić Laidlaw, I., Caratan, S. (2017). Maligne bolesti i psihički poremećaji – prevalencija, mortalitet, terapijski izazov. Socijalna psihijatrija, 45(3): 187-201.

World Health Organization – WHO. (2023a). Noncommunicable diseases. Available at: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases (Accessed date: February 12, 2024)

World Health Organization – WHO. (2023b). Smoking is the leading cause of chronic obstructive pulmonary diseases. Available at: https://www.who.int/news/item/15-11-2023-smoking-is-the-leading-cause-of-chronic-obstructive-pulmonary-disease (Accessed date: February 10, 2024)

World Health Organization – WHO. (2024). Global cancer burden growing, amidst mounting need for services. Available at: https://www.who.int/news/item/01-02-2024-global-cancer-burden-growing--amidst-mounting-need-for-services (Accessed date: February 1, 2024)

Zavod za javno zdravlje Pančevo. (2023). Svetski dan borbe protiv dijabetesa. Available at: https://www.zjzpa.org.rs/svetski-dan-borbe-protiv-dijabetesa/ (Accessed date: February 12, 2024)

Andyni Manalu, E. P., & Resi Utomo, B. S. (2024). Characteristics of tonsillitis patients in children at univesitas kristen Indonesia hospital, 2010-2017, *MEDIS - Medical Science and Research, 3*(1), 27-30. doi: 10.35120/medisij030127p
UDK: 616.322-002-053.2(594)"2010/2017"

CHARACTERISTICS OF TONSILLITIS PATIENTS IN CHILDREN AT UNIVESITAS KRISTEN INDONESIA HOSPITAL, 2010-2017

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Abstract: Tonsillitis is a common disease in Ear Nose Throat (ENT) clinic, especially in the age of children and adolescents. Tonsillitis is inflammation of the palatine tonsils caused by bacteria, viruses or other immunological factors. The research is to find the characteristic of patients tonsillitis at Christian University of Indonesia Hospital. Method: This research uses descriptive method with retrospective approach done at Christian University of Indonesia General Hosipital with sample number of 40 patient. Statistical data checks using SPSS version 25. Result: Based on the medical record data obtained patients tonsillitis in children most often in the age group 0-6 62.5%, male gender 55%, have good nutrition status 57.5%, the main complaints of sorethroat 60%, size of T2-T2 tonsils 40%, medical diagnosis is acute tonsilitis 75%, medical treatment 77.5%. Conclusion: The profile of patients with tonsillitis in children was predominantly in the age group 0-6 years, male gender with good nutritional status had major complaints was swallowing pain, tonsils size T2-T2 and diagnosed acute tonsillitis. Medicamentous administration was an option in the treatment of tonsillitis.

Keywords: *Tonsillitis, children, prevalence*

1. INTRODUCTION

Tonsils are a part of the body's defense system. Palatine tonsils are part of Waldeyer's ring, then if there is inflammation it is called tonsillitis. Tonsillitis is still a health problem in Indonesia and is commonly often occurs in children. This disease is treated by many specialists in the ear, nose, throat, head and neck department (ENT-KL), pediatricians and other health services. Important causes of tonsillitis are group A beta-hemolytic streptococcus (GABHS) and Staphylococcus aureus, cause 15-30% of tonsillitis. Viral infections (Rhinovirus, Influenza A, Adenovirus, Herpes Simplex virus, Epstein Barr virus (EBV), Metapneumovirus, Respiratory Syncytial Virus (RSV), and Parainfluenza) are the primary etiology of tonsillitis. Infection can handily transmission through close contact with an infected person, when an infected person coughs or sneezes, the germs are contained in droplets that come from the nose or mouth, can occur at all ages, especially in children.1,2,3

The pattern of ENT disease varies in each country. Many environmental and social factors are assured to be responsible for the infectious etiology of this disease. Based on data from the Indonesian Ministry of Health in 2012, the incidence of tonsillitis in Indonesia is around 23%. According to data from the World Health Organization (WHO) in 2005, approximately 616 million cases of streptococcal tonsillitis are diagnosed each year. According to the Survei Kesehatan Rumah Tangga (SKRT), the highest morbidity rate for children aged 5-14 years and chronic tonsillitis ranks fifth (10.5% of males and 13.7% of females). Clinical symptoms of chronic tonsillitis are preceded by symptoms of acute tonsillitis such as sore throat that does not go away completely. The duration of sore throat and painful swallowing is felt for more than 4 weeks and can sometimes persist. Other clinical symptoms include fever, malaise, swollen lymph nodes in the neck and tonsillar redness or swelling, sometimes with white patches. Research on children in Padang in 2013 found the highest frequency of chronic tonsillitis in the age range of 10-14 years, female sex, the main complaint was painful swallowing, tonsil size T3-T3 and operative management.3,4 Based on the above background it can be concluded that tonsillitis is still is a health problem that needs special attention, especially in children, so researchers are interested in conducting research on the characteristics of tonsillitis in children at the Universitas Kristen Indonesia Hospital in 2010-2017.

2. METHOD

The type of research used is descriptive research with a retrospective approach. Data obtained based on medical records of patients with tonsillitis inc children at Universitas Kristen Indonesia (UKI) Hospital during August-December 2017. The number of samples used total sampling and obtained

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40 pediatric patients who suffered from chronic tonsillitis and went to the UKI Hospital for the ENT-KL section in 2010-2017. The research source used medical records, and the data collected will be analyzed which includes univariate analysis. Univariate analysis was used to see the description of the frequency distribution of each research variable. Data analysis was carried out descriptively using the Statistical Product and Service Solution (SPSS) version 25.0 program. Variables with categorical scales are expressed in frequency distributions and percentages are then presented in tabular form. This research follows the rules following applicable research ethics.

3. RESULT

Based on medical record data from the Universitas Kristen Indonesia Hospital, the distribution of tonsillitis patients in children in 2010-2017 was 40 people who met the inclusion and exclusion criteria. The data obtained are as follows:

Table 1. Age Frequency Distribution in Tonsillitis Patients

Age	frequency	%
0-6	25	62.5%
7-12	11	27.5%
13-18	4	10%

Table 2. Gender Frequency Distribution in Tonsillitis Patients

Gender	frequency	%
Male	22	55%
Female	18	45%

Table 3. Frequency Distribution of Nutritional Status in Tonsillitis Patients

Nutritional Status	frequency	%
Underweight/wasting	6	15%
Good nutritional status/normal	23	57.5%
Overweight/obese	11	27.5%

Table 4. Frequency Distribution of Chief Complaints in Tonsillitis Patients

Chief Complaints	frequency	%
Fever	12	30%
Sore throat	24	60%
Vomiting	2	5%
Cough with phlegm	2	5%

Table 5. Frequency Distribution of Tonsil Size in Tonsillitis Patients

Tonsil Size	frequency	%
T1-T1	11	27.5%
T2-T2	16	40%
T3-T3	11	27.5%
T4-T4	2	5%

Table 6. Frequency Distribution of Medical Diagnosis in Tonsillitis Patients

Medical Diagnosis	frequency	%
Acute Tonsillitis	30	75%
Chronic Tonsillitis	10	25%

Table 7. Frequency Distribution of Treatment in Tonsillitis Patients

Treatment	frequency	%
Medicine	31	77.5%
Operative	9	22.5%

Based on the reported age range, cases of tonsillitis were dominated by the age group of children (0-6 years) as much as 62.5%, preadolescents (7-12 years) as many as 27.5%, and adolescents (13-18 years) as many as 10%. Distribution of tonsillitis more male patients (55%) compared to women (45%). In addition, the distribution of diseases based on nutritional status, 57.5% of patients had good nutritional status/normal, 27.5% overweight/obese nutritional status, 15% underweight/wasting. Symptoms of Sore throat were experienced by 60% of the total patients, 30% had fever, 5% complained of vomiting and 5% coughed up phlegm. T2-T2 size is the largest tonsil size, as much as 40%, T1-T1 and T3-T3 each as much as 27.5% and only T4-T4 as much as 5%. Based on disease category, acute tonsillitis is 75% and chronic tonsillitis is 25%. Medicine is the most treatment option, as much as 77.5%, while surgery is 22.5%.

The incidence of tonsillitis regarding the distribution of the population varies from region to region. Based on the age group, 0-6 years is the largest age range, namely 63.5%. A parallel study by Khasanov

et al, regarding the prevalence of chronic tonsillitis in families, it was found that 335 children aged 1-15 years from 321 families had chronic tonsillitis.5 According to research by Raju, the highest distribution was found in the age range 1-10 years. suggested that children are the age group most susceptible to attacks of acute tonsillitis, with a peak at the age of 10 years. Nave stated that this was due to the greatest immunological activity of the tonsils found in the age range of 3-10 years. One of the predisposing factors for the emergence of chronic tonsillitis in children is the influence of several types of food, this is because children often consume foods such as foods with artificial sweeteners, preservative foods, and poor oral care. Based on gender, according to the results of research conducted by Kartika in 2015, there were 64% more boy than girl. Abouzied and Emad's research explains that there is no involvement of genetic and cultural factors in sex differences that often experience tonsillitis. This can be due to the influence of the population in a population related to the dominance of a certain sex on the incidence of tonsillitis, both men and women.6,7,9,10

Profile of patients based on nutritional status was dominated by good nutritional status/normal as many as 23 people (57.5%). However, Triastuti's study showed a significant relationship between nutritional status and chronic tonsillitis in children.11 Tonsillitis is generally caused by viruses which must be treated symptomatically and by increasing the body's resistance. Lack of food nutrients greatly affects the body's resistance, especially against diseases such as tonsillitis which is caused by a virus. Nutritional status is an indicator in determining the health status of children, but there are still many predisposing factors for chronic tonsillitis, including chronic irritation (due to smoking, pollution, and food), low nutrition or immune system, weather influences, actively choosing the food you like so that you can affect eating habits, and poor oral hygiene.12 Based on the main complaint, swallowing pain was dominated by 24 people (60%), this was caused by something that was swallowed touching an area that was experiencing inflammation, causing complaints of discomfort to patients in the form of pain when swallowing. Safitri's research also explained that most patients with chronic tonsillitis complain of sore thorat. Recurrent events in chronic tonsillitis are due to incomplete healing due to inadequate initial treatment, so that pathogenic bacteria that still persist in the tonsils can at any time attack the tonsils again if the body's resistance decreases. Complaints of fever in this study were as much as 30%, this could occur due to the body's response due to foreign antigens that attack the body's defense system.11,13

Based on the size of the tonsils, it was dominated by T2-T2 with 16 patients (40%). This is in accordance with Farokah's study of elementary school children where there were 83 students with T2 tonsil sizes, while 62 students with T3 tonsil sizes and no students with T4 tonsil sizes. Enlarged tonsils due to parenchymal hyperplasia or fibrinoid degeneration with obstruction of the tonsillar crypts. Recurrent infections and obstruction of the tonsillar crypts result in increased debris and antigen stasis in the crypts, as well as a decrease in the integrity of the crypt epithelium, making it easier for bacteria to enter the tonsillar parenchyma. Bacteria that enter the tonsillar parenchyma will result in tonsillar infection. The size of T2-T2 often occurs in acute tonsillitis, even if left unchecked, it can lead to chronic tonsillitis.14,15 Based on medical diagnosis, acute tonsillitis is dominated by 30 people (75%). The corresponding research by Preti in 2016 at the Indonesian Christian University General Hospital was dominated by acute tonsillitis in 76 people (76%) while chronic tonsillitis was in 24 people (24%).16 The patient profile based on management was dominated by medical treatment in 31 people (77.5%). This is due to the fact that more pediatric patients who come to the Universitas Kristen Indonesia Hospital are diagnosed with acute tonsillitis, so medical therapy is given. Tonsillectomy is aimed at cases where there are indications for surgery, such as chronic tonsillitis, which are not many. The results of this study are in accordance with those conducted by Amalia in 2011, which recorded more medicine therapy than surgery.17

4. CONCLUSION

The characteristics of tonsillitis patients in children obtained the most description in the age group 0-6 years as much as 62,5%, male sex as much as 55%, the main complaint of repeated sore throat as much as 60%, and 57.5% of patients had good nutritional status/normal, size tonsils T2-T2 as much as 40, based on disease category that acute tonsillitis is 75% and the most treatment medicine option, as much as 77.5%. Therefore, it is hoped that future researchers need to develop and take into account other variables that have not been studied, such as history of eating/smoking habits, oral hygiene, and climate/weather factors. Further research is needed using a larger number of samples in other hospitals or other populations.

REFERENCES

Yeoh YK, Chan MH, Chen Z, Lam EW, Wong PY, Ngai CM, Chan PK, Hui M. The human oral cavity microbiota composition during acute tonsillitis: a cross-sectional survey. BMC oral health. 2019 Dec 1;19(1):275.

Najim JM, Alsaimary IE, Alshareida AM. Pathogenicity of Streptococcus pyogense associated among tonsillitis patients and Tonsillectomy. In Journal of Physics: Conference Series,2019:1:1294(6):062002. IOP Publishing.

Sembiring RO. Identifikasi Bakteri dan Uji Kepekaan terhadap Antibiotik pada Penderita Tonsilitis di Poliklinik THT-KL BLU RSU Prof. Dr. RD Kandou Manado Periode November 2012-Januari 2013. Jurnal E-biomedik. 2014 Aug 19;1(2):1053-7.

Soepardi EA, Iskandar N, Bashiruddin J, Restuti RD. Buku Ajar Ilmu Kesehatan Telinga Hidung Tenggorok Kepala dan Leher. Edisi ke-6. Jakarta: Fakultas Kedokteran Universitas Indonesia; 2011.

Khasanov SA, Asrorov AA. Prevalence of Chronic Family Tonsilitis and Its Prevention. Vestn Otorinolaryngology. 2006;4:38-40

Raju G, Selvam EM. Evaluation of Microbial Flora in Chronic Tonsillitis and The Role of Tonsillectomy. Bangladesh Journal of Otorhinolaryngology. 2012 Nov 24;18(2):109-13.

Palandeng AC, Tumbel RE, Dehoop J. Penderita Tonsilitis di Poliklinik THT-KL BLU RSUP Prof. Dr. RD Kandou Manado Januari 2010-Desember 2012. e-CliniC. 2014;2(2).

Kartika. Faktor-Faktor yang Berhubungan dengan Angka Kejadian Tonsilitis pada Anak Usia 5-18 Tahun di Poliklinik THT RSUD Karawang Tahun 2015. Jurnal Kesehatan Bhakti Husada. 2017 Oct 21;3(1):23-32

Thios RL. Profil Penderita Tonsilitis di Poliklinik THT-KL BLU RSUP Prof. Dr. R. D. Kandou – Manado, Januari 2008 – Desember 2010. Manado: Universitas Sam Ratulangi; 2011.

Abouzied A, Emad M. Sex Differences in Tonsillitis. Dalhausie Medical Journal. 2008;35(1):8-10.

Triastuti NJ, Rahman F, Akbar MA, Dasuki MS, Sintowati R. Pengaruh Status Gizi dan Tonsilitis Kronik terhadap Prestasi Belajar pada Siswa Sekolah Dasar. Biomedika. 2015 Feb 2;7(1):27-34.

Harrypana IGNG, Putra DGAE. Distribusi tonsilitis kronis pada siswa di SD 1 Ubung Denpasar dan SD 2 Abang Karangasem. Medicina. 2019;50(2):281-286.

Safitri R. Karakteristik Penderita Tonsilitis Kronis yang Diindikasikan Tonsilektomi (Tesis). Jambi: Fakultas Kedokteran Ilmu Kesehatan Universitas Jambi. 2013.

Sanpardi GP, Dehoop J, Mengko SK. Survei Kesehatan Tenggorok pada Masyarakat.

Pesisir Pantai Bahu. e-CliniC. 2015;3(1):550-3.

Farokah. Hubungan Tonsilitis Kronis dengan Prestasi Belajar pada Siswa Kelas II Sekolxah Dasar di Kota Semarang. Semarang: Universitas Diponegoro; 2005.

Roseli P. Profil Penderita Tonsilitis di Rumah Sakit Umum Universitas Kristen Indonesia Tahun 2011-2016 (Tesis). Jakarta: Universitas Kristen Indonesia;2016.

Amalia N. Karakteristik Penderita Tonsilitis Kronis Di RSUP H. Adam Malik Medan Tahun 2009 (Tesis). Medan: Universitas Sumatera Utara; 2011.

Dimitrovska, M. (2024). Personalized medicine as trend in pharmaceutical industry, *MEDIS - Medical Science and Research, 3*(1), 31-35. doi: 10.35120/medisij030131d
UDK: 601.4:575.113]:614.254..256

PERSONALIZED MEDICINE AS TREND IN PHARMACEUTICAL INDUSTRY

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Abstract: Personalized medicine is indeed a significant trend in the pharmaceutical industry, revolutionizing the way treatments are developed and administered. It is an innovative perspective that ultimately magnifies the quality of healthcare and creates multiple opportunities in transforming the prospects of medicine development, clinical trials, and patient care. Genomics and data analytics are essential in advancing personalized medicine. The challenges in implementing personalized medicine are numerous, yet the opportunities to remodel healthcare are immense. The perspectives of personalized medicine in the pharmaceutical industry are encouraging, with great potential to inspire innovation and establish transformation od drug development.

Keywords: *precision medicine, individualized treatment, targeted therapy, patient-centered care*

1. INTRODUCTION

Personalized medicine, known also as precision medicine, is a pioneering method that customizes medical treatment according to individual features, such as genetics, lifestyle, and environment. This innovative concept moves away from the traditional one-size-fits-all approach to healthcare, recognizing that each person is unique and may respond differently to treatments.

The importance of personalized medicine in healthcare cannot be overstated. By analyzing a patient's genotype and other factors, healthcare providers can forecast how a person may respond to a treatment, allowing for more targeted and effective interventions. This personalized approach not only improves patient outcomes but also minimizes adverse effects and unnecessary treatments, ultimately leading to better overall healthcare quality.

Furthermore, personalized medicine has the capacity to metamorphose disease prevention, early detection, and management. It enables healthcare professionals to identify individuals at higher risk of certain diseases and provide proactive interventions to prevent or delay the onset of illness. This proactive and individualized approach has the power to transform the healthcare landscape, offering patients more personalized and precise care tailored to their specific needs.

Personalized medicine represents a backtracking in healthcare, offering a more precise, effective, and patient-centered approach to treatment and prevention. Its importance lies in its ability to improve outcomes, decrease healthcare expences, and enhance the quality of care for individuals worldwide.

2. TRANSFORMATION OF LANDSCAPE OF DRUG DEVELOPMENT

Personalized medicine is indeed changing the landscape of drug development in profound ways. Traditionally, drug development has followed a one-size-fits-all approach, where medications are designed to treat a broad population without considering individual variations. However, personalized medicine takes a more targeted approach by considering the genetic makeup and biomarkers as unique characteristics of each patient.

An individual's genetic makeup, also known as their genome, refers to the complete set of genetic material (DNA) present in their cells. The genome contains all the information needed to build and maintain an organism. It is inherited from parents and influences various traits, characteristics, and susceptibility to certain diseases. The key aspects of genetic makeup are DNA, genes, chromosomes, genotype, phenotype, genetic variations, inheritance, and mutations.

Understanding an individual's genetic makeup is crucial for various applications, including genetic testing, personalized medicine, forensic identification, population genetics. Advances in genomics and genetic research have provided insights into the complexity of the genetic makeup and its role in health, disease, and human diversity. The Human Genome Project, completed in 2003, played a pivotal role in mapping and sequencing the entire human genome, laying the foundation for ongoing research and

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applications in genetics.

Biomarkers are measurable indicators that are used to evaluate various biological or pathological processes, conditions, or responses within an organism. These markers can be found in tissues, cells, blood, urine, or other bodily fluids. Biomarkers play a crucial role in medical research, diagnosis, prognosis, monitoring of diseases, and assessing the effectiveness of treatments. They provide valuable information about the physiological or pathological status of an individual, aiding in the understanding and management of health conditions. They aid in early detection, accurate diagnosis, and effective management of diseases, ultimately improving patient outcomes and guiding therapeutic decisions.

This shift towards personalized medicine has revolutionized drug development by enabling pharmaceutical companies to create treatments that are more effective and safer for specific patients. Through determination of genetic variations that influence drug response, researchers can develop medications that are customized to individual patients, maximizing efficacy and minimizing adverse reactions.

Furthermore, personalized medicine has led to the development of companion diagnostics, which are tests that help identify patients who are most likely to benefit from a specific and individual treatment. This approach not only streamlines the drug development process but also ensures that medications are prescribed to those who will benefit the most, leading to better outcomes and reduced healthcare costs.

Personalized medicine is driving a paradigm shift in drug development, moving towards a more precise and individualized approach that has the capacity to revolutionize the way we treat diseases and improve patient care. This shift towards personalized medicine has the potential to transform drug development by creating more successful and aimed treatments that improve patient's welfare.

3. IMPACT ON CLINICAL TRIALS AND PATIENT CARE

Personalized medicine has had a significant impact on both clinical trials and patient care. In the realm of clinical trials, personalized medicine has revolutionized the way new treatments are tested and evaluated. By incorporating genetic information, biomarkers, and other individual characteristics into trial design, researchers can single out patient subgroups that are more likely to respond positively to a specific treatment. This targeted process not only increases the likelihood of successful trial outcomes but also reduces the time and resources needed to bring new therapies to market. Additionally, personalized medicine has led to the establishment of adaptive clinical trial designs, which allow for real-time adjustments based on patient responses, further enhancing the efficiency and effectiveness of trials.

Patient-centred care is an approach to healthcare that emphasizes the active involvement of patients in their own care and considers their preferences, values, and needs. It is a holistic and collaborative approach that goes beyond just treating the medical condition and focuses on the overall well-being of the patient. Key principles of patient-centred care include:

• Respect for patient values and preferences-healthcare providers should actively listen to patients, respect their cultural and personal values, and consider their preferences in decision-making regarding their care.

• Information sharing- patients have the right to receive clear, accurate, and understandable information about their health condition, treatment options, and the possible risks and benefits connected with each option. This enables them to make informed decisions about their care.

• Involvement in decision-making: patients are encouraged to actively participate in decisions about their healthcare. This includes discussing treatment options, setting goals, and collaborating with healthcare providers to create a care plan that aligns with the patient's values and preferences.

• Holistic approach: patient-centred care considers the physical, emotional, social, and spiritual aspects of a patient's welfare. It recognizes that these factors can influence health outcomes and seeks to address them in a comprehensive manner.

• Coordination and integration of care- healthcare should be well-coordinated and integrated across different providers and settings. This ensures that patients receive seamless and continuous care, preventing gaps or duplications in treatment.

• Empathy and compassion-healthcare providers should demonstrate empathy and compassion, acknowledging the emotional and psychological aspects of illness. Building a trusting and supportive relationship between the patient and the healthcare team is crucial.

• Access to car: patient-centred care also involves ensuring that healthcare services are accessible and responsive to the diverse needs of patients, including those related to language, cultural background, and physical abilities.

• Shared responsibility-patients and healthcare providers share the responsibility for the patient's

care. Encouraging self-management and providing support for patients to actively participate in their own health can lead to better outcomes.

Patient-centred care is considered essential for achieving positive health outcomes, enhancing patient satisfaction, and improving the overall healthcare experience. It requires a shift in the healthcare culture towards recognizing and valuing the unique perspectives and needs of individual patients. This approach fosters a partnership between patients and healthcare providers, ultimately leading to more personalized and effective healthcare delivery.

In terms of patient care, personalized medicine has remodeled the way healthcare is delivered. By customizing treatments to individual characteristics, such as genetics, lifestyle, and environment, healthcare providers can offer more precise and effective interventions that are customized to each patient's unique needs. This personalized approach not only improves treatment outcomes but also minimizes adverse reactions and unnecessary treatments, leading to better overall patient care. Furthermore, personalized medicine enables healthcare professionals to identify individuals at higher risk of certain diseases and provide proactive interventions to prevent or delay the onset of illness. This proactive and individualized approach has the capacity to transform disease prevention, early detection, and management, ultimately elevating the life quality worldwide.

4. THE ROLE OF TECHNOLOGY IN ADVANCING PERSONALIZED MEDICINE

Technology, such as genomics, pharmacogenomics and data analytics, plays a crucial role in advancing personalized medicine. Genomics, the study of an individual's genetic makeup, provides valuable insights into how genes influence health and disease. By analyzing a person's genetic information, healthcare providers can determine genetic variations that may impact drug response, disease risk, and treatment outcomes. This information allows for the development of personalized treatment plans adjusted to everyone's unique genetic profile, maximizing efficacy and minimizing adverse reactions.

Pharmacogenomics is a study of how an individual's genotype influences their response to drugs. It combines the fields of pharmacology (the study of medicines) and genomics (the study of genes and their functions) to understand how genetic variations can affect an individual's response to medications. The goal of pharmacogenomics is to customize drug treatments to the unique genetic characteristics of each patient, optimizing therapeutic outcomes while minimizing adverse effects.

Key aspects of pharmacogenomics include: genetic variations (individuals can have genetic variations that influence how their bodies metabolize, transport, or respond to drugs); drug metabolism (the activity of enzymes involved in drug metabolism); drug targets (receptors or proteins in the body; individualized treatment (by understanding a patient's genetic profile, healthcare providers can potentially anticipate how a patient will respond to a particular drug); reducing adverse drug reactions by identifying individuals who may be at higher risk due to their genetic makeup; development of personalized medicine, where treatments are adjusted to the specific characteristics of each patient, maximizing therapeutic efficacy and minimizing adverse effects.

Pharmacogenomic testing is increasingly being integrated into clinical practice to guide treatment decisions and enhance medication safety and effectiveness. However, its widespread adoption is still evolving, and more research is needed to entirely apprehend the potential of pharmacogenomics in improving patient outcomes.

Data analytics, on the other hand, enables healthcare workers to analyze large amounts of information to identify patterns, trends, and correlations that can inform personalized treatment decisions. By leveraging advanced analytics techniques, such as machine learning and artificial intelligence, healthcare professionals can extract valuable insights from complex datasets, such as electronic health records, imaging studies, and genetic information. These insights can help identify patient subgroups that are more likely to benefit from specific treatments, predict disease progression, and optimize treatment strategies for better outcomes.

Together, genomics, pharmacogenomic and data analytics empower healthcare providers to deliver more precise, individualized care to patients, leading to improved treatment outcomes and patient satisfaction. By harnessing the power of technology, personalized medicine is advancing rapidly, transforming the way healthcare is delivered and revolutionizing the field of medicine. The integration of genomics and data analytics into clinical practice holds great promise for improving patient care, driving innovation in drug development, and ultimately shaping the future of healthcare.

5. CHALLENGES AND OPPORTUNITIES

Implementing personalized medicine presents both challenges and opportunities in healthcare. One of the main challenges is the complexity of integrating genetic and molecular data into clinical practice. Healthcare providers may face obstacles in interpreting and applying genetic information to make treatment decisions, as well as in ensuring the privacy and security of patient data. Additionally, there may be challenges in standardizing and regulating personalized medicine practices to ensure consistency and quality of care across different healthcare settings.

On the other hand, implementing personalized medicine also offers numerous opportunities for improving patient outcomes and healthcare delivery. By customizing treatments to individual characteristics, healthcare providers can optimize treatment efficacy, minimize adverse effects, and enhance patient satisfaction. Personalized medicine has the capacity to completely remodel disease prevention, early detection, and management, leading to better overall health outcomes and quality of life for patients. Furthermore, personalized medicine can drive innovation in drug development, as pharmaceutical companies can develop targeted therapies based on specific genetic markers and patient subgroups.

In general, while there are challenges to overcome in implementing personalized medicine, the opportunities for enhancing patient care, elevating medical research, and catapulting an evolution in healthcare are vast. By leveraging technology, such as genomics and data analytics, and addressing regulatory and ethical considerations, personalized medicine has the potential to alter the way healthcare is provided, ultimately leading to more effective, efficient, and patient-centered care.

6. CONCLUSIONS

The prospects of personalized medicine hold great promise for the pharmaceutical industry, with the power to make far-reaching changes in drug development, improve treatment outcomes, and drive innovation. Personalized medicine aims to adjust treatments to individual characteristics, such as genotype, lifestyle factors, and disease biomarkers, to optimize efficacy and minimize adverse effects. By leveraging advanced technologies, such as genomics, data analytics, and precision medicine approaches, pharmaceutical companies can develop targeted therapies that are more effective and safer for specific patient groups. This shift towards personalized medicine has the potential to transform the conventional one-size-fits-all approach to drug development and healthcare delivery.

The impact of personalized medicine on the pharmaceutical industry is multifaceted. On one hand, personalized medicine presents new opportunities for pharmaceutical companies to develop innovative therapies that target specific genetic mutations or disease pathways. This targeted approach can lead to more successful clinical trials, faster drug approvals, and increased market penetration for pharmaceutical products. Additionally, personalized medicine can improve patient outcomes and satisfaction, as treatments are tailored to individual needs and characteristics, leading to better adherence and overall health outcomes.

However, the adoption of personalized medicine also poses challenges for the pharmaceutical industry. Companies may need to invest in new technologies, infrastructure, and expertise to incorporate personalized medicine approaches into their drug development pipelines. Regulatory and reimbursement challenges may also arise, as personalized therapies may require new approval pathways and payment models to ensure access for patients. Furthermore, the shift towards personalized medicine may disrupt traditional business models in the pharmaceutical industry, requiring companies to adapt to new market dynamics and competitive pressures.

Overall, the prospects of personalized medicine in the pharmaceutical industry are promising, with the capacity to inspire innovation, improve treatment results, and transform the entire healthcare systems worldwide. By embracing personalized medicine approaches and leveraging advanced technologies, pharmaceutical companies can position themselves at the forefront of this transformative shift in healthcare, ultimately leading to better treatments, improved health outcomes, and enhanced value for patients and stakeholders.

REFERENCES

Jameson, J. L., & Longo, D. L. (2015). Precision medicine-personalized, problematic, and promising. New England Journal of Medicine, 372(23), 2229-2234.
Hamburg, M. A., & Collins, F. S. (2010). The path to personalized medicine. New England Journal of Medicine, 363(4), 301-304.
Collins, F. S., & Varmus, H. (2015). A new initiative on precision medicine. New England Journal of Medicine, 372(9), 793-795.

Snyder, M. (2016). Genomics and Personalized Medicine: What Everyone Needs to Know, Oxford University Press
Prainsack, B (2017). Personalized Medicine: Empowered Patients in the 21st Century?, NYU Press
Topol, E. J. (2019). Deep medicine: How artificial intelligence can make healthcare human again. Hachette UK
De Vries, G. (2020). The Patient Equation: The Precision Medicine Revolution in the Age of COVID-19 and Beyond, Wiley.
Jain, K.K. (2020). Textbook of Personalized Medicine. Springer Cham, 978-3-030-62079-0
Al-Worafi, Y.M (2023). Technology for Drug Safety: Current Status and Future Developments, Springer Science and Business Media LLC
Malionwski, M.J. (2023). Personal Genome Medicine, Cambridge University Press
Lee, P., Goldberg, A., Kohane, I. (2023). The AI Revolution in Medicine: GPT-4 and Beyond, Pearson
National Institutes of Health. (2018). All of Us Research Program. Retrieved from https://allofus.nih.gov/

Tosev, G. et al. (2024). Low-intensity shockwave treatment for neurogenic bladder with chronic urine retention - case report, *MEDIS - Medical Science and Research, 3*(1), 37-40. doi: 10.35120/medisij030137t
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LOW-INTENSITY SHOCKWAVE TREATMENT FOR NEUROGENIC BLADDER WITH CHRONIC URINE RETENTION - CASE REPORT

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Abstract: We present a case of neurogenic bladder accompanied by chronic urine retention in a patient diagnosed with multiple sclerosis (MS). This condition was effectively managed by low-intensity shockwave therapy (Li-ESWT).

Low-intensity focused shockwave therapy (Li-ESWT) is becoming increasingly important in the treatment of urological problems. This case study investigates the feasibility and efficacy of using Li-ESWT to reduce post-void residual volume in persons with neurogenic bladder, representing the first examination of its sort.

Bladder dysfunction (BD) frequently occurs in patients who have been diagnosed with multiple sclerosis (MS). Bladder dysfunction (BD) can occur due to the impairment of nerve impulses in the central nervous system regions involved for regulating bladder function and managing the contractions of the urinary sphincters, which is caused by the lesions associated with multiple sclerosis (MS). Urinary retention can cause various symptoms, including insufficient bladder emptying, urinary incontinence, frequent urinary tract infections, urosepsis resulting in the development of kidney abscesses due to localised kidney infection, and reduced kidney function.

Optimal bladder function is essential for individuals with MS, as it plays a critical role in preserving kidney health, preventing urinary tract infections and incontinence, reducing the frequency of MS episodes, and improving their overall well-being.

A 31-year-old woman was referred to our urology office with a chronic urinary tract infection caused by a neurogenic bladder with a significant volume of residual urine. A kidney abscess formation was identified as a complication. Li-ESWT, which stands for low-intensity extracorporeal shockwave therapy, was used as a part of a multimodal strategy to treat the urinary bladder. This treatment was delivered off-label. The therapy was given on a weekly basis for a period of 6 weeks. The procedure included administering 2500 shocks at a rate of four pulses per second, with an energy flux density (EFD) of 0.25 millijoules per square millimetre. The EFD (Energy Flux Density) used in our study exceeded 0.32 mJmm2,4, the fR (frequency rate) was set at 8 Hz (pulses per second), the treatment sessions consisted of 12 cycles of Li-ESWT (Low-Intensity Extracorporeal Shockwave Therapy), and a total of 3000 shocks were administered. At the intervals of one week, three months, six months, nine months, and twelve months following the administration of Li-ESWT and tadalafil 2.5 mg, the post-void residual (PVR) volume was consistently below 50 ml. The Li-ESWT treatment effectively reduced the post-void residual urine volume.

Low-intensity extracorporeal shockwave therapy (Li-ESWT) can safely and efficiently decrease the amount of urine left in the bladder after voiding in individuals with neurogenic bladder caused by multiple sclerosis (MS). We have effectively demonstrated that Li-ESWT is a feasible and safe treatment for chronic urine retention, resulting in a decrease of post-void residual (PVR) volume from 200 ml to 50 ml. In the future, Li-ESWT has the potential to be advanced as a more efficacious alternative therapy for individuals experiencing chronic urinary retention. Further investigation is necessary to confirm the effectiveness of ESWT in addressing the neurogenic bladder.

Keywords: *neurogenic bladder, multiple sclerosis, low intensity shockwave therapy, post-void residual volume, detrusor underactivity.*

Field: Medical sciences and Health

1. INTRODUCTION

Low-intensity focused shockwave therapy (Li-ESWT) is gaining significance in the management of urological disorders. This case study examines the feasibility and efficacy of utilising Li-ESWT to decrease post-void residual volume in individuals with neurogenic bladder, marking the first investigation of its kind.

Bladder dysfunction (BD) commonly manifests in individuals diagnosed with multiple sclerosis (MS). Bladder dysfunction (BD) can arise when the lesions associated with multiple sclerosis (MS) impair the nerve impulses in the central nervous system regions responsible for regulating bladder function and

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controlling the contractions of the urine sphincters. Urinary retention can lead to many symptoms, such as incomplete bladder emptying, urinary incontinence, frequent urinary tract infections, urosepsis with the formation of kidney abscesses as a result of localised kidney infection, and decreased kidney function.

2. CASE DESCRIPTION

A 31-year-old female patient diagnosed with Multiple Sclerosis (MS) has been receiving frequent urological check-ups at our urology clinic since April 2020. The patient was consistently taking dimethyl fumarate as part of their treatment for multiple sclerosis. Neurological evaluations, including MRI scans of the head and spine conducted in March 2020 and March 2022, revealed that the condition remained stable, with no signs of abnormal growths in the specific area of the brain responsible for controlling urination. During the initial presentation, the patient was diagnosed with pyelonephritis affecting the right kidney. The patient's ability to empty their bladder was normal, with a post-void residual volume (PVR) of 50 ml. Hematuria was identified during routine urological evaluation. A cystoscopy was conducted in June 2021. No anomalies were detected. The examination of the upper urinary tract using magnetic resonance urography (MRU) did not reveal any significant findings. Based on the patient's age and absence of other medical conditions, we maintain a strong belief that multiple sclerosis is the underlying cause of the urinary impairment.

In September 2021, the female patient experienced repeated episodes of inflammation in her right kidney, known as recurrent pyelonephritis. A worsening of micturition was reported. The sonography of the urine bladder detected a post-void residual (PVR) volume over 100 ml. After administering suitable antibiotic therapy, the patient's laboratory findings and physical state returned to normal.

In October 2021, the patient experienced a novel urinary tract infection and a fever. The patient had inpatient therapy involving the intravenous infusion of antibiotics and the installation of a bladder catheter. The MRI and urography detected a renal abscess in the right kidney measuring 1.7 cm in diameter, although there was no blockage in the upper urinary system. The abscess could not be punctured due to its inaccessible placement. Consequently, the abscess was managed conservatively by using extended intravenous antibiotics.

Following her release from the hospital, sonography revealed the presence of residual urine over 200 ml on many occasions. As an additional treatment option, the patient began intermittent self-catheterization along with intravesical bladder instillation of chondroitin sulphate. This active ingredient helps temporarily replace the protective layer of sulfated glycosaminoglycan in the bladder. Additionally, the patient started pelvic floor muscle training. The patient declined to have a urodynamic study, which was subsequently not conducted.

Four cycles of single-dose intravesical treatment with chondroitin sulphate were given within a period of four weeks. The post-void residual (PVR) was assessed using disposable catheters during intravesical therapy, producing approximately 200 to 250 ml volume. The administration of distigmine (5 mg) orally twice a day was started as the initial treatment option (Bougas DA, 2004), but it was discontinued after 4 weeks due to its lack of effectiveness.

Subsequently, the patient underwent 12 cycles of low intensity shockwave therapy (Li-ESWT) administered on a weekly or biweekly basis to the urinary bladder as an off-label treatment from January 2022 to April 2022. We employed the PiezoWave (Lee Y-C, 2020) shockwave apparatus, manufactured by Richard Wolf GmbH and ELvation Medical in Germany. Similar to a previous investigation on the treatment of an overactive bladder utilising Li-ESWT (Lee Y-C, 2020), the number of delivered pulses, the F10G10 applicator, the region of administration, and the shockwave penetration were utilised. The energy distribution at energy level 20 yielded a peak energy flux density (EFD) of 0.32 mJ/mm2 at a frequency (fR) of 8 Hz (pulses per second). A total of 36,000 shockwaves were administered throughout the whole 12-week therapy duration. Tadalafil 2.5 mg was prescribed as an off-label application and used once a day as an adjuvant till the completion of Li-ESWT. At the intervals of one week, three months, six months, nine months, and twelve months following the administration of Li-ESWT and tadalafil 2.5 mg, the post-void residual (PVR) volume was consistently below 50 ml.

3. RESULTS AND DISCUSSION

Optimal bladder function is crucial for individuals with MS, specifically in maintaining their kidney health, preventing urine infections and incontinence, minimising the frequency of MS episodes, and enhancing their overall well-being. Based on the neurological follow-up, which involved conducting MR scans of the head and spine, it was determined that the urinary dysfunction in this patient was not caused

by an acute attack of multiple sclerosis (MS).

An in vivo study has investigated the impact of Li-ESWT on bladder function. (Wang HS, 2018). The study demonstrated that Li-ESWT improved the condition of underactive bladder (UAB) and urine incontinence in a rat model of diabetic underactive bladder. This study proposes that the enhancement may be attributed to the repair of the bladder and urethral structure and function, which is facilitated by the preservation of neuronal integrity and innervation through Li-ESWT.

The initial clinical investigation of Li-ESWT demonstrated a statistically significant reduction in symptoms of Detrusor underactivity (DU)/UAB, as well as a tendency to lower post-void residual (PVR) volume compared to the placebo group (Shen YC, 2023). The treatment was administered weekly for a duration of 6 weeks. It involved the delivery of 2500 shocks, with a frequency rate of four pulses per second and an energy flux density (EFD) of 0.25 millijoules per square millimetre. In our situation, the EFD (Energy Flux Density) employed was higher than 0.32 mJmm2,4, the fR (frequency rate) was 8 Hz (pulses per second), the treatment sessions consisted of 12 cycles of Li-ESWT (Low-Intensity Extracorporeal Shockwave Therapy), and a total of 3000 shocks were administered. The study conducted by Shen et al. suggests that Extracorporeal Shock Wave Therapy (ESWT) may have a positive impact on enhancing bladder sensation (Shen YC, 2023).

Another investigation discovered that Li-ESWT alleviated symptoms of overactive bladder and enhanced bladder voiding function in female patients (Lee Y-C, 2020).

Temporary ischemia and flow return to basal levels after drainage in male Sprague Dawley rats, as a result of acute urine retention (Shimizu S, 2009). Transient bladder ischemia is believed to cause a temporary reduction in detrusor compliance (Tracey AT, 2019). In this particular instance, the patient is experiencing chronic urine retention as a result of multiple sclerosis (MS). Prior research has linked persistent ischemia to the pathological advancement towards detrusor overactivity, ultimately resulting in DU (Andersson K-E, 2017).

VEGF is a signal protein that stimulates angiogenesis and reestablishes oxygen delivery to tissues in cases of insufficient blood flow, such as in hypoxic circumstances (Shen Y-C, 2021). Interleukin 9 (IL-9) is a cytokine produced by CD4+ helper cells that controls various hematopoietic cell types, increasing cell proliferation and preventing apoptosis (Perumal NB, 2011)Sugaya et al. found that approximately 35% of the individuals in their study who had interstitial cystitis also had an allergy or autoimmune condition linked to the excessive production of IL-4. The IL-4 and its receptor genes are robustly associated with immunological diseases (Sugaya K, 2002).

Under pathological hydrostatic pressure, the β-Adrenoceptor regulates the expression of inflammatory cytokines and contraction in human bladder smooth muscle cells through autophagy1 (Chen G, 2020). Shen et al. conducted a study where they found that patients with refractory interstitial cystitis and bladder pain syndrome who were randomly assigned to receive Li-ESWT had improved symptoms and urine biomarkers compared to those who received a placebo. At 4 weeks, the group that received Extracorporeal Shock Wave Therapy (ESWT) exhibited a decrease in the expressions of Vascular Endothelial Growth Factor (VEGF) and Interleukin-4 (IL-4), whereas the expression of Interleukin-9 (IL-9) increased. These authors proposed that Extracorporeal Shock Wave Therapy (ESWT) may exert an influence on immunological regulation by affecting mast cells and their IL4 reaction (Shen Y-C, 2021)

Adjuvant daily therapy with tadalafil 5 mg (PDE5i) effectively enhanced the effectiveness and duration of the advantages of Li-ESWT in patients with erectile dysfunction by preventing the breakdown of cGMP (Gallo L, 2022). The NO/cGMP/G Kinase pathway appears to have a significant impact on the regulation of bladder myocyte tone (Deka DK, 2004). Additionally, treatment with PDE5i may help reduce the progression of ischemia-related functional and structural changes in the bladder (Andersson K-E, 2017).

This case report aims to investigate the possible advantages of Li-ESWT, taking into account its anti-inflammatory and anti-apoptotic properties, as well as its capacity to stimulate stem cells. Therefore, Li-ESWT may be efficacious for urinary bladder conditions that are characterised by reduced inflammatory reactions, heightened innervation of bladder nerves, tissue regeneration, and enhanced blood vessel formation via angiogenesis. Furthermore, Li-ESWT can result in improved contractile activity of the bladder and urethra muscles and improved composition of the bladder wall. The bladder experienced ischemia and a decline in innervation, resulting in impaired transmission of nerve impulses due to multiple sclerosis (Shen Y-C, 2021) (Jin Y, 2017).

The main processes underlying the action of Li-ESWT on the bladder include modulated local immune responses, increased bladder nerve innervation, enhanced vascularization and angiogenesis, regulation of β-Adrenoceptors response, activation of stem cells, reduction of bladder ischemia, and inhibition of urothelial cell apoptosis.

Our case demonstrated a substantial enhancement of post-void residual volume (PVR) from over 200 ml to less than 50 ml after undergoing treatment with low-intensity extracorporeal shockwave therapy (Li-ESWT) in combination with adjuvant therapy involving the administration of tadalafil 2.5 mg. This improvement has been sustained for a duration of 9 months thus far.

The patient has reported the absence of any negative consequences experienced during the treatment, as well as a notable enhancement in voiding function following Li-ESWT. There was no observed enhancement following the initial pharmacological intervention.

Prior to the multimodal Li-ESWT therapy, the administration of distigmine and chondroitin sulphate was carried out. Nevertheless, we cannot simply attribute the outcome in this case to the initial treatment, as there was no immediate observation of clinical improvement. Observable progress in the patient's condition was apparent with the implementation of a comprehensive treatment strategy that included Lithotripsy-Enhanced Extracorporeal Shock Wave Therapy (Li-ESWT) and Tadalafil medication.

In the present case, PVR served as the primary diagnostic instrument for assessing treatment efficacy, and it was not possible to conduct a urodynamic examination prior to and following the treatment. This is because of the rapid alleviation of symptoms and the patient's failure to comply with additional intrusive procedures. Hence, the alleviation of symptoms and the notable enhancement in clinical presentation provide robust evidence in favour of the positive result of PVR following Li-ESWT, thereby minimising the likelihood of alternative factors contributing to better PVR.

4. CONCLUSION

This case report is the initial documentation of the application of Li-ESWT in the treatment of a patient presenting with neurogenic bladder and chronic urine retention. We have successfully shown that Li-ESWT is a viable and secure therapy for persistent urine retention, reducing post-void residual (PVR) volume from 200 ml to 50 ml. In the future, Li-ESWT could be developed as a more effective alternative treatment for people suffering from chronic urine retention. Additional research is required to validate the efficacy of ESWT in treating the neurogenic bladder.

REFERENCES

Bougas DA, M. I. (2004). Clinical efficacy of distigmine bromide in the treatment of patients with underactive detrusor. Int Urol Nephrol, 36: 507–512.

Lee Y-C, C. S.-M.-L. (2020). ow-Intensity Extracorporeal Shock Wave Therapy Ameliorates the Overactive Bladder: A Prospective Pilot Study. . Biomed Res Int , 9175676.

Wang HS, O. B. (2018). Low-intensity extracorporeal shockwave therapy ameliorates diabetic underactive bladder in streptozotocin-induced diabetic rats. . BJU Int, 122: 490–500.

Shen YC, C. C. (2023). Prospective, Randomized, Double-blind, Placebo-controlled, Pilot Study of Extracorporeal Shock Wave Therapy for Detrusor Underactivity/Underactive Bladder. . Eur Urol Focus, 9: 524–530.

Shimizu S, S. M. (2009). Acute urinary retention and subsequent catheterization cause lipid peroxidation and oxidative DNA damage in the bladder: preventive effect of edaravone, a free-radical scavenger. . BJU Int , 104: 713–717.

Tracey AT, A. U. (2019). Bladder attack: transient bladder ischemia leads to a reversible decrease in detrusor compliance. . Translational Andrology and Urology , 8: 703–711, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6987606/ .

Andersson K-E, B. D. (2017). The link between vascular dysfunction, bladder ischemia, and aging bladder dysfunction. . Ther Adv Urol , 9: 11–27.

Shen Y-C, T. P.-C. (2021). Improves symptoms and urinary biomarkers in refractory interstitial cystitis/bladder pain syndrome patients randomized to extracorporeal shock wave therapy versus placebo. . Sci Rep, 11: 7558.

Perumal NB, K. M. (2011). Regulating Il9 transcription in T helper cells. Trends Immunol, 32: 146–150.

Sugaya K, N. S. (2002). Molecular analysis of adrenergic receptor genes and interleukin-4/interleukin-4 receptor genes in patients with interstitial cystitis. . J Urol , 168: 2668–2671.

Chen G, J. X. (2020). β-Adrenoceptor regulates contraction and inflammatory cytokine expression of human bladder smooth muscle cells via autophagy under pathological hydrostatic pressure. . Neurourol Urodyn, 39: 2128–2138.

Jin Y, X. L. (2017). Endogenous Stem Cells Were Recruited by Defocused Low-Energy Shock Wave in Treating Diabetic Bladder Dysfunction. . Stem Cell Rev Rep, 13: 287–298.

Gallo L, P. S. (2022). single-blinded study with 1-year follow-up. Investig Clin Urol , 63: 83–91.

Deka DK, B. A. (2004). Nitric oxide activates glibenclamide-sensitive K+ channels in urinary bladder myocytes through a c-GMP-dependent mechanism. Eur J Pharmacol, 492: 13–19.

Stoimenova, P., Mandadzhieva, S., & Marinov, B. (2024). Forced oscillation technique (fot) – a novel method for the detection of early airway changes, *MEDIS - Medical Science and Research, 3*(1), 41-46. doi: 10.35120/medisij030141s
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FORCED OSCILLATION TECHNIQUE (FOT) – A NOVEL METHOD FOR THE DETECTION OF EARLY AIRWAY CHANGES

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Abstract: According to the World Health Organization in 2019 chronic obstructive pulmonary disease (COPD) was the third leading cause of death worldwide, causing more than 3 million deaths whereas bronchial asthma affected more than 250 million people and caused 455 000 deaths. Both diseases are chronic obstructive conditions which need to be diagnosed early in order to prevent or slow down the complications. Consequently the world requires new effortless methods for diagnosis of airway obstructions, especially for small children and people who cannot perform the spirometry maneuver. The purpose of this report is to describe the objectives of the forced oscillation technique (FOT) and to establish its applications in the clinical practice. Studies and clinical cases regarding pulmonary function testing are summarized and analyzed. They are found in the following databases - PubMed, Google Scholar and Science Direct. Spirometry is the 'gold standard' for the diagnosis of airflow obstruction but it requires effort and can be difficult for patients to perform. Forced oscillation technique (FOT) on the other hand is a relatively new method that may hold the key to identifying smoking-related respiratory early alterations and childhood asthma. FOT requires tidal breathing while applying external, small amplitude oscillations in order to determine the response of the respiratory system. Therefore, it is easy for pre-school children to perform. The benefit of FOT should be taken into account for patients who cannot perform spirometry or other pulmonary function ttests. The minimal cooperation of the patient and the easy tidal breathing maneuvers make this method a great option for every pulmonologist. Compared to spirometry this technique may be more sensitive in the detection of disturbances of the peripheral airways and may be effective for the control of therapy at a long term. The Forced oscillation technique has been successfully applied in many pediatric respiratory disorders, such as asthma, cystic fibrosis, and chronic lung disease. Considering these qualities FOT may be used as an alternative of spirometry in heterogenous ventilatory disturbances of the small airways.

Keywords: Forced oscillation technique, airway obstruction, heterogenous ventilatory conditions

Field: Medical sciences and Health

1. INTRODUCTION

The bronchoobstructive diseases are different conditions in which there is obstruction of airflow of the respiratory tract and heterogeneous ventilation of the alveoli. They result from the narrowing of the bronchial lumen and smaller bronchioles due to inflammation or bronchospasm. (Yaegashi, 2006) Obstructive lung diseases include bronchial asthma, COPD, cystic fibrosis and bronchitis. According to the World Health Organization in 2019 chronic obstructive pulmonary disease (COPD) was the third leading cause of death worldwide, causing more than 3 million deaths whereas bronchial asthma affected more than 250 million people and caused 455 000 deaths. (Boers, 2023) The "golden" standard in the diagnosis of these diseases nowadays is spirometry, but this method turns out to be complicated and unsuitable for certain groups of people such as pre-school children (especially <6 years old), elderly people and minority groups. Performing good spirometry test is often a problem among these groups because the maneuvers involve forced exhalations and very close adherence to the health professional's instructions. Due to these limitations the diagnosis and treatment of these diseases are sometimes delayed.

The forced oscillation technique (FOT) is a relatively new but reliable diagnostic tool used for assessment of bronchial hypersensitivity in adults and children. (Yaegashi, 2006)(Alblooshi, 2017, p.129-138) This method doesn't inquire deep inspirations and forced expirations like in spirometry therefore it doesn't affect the smooth muscle tone of the bronchial tree. Along with the increasing numbers of smoking children and teenagers it is essential FOT is sensitive enough to detect early impairments in the lung functions and can be used for prevention and early diagnosis of COPD in adults. (Faria, 2009)

The aim of this literature review is to present this method as a new option for easier diagnosis of obstructive lung disease and to show the possibilities for the inclusion of FOT in the everyday clinical practice.

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2. METHODS

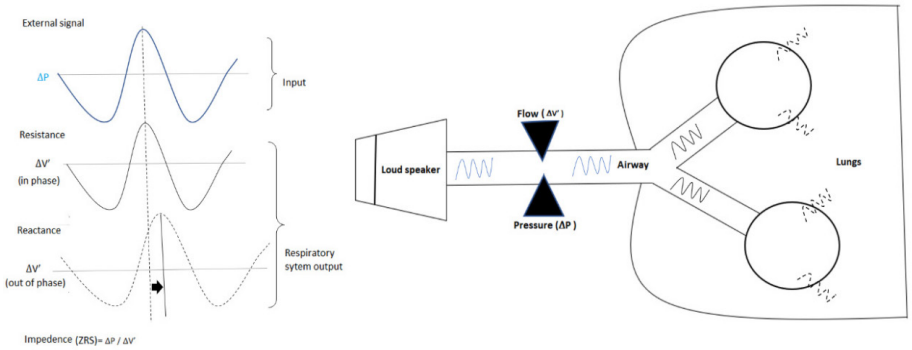
Forced oscillation technique (FOT) is a non-invasive method to assess lung function that uses an oscillating signal and requires only quiet tidal breathing. Measurements were carried out through a mouthpiece. The patient is seated comfortably with a well-straightened back and a slightly extended head position. He is invited to breathe calmly with a tidal volume, the nose is occluded with a nose clip, and the palms and fingers of the patient are on his cheeks lightly pressing them in order to avoid any upper airways artifacts. FOT is processed for 30 seconds tidal breathing and a total of three to five technically acceptable measurements are required. (Kaminsky, 2004) (Bickel, 2014)

Figure 1: Both pictures show the right position of the patient (adult or child). The position of the head is slightly extended, the nose is clipped and the hands of the medical technician lightly compress the cheeks.

Source: www.mgcdiagnostics.com

Oscillometry stimulates the respiratory system with external pressure created by a loudspeaker that is distributed faster than the normal breathing rate. That allows the flow generated by the apparatus to be measured. The “speed” of an oscillation is measured in Hz that is the number of times pressure/ flow oscillates in a second. FOT easily assesses the respiratory system’s response to small pressure oscillations sent to the opening of the airway into the lungs at different frequencies. (Kaminsky, 2004)

Figure 2: Forced oscillation technic apparatus - schematic picture.

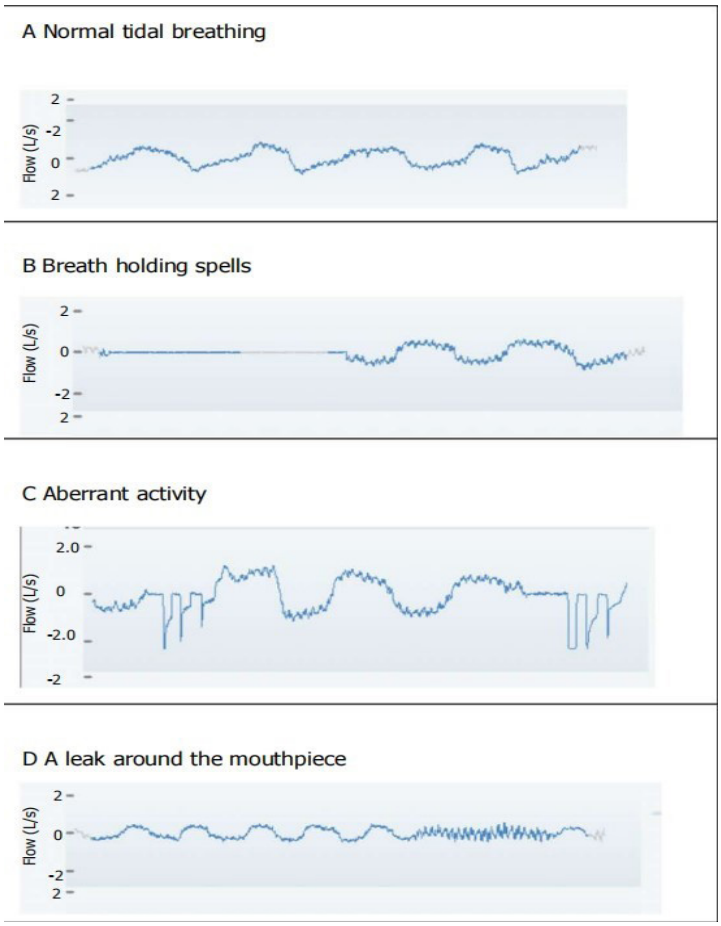


Source: J. Clin. Med. 2020, 9, 2778

It is an effort-independent way to detect airways obstruction and localize it as peripheral, central or heterogeneous. During the test the apparatus measures small and central airway function and assesses tidal expiratory flow limitation (EFL) in adults while aiding in bronchial reversibility testing or trending it over time for therapeutic monitoring. The main parameters that are clinically significant are Rrs (respiratory resistance) and Xrs (respiratory reactance). The respiratory resistance (Rrs) is a measurement of the

degree of obstruction and is a sum of the resistances of all the stimulated segments. It specifically detects central obstruction of the bigger airways and is very informative in cases of bronchoconstriction, excessive mucus production and airway inflammation. Respiratory reactance (Xrs), especially at low frequencies (5 Hz – 8 Hz), measures the elasticity of the air and the structures in the airways and alveoli being stimulated. It is a useful parameter for detection of peripheral obstruction.

Figure 3: The graphs are picturing the oscillations (Flow (L/s) in the airways shown on the screen of the FOT apparatus. A.Normal tidal breathing, B. Breath holding spells, C. Aberrant activity, D. A leak around the mouthpiece (Alblooshi, 2017, p. 129-138)



Source: World J Methodol. Dec 26, 2017; 7(4): 129-134

3. FORCED OSCILLATION TECHNIQUE AND COPD

Chronic obstructive pulmonary disease (COPD) is common progressive lung disease that includes emphysema and chronic bronchitis. COPD is associated strongly with prolonged exposure to harmful particles and gases, among which the most significant cause is cigarette smoke. According to CDC, 8 out of 10 people who die from COPD are smokers.

The chronic inflammation and alveoli destruction are leading to continuous airflow limitation and tissue destruction. This destruction is considered to involve oxidative stress and imbalances in protease-antiprotease enzymes and as a result the protease-mediated reduction of elastin leads to a loss of elastic recoil and airway collapse during exhalation. The inflammatory response and airway obstruction induce a decrease in the forced expiratory volume (FEV1) as well as impaired gas exchange due to severe changes of the aalveoi and pulmonary capillaries.

The standard for COPD severity is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and grounded on constant airflow limitation tested on spirometry. Unfortunately, spirometry has at least three main drawbacks that should be considered:

1. It is not suitable for detection of early changes of the airways, because this method focuses on the larger airways, whereas the early disease starts from smaller airways.

2. The spirometry indices don`t always correlate with the symptoms of the patient.
3. The method is requiring effort and forced expiration, which are complicated and exhausting for children and elderly people.

Forced Oscillation Technique is a non-invasive, effort-independent test to assess the respiratory resistance and reactance. The study of Dellacà et al. shows that the use of the index expiratory flow limitation (EFL) in COPD patients and the within-breath reactance (ΔXrs5Hz) provide a valid information for airway changes. (Dellacà, 2004) FOT can also be used for evaluation of post-bronchodilator response and for monitoring and control of the disease. Some scientists even suggest the option of home monitoring (telemonitoring) as a method for detection of acute exacerbations of COPD (AECOPD). (Walker, 2018) (Zimmermann, 2020) During hospitalization due to AECOPD, FOT was proven useful and Alqahtani et. al discover that the severity of EFL negatively corresponded with the obstrucion of the airflow. They also noticed position-dependent changes in the patient's EFL – the limitation increased in supine position The reduction of dyspnea also was corresponding with improvements in EFL. (Alqahtani, 2021)

Several studies evaluate different FOT parameters in order to analyze their effectiveness in detecting early airway changes in smokers. (Ribeiro, 2018) (Bhattarai, 2020) These studies have certainly implied that the sensitivity of FOT for detecting early airflow obstruction increases with the use of multiple frequencies - lower frequency (5 Hz) going to the peripheral airways, whereas higher frequencies (20 Hz) are limited to proximal airways. Therefore, the resistance (Rrs) and the reactance (Xrs) at low frequency (4–6 Hz) is comparably more relevant in identifying the smoking linked airway changes as they mainly start from the small airways. Sensitive parameters for passive smoking are changes in R5 and R5–20 examined in adolescents who were exposed to maternal smoking. (Faria, 2010) (Kolsum, 2009)

When compared to spirometry FOT appears to be more efficient in the detection of early abnormalities of the small airways and is proven to be a useful diagnostic tool.

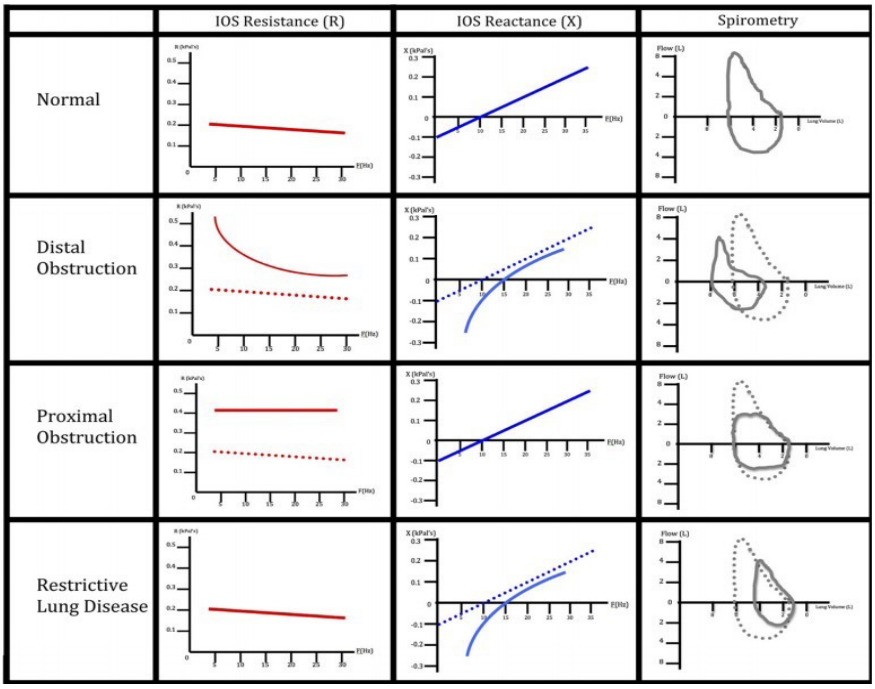
4. FORCED OSCILLATION TECHNIQUE AND BRONCHIAL ASTHMA IN CHILDREN

Bronchial asthma is a chronic inflammatory disease of the airways characterized with episodes of bronchial obstruction caused by inflammation, bronchospasm and mucus production. Often asthma is linked to seasonal allergies and eczema. This is the leading purpose for chronic disease and missed days at school in children.

The "golden" standard in the diagnosis of asthma is spirometric measurement of lung function but it acquires forced techniques and the patient`s cooperation. Whole bodyplethysmography also is difficult for the patient and needs expensive devices. Consequently, FOT is suitable for asthma diagnosis, treatment control and follow-up especially for preschool children, elderly patients, minority groups and people with neuromuscular diseases who cannot perform spirometry properly. Alblooshi et al. in their article for the methodology of FOT advice the clinicians to "understand the emerging role of FOT in clinical practice and how to interpret its results in order to improve management of children with asthma." (Alblooshi, 2017, p.129-138) The tidal breathing and the shortness of the test allow experienced physicians to examine children as young as two years of age, which is not possible in standard spirometry. The success rate in 4 years of age is around 80%, whereas in healthy children older than 6 years is close to 100%. In children with asthma aged between 3 to 5 years the success is from 57-100%.

Several studies established that young children with bronchial astma had impaired baseline lung function even when asymptomatic. Bronchodilator response assessed by FOT can also be used in identifying bad asthma control, which is especially suitable in the clinical management of asthma. (Delacourt, 2001) FOT`s feasibility has been assessed also in bronchoprovocation challenge testing in children with inhaled adenosine monophosphate (AMP), free running, methacholine, hypertonic saline, cold air or mannitol challenge. Actually, significant bronchospasm can be accomplished with lower doses of bronchoprovocative methods. Schulze et al reported that oscillation techniques are more efficient than spirometry because at lower doses of methacholine the resistance had a relevant increase before a change in FEV1 was observed. People with neuromuscular diseases and muscle weakness who are not able to perform forced expirations are also indicated for FOT. The study of Gauld et al. describes 12 children (mean age of 6 years) with spinal muscle atrophy that had abnormal respiratory reactance (Xrs 8) and resistance at 8 Hz (Rrs 8) and in the follow-up of these children the Xrs 8 z-score and Rrs 8 z-score worsened. Only 4 of the patients succeeded in performing spirometry.

Figure 4 Graphs of Impulse Oscillometry (IOS) and spirometry in patients with normal, obstructive, and restrictive lung disease. Dotted lines indicate the normal tracing, whereas solid lines show pathological tracings.



Source: Ann Allergy Asthma Immunol. 2011 Mar; 106(3): 191–199.

5. CONCLUSION

The forced oscillation technique (FOT) is a novel method that is easy to perform during quiet breathing and is perfect for preschool children. This method is very informative and should be broadly used in the diagnosis, control and progression follow-up of chronic obstructive diseases as COPD and bronchial asthma. Many studies suggest that compared with spirometry FOT is quick, effort-independent test that is more sensitive to early changes in the airways and can be used as a screening method for cigarette smoke-induced COPD.

LITERATURE

Alblooshi A. et al (2017). Is forced oscillation technique the next respiratory function test of choice in childhood asthma. World J Methodol 2017 December 26; 7(4): 129-138

Alqahtani J. et al. (2021). The clinical utility of forced oscillation technique during hospitalization in patients with exacerbation of COPD. ERJ Open Research 2021 7: 00448-2021; doi: 10.1183/23120541.00448-2021

Bhattarai P. et al. (2020). Clinical Application of Forced Oscillation Technique (FOT) in Early Detection of Airway Changes in Smokers. J. Clin. Med. 2020, 9, 2778; doi:10.3390/jcm9092778

Bickel S. et al. (2014). Impulse Oscillometry. Interpretation and Practical Applications. CHEST doi:10.1378/chest.13-1875

Boers E. et al. (2023). Global Burden of Chronic Obstructive Pulmonary Disease Through 2050. Published online 2023 Dec 7. Doi: 10.1001/jamanetworkopen.2023.46598

Cottee A. et al. (2020). Bronchodilator Response Assessed by the Forced Oscillation Technique Identifies Poor Asthma Control With Greater Sensitivity Than Spirometry. American College of Chest Physician Published by Elsevier https://doi.org/10.1016/j.chest.2019.12.035

Delacourt C. et al. (2001). Comparison of the Forced Oscillation Technique and the Interrupter Technique for Assessing Airway Obstruction and Its Reversibility in Children. Am J Respir Crit Care Med 2001 Sep 15;164(6):965-72. doi: 10.1164/ajrccm.164.6.2010153.

Dellacà R. et al. (2004). Detection of expiratory flow limitation in COPD using the forced oscillation technique. Eur Respir J 2004 Feb;23(2):232-40. Doi: 10.1183/09031936.04.00046804.

Faria A. et al. (2009). Evaluating the forced oscillation technique in the detection of early smoking-induced respiratory changes. BioMedical Engineering OnLine 2009, doi:10.1186/1475-925X-8-22

Faria A. et al. (2010). Forced oscillation technique in the detection of smoking-induced respiratory alterations: diagnostic accuracy and comparison with spirometry. CLINICS 2010;65(12):1295-1304 doi:10.1590/S1807-59322010001200012

Kaminsky D. et al. (2004). Oscillation mechanics of the human lung periphery in asthma. J Appl Physiol 97: 1849–1858, 2004. Doi:10.1152/japplphysiol.00300.2004.

Kolsum U. et al. (2009). Impulse oscillometry in COPD: Identification of measurements related to airway obstruction, airway conductance and lung volumes. Elsevier Respiratory Medicine (2009) 103, 136-143 doi:10.1016/j.rmed.2008.07.014

Ribeiro C. et al. (2018). Forced oscillation technique for early detection of the effects of smoking and COPD: contribution of fractional-order modeling. International Journal of COPD 2018:13 3281–3295 http://dx.doi.org/10.2147/COPD.S173686

Walker P. et al. (2018). Telemonitoring in Chronic Obstructive Pulmonary Disease (CHROMED). Am J Respir Crit Care Med Vol 198, Iss 5, pp 620–628, Sep 1, 2018 doi: 10.1164/rccm.201712-2404OC

World Health Organization – Chronic obstructive pulmonary disease (COPD) https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)

Yaegashi M. et al. (2006). The utility of the forced oscillation technique in assessing bronchodilator responsiveness in patients with asthma. Respir Med. 2007 May;101(5):995-1000. doi: 10.1016/j.rmed.2006.09.001

Zimmermann S. et al. Day-to-day variability of forced oscillatory mechanics for early detection of acute exacerbations in COPD Eur Respir J 2020; 56: 1901739 https://doi.org/10.1183/13993003.01739-2019

Jovanovski, S., & Mijoska, A. (2024). New concept of frontal teeth restauration for excellent function and aesthetic, *MEDIS - Medical Science and Research, 3(1),* 47-51. doi: 10.35120/medisij030147j
UDK: 616.314.18:616.314-74

NEW CONCEPT OF FRONTAL TEETH RESTAURATION FOR EXCELLENT FUNCTION AND AESTHETIC

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Abstract: This clinical case report aimed to investigate impact of a novel inner ferrule (IF) preparation around root canal on the subsequent esthetic restoration. Material and Methods: This clinical research involved a case report featuring endodontically treated teeth (ETT) restored using a newly developed ceramic post. Special drills (Edenta AG GmbH, Switzerland) were utilized for root canal preparation, involving horizontal preparation around the cervical portion of the root canals and post spaces. Experimental samples (ETT) were prepared with and without a 2mm IF preparation. The newly designed zirconia ceramic posts (TZ-3Y-SBE, Tosoh, Japan) were cemented with Multilink Automix (Ivoclar), upgraded with MultiCore (Ivoclar), and crowned with an all-ceramic zirconia crown (Zirkonzahn, Italy). Results: Our clinical case provided insights into a new type of all-ceramic aesthetic restoration of prepared teeth (ETT) with a new IF preparation design and a new zirconia post-core design. Conclusion: The novel horizontal IF preparation around the root canal was developed to accommodate the initial retentive coronal ring of the newly designed zirconia posts. The incorporation of IF preparation and coronal retentive rings within the zirconia post structure effectively enhances the fracture resistance of ETT. This new modern aesthetic rehabilitation in all restored teeth significantly reduces the severity of root fractures for excellent function and aesthetic restoration of ETT.

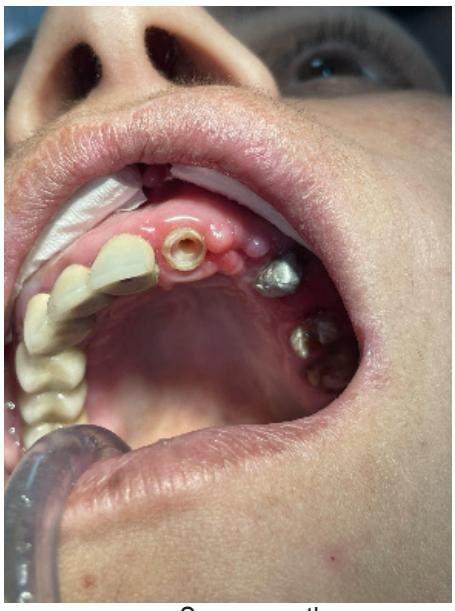
Keywords: Endodontically treated teeth, zirconia post, inner ferrule, aesthetic restoration

Field: Medical Sciences and Health

1. CASE REPORT

Modern trends have led to the widespread use of metal-free ceramics for ETT restoration, enhancing esthetics with tooth-colored posts and cores. This report elaborates on the treatment of a 48-year-old female patient presenting with more than ten years old metal ceramic crowns restorations in the anterior region. The treatment involved the placement of metal-free zirconia ceramic crowns supported by novel Y-TZP ceramic posts featuring retentive coronal segments for the left upper central incisor (Fig. 1).

Fig. 1. INNER FERRULE PREPARATION



Source: author

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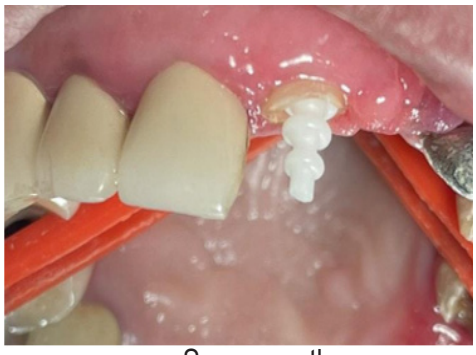
Dental examination and treatment plan

The intraoral examination of the patient unveiled a substantial loss of remaining dentin in the endodontically treated left upper central incisor, requiring restoration (Fig. 1). Our new contemporary treatment included preparing of ETT for application of new zirconia ceramic post (Fig. 2).

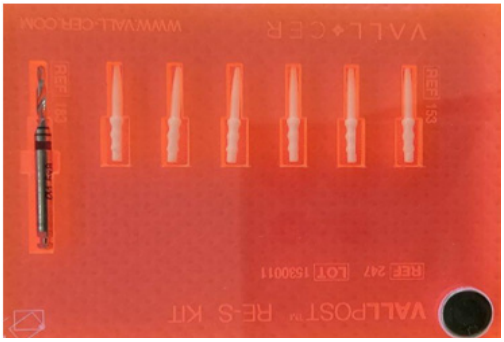
Fig. 2. 2mm IF PREPARATION FOR Y-TZP RETENTIVE POST



Source: author

The initial step involved the preparation of the remaining coronal dentin (Fig. 1). Subsequently, root preparation was carried out using specialized drills (Edenta AG GmbH, Switzerland) until reaching the final post length (Fig. 3).

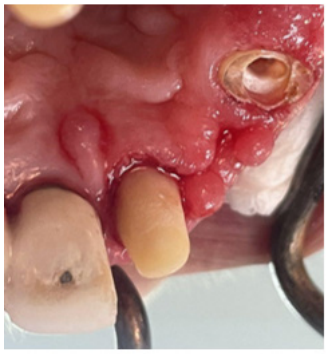
Fig. 3. SPECIAL DRILLS AND Y-TZP RETENTIVE POST



Source: author

To mitigate the risk of root perforation, two-thirds of the gutta-percha point were removed, creating ample space for the zirconia post. Simultaneously, a 2 mm depth of inner ferrule (IF) was established in the cervical region surrounding the endodontically treated canal (Fig. 1) to accommodate the initial retention ring (Fig. 2). Subsequent to the completion of the ETT preparation, the cementation process used composite cement (Multilink Automix, Ivoclar) in accordance with the manufacturer's guidelines. The dentin was conditioned with 37% orthophosphoric acid for 15 seconds, followed by the application of a primer (Syntac Primer, Ivoclar) for an additional 15 seconds. After that, the working area was dried. Subsequently, a dentinal adhesive (Syntac Adhesive, Ivoclar) was applied for 10 seconds.

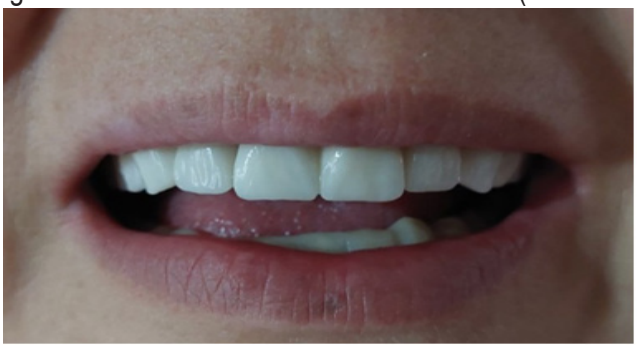
Fig. 4. COMPOSITE MULTICORE (Ivoclar)



Source: author

A thin layer of luting agent (Heliobond, Ivoclar Vivadent) was applied to both the dentin and post surfaces for 10 seconds. The composite cement's base and catalyst were mixed and subsequently applied to the root and post surfaces. Following the insertion of the post into the canal, core buildup was executed using MultiCore (Ivoclar) (Fig. 4), utilizing a lamp for 40 seconds polymerization. After all that procedure of remaining prepared dentin in the coronal part of the tooth, an impression was taken utilizing a silicone-based material (Zetaplus and Oranwash L, Zhermack, Italy). In laboratory setting, the crown was meticulously crafted using zirconia ceramic via the dental MAD/MAM system and then in clinical setting, was successfully cemented (Fig. 5). The crown's cementation process replicated that of the zirconia post. Following the placement of the final zirconia crown onto the tooth, a thorough evaluation of marginal fit was conducted using a dental explorer.

Fig. 5. FINAL ZIRCONIA CERAMIC CROWN (Zirkonzahn, Italy)



Source: author

2. DISCUSSION

For teeth exhibiting severe coronal destruction, the translucency of all-ceramic crowns can be effectively preserved through the utilization of ceramic post-core materials, as highlighted by Kramer EJ. et al. (2019) and Kharboutly NA. et al. (2023). The study aims to present the contribution of the new inner ferrule, in addition to outer ferrule preparation, to achieve a double ferrule effect, significantly increasing fracture resistance and retention, reducing micro leakage, improving light transmission, enhancing esthetic advantages, and increasing the radio density of zirconia posts. This clinical case discusses the patient with post-endodontic restauration of upper left incisor. With the treatment of this female patient an aesthetic and functional dental concerns was attained. An aesthetic improvement was accomplished by utilizing Y-TZP dowel. For core buildup was used MultiCore to uphold the all-ceramic crown.

According to Ozkurt Z. (2010); Faria A. (2011); Sawant A. (2017); Qudaih AM. (2020); and Badami V, Ketineni H. (2022), the selection of a post should adhere to various principles, including the IF preparation for obtaining additional retention and stabilization and reparable failure mode.

Jovanovski S., Cotic J. et al. (2018) and Jovanovski S., Marion L. (2021) affirm that the primary advantage of their new zirconia post lies in their cylindrical conical post and retentive coronal rings, which mitigate the risk of root fracture.

Oblak et al. (2004); Dakskobler A., et al. (2007) and Jovanovski S. (2012) have introduced prefabricated zirconia ceramic post systems with a retentive design in the coronal portion, primarily increasing the fracture strength of restored ETT, and secondarily, satisfying the trend towards heightened esthetic awareness.

The author, Jovanovski (2012), in this clinical case report, underscores the significance of adequately preparing the coronal tooth structure for a new designed zirconia retentive post. This preparation establishes a ferrule effect, facilitating optimal stress distribution from the crown, core, and post to the dentin. However, a new IF preparation method was introduced for the restoration of ETT using the metal-free Y-TZP ceramic post and crown for tooth restoration. In modern dentistry, the need for new aesthetic solutions and the use of zirconium oxide ceramics as one of the leading materials for achieving biocompatibility and high aesthetics, as well as anatomical-morphological, functional and aesthetic restoration with increased fracture resistance is more pronounced.

The increase in fracture resistance and significant increase in repairable fractures in modern esthetic prosthetic restorations is extremely important for the success of our restorations in daily clinical prosthetic practice.

The process of obtaining a new type of internal (radicular) preparation around the endodontically

treated canal was shown for precisely fitting the retentive form of the newly designed zirconium oxide post to obtain an internal "Ferrule effect" which, in addition to the external one, significantly increases the strength of the entire restored radicular-coronal dental complex.

3. CONCLUSIONS

In this clinical report,

- A Y-TZP ceramic post upheld the all-ceramic crown of the upper left incisor.
- IF dentin preparation was performed to facilitate the placement of the Y-TZP post retentive ring.
- The implementation of IF preparations and retentive zirconia post aids in augmenting the ETT strength and reducing the severity of unrepairable fractures.
- Irrespective of the number of older dilemmas regarding restoring ETT in the literature, we managed to achieve biocompatibility, high fracture resistance and an aesthetic restoration.
- This newly innovative treatment strategy provided the patient with a dentition that looks natural, ensuring excellent functionality and aesthetic restoration of ETT.

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REFERENCES

Akkayan B. (2004) An in vitro study evaluating the effect of ferrule length on fracture resistance of endodontically treated teeth restored with fiber-reinforced and zirconia dowel systems. The Journal of Prosthetic Dentistry; 92 (2): 155-162.

Badami V, Ketineni H, et al. (2022) Comparative Evaluation of Different Post Materials on Stress Distribution in Endodontically Treated Teeth Using the Finite Element Analysis Method: A Systematic Review. Sep 29;14 (9): e29753. doi: 10.7759/cureus.29753.

Batista VES, Bitencourt SB, Bastos NA, Pellizzer EP, Goiato MC, Dos Santos DM. (2020) Influence of the ferrule effect on the failure of fiber-reinforced composite post-and-core restorations: a systematic review and meta- analysis. J Prosthet Dent. 23: 239–245.

Bateli M, Kern M, Martin Wolkewitz, Jörg R. Strub & Wael Att. (2004) A retrospective evaluation of teeth restored with zirconia ceramic posts: 10-year results. The Journal of Prosthetic Dentistry Volume 92, Issue 2, August 2004, Pages 116-119

Bateli M, Kern M, +2 authors Wael Att. (2014) A retrospective evaluation of teeth restored with zirconia ceramic posts: 10-year results. Clinical Oral Investigations; 18(4):1181-1187.

Clarisse CHN, Dumbrigue HB, Al-Bajat IM, Griggs AJ, Wakefield WC. (2006) Influence of remaining coronal tooth structure location on the fracture resistance of restored endodontically treated anterior teeth. J Prosthet Dent. 95: 290-96.

Cloet E, Debels E, Naert I. (2017) Controlled clinical trial on the outcome of glass fiber composite cores versus wrought posts and cast cores for the restoration of endodontically treated teeth: a 5-year follow-up study. Int J Prosthodont. 30:71–79. doi: 10.11607/ijp.4861.

Dakskobler A, Jevnikar P, Oblak C, Kosmac T. (2007). The processing-related fracture resistance and reliability of root dental posts made from Y-TZP. J Eur Ceram Soc; 27: 1565-70.

Faria A, Rodrigues R, Antunes R, Mattos M, Ribero R. (2011) Endodontically treated teeth: Characteristics and considerations to restore them. Journal of Prosthetic Research. 55: 69-74.

Fraga RC, Chaves BT, Melo GS, Siquera JFJ. (1998) Fracture resistance of endodontically treated roots after restoration. J Oral Rehabil; 25: 809-813.

Fernandes AS, Dessai GS. (2001) Factors affecting the fracture resistance of post-core reconstructed teeth: a review. Int J Prosthodont; 14: 355-363.

Friedel W, Kern M. (2006) Fracture strength of teeth restored with all-ceramic posts and cores. Quintessence Int. 37: 289-295.

Gegauf AG. (2000) Effect of crown lengthening and ferrule placement on static load failure of cemented cast post-cores and crowns. J Prosthet Dent 2000; 84: 169-79.

Goodacre CJ, Spolnik KJ. (1994) The prosthodontic management of endodontically treated teeth: a literature review. Part I. Success and failure data, treatment concepts. J Prosthodont; 3: 243-250.

Jovanovski S. (2012) Assessment of the effect of treatments of the ceramic posts and their effect on resistance on the endodontically treated teeth. PhD, Faculty of Dental Medicine, Skopje, Macedonia.

Jovanovski S. et al. (2015) The effect of crown ferrule on endodontically restored teeth with zirconia posts and all ceramic crowns. Mac J Dent Med; 49-61.

Jovanovski S., Popovski J., Dakskobler A., Marion Lj., Jevnikar P. (2017) The influence of Crown Ferrule on Fracture Resistance of Endodontically Treated Maxillary Central Incisor. Balk J Dent Med; 21: 44-49.

Jovanovski S., Cotic J., Kocjan A., Oblak C., Jevnikar P. (2018) Fracture resistance of endodontically treated maxillary incisors restored with zirconia posts: effect of the internal plateau preparation. Advanced in Applied Ceramics. 75.

Jovanovski S., Marion Lj. (2021) The effect of new internal ferrule design preparation on the fracture resistance of endodontically

treated central incisors. UBT Knowledge International Center: 552-570
Kharboutly NA, Allaf M, Kanout S. (2023) Three-Dimensional Finite Element Study of Endodontically Treated Maxillary Central Incisors Restored Using Different Post and Crown Materials. 14;15(1)
Kramer EJ, Meyer-Lueckel H, Wolf TG, Schwendicke F, Naumann M, Wierichs RJ. (2019) Success and survival of post-restorations: six-year results of a prospective observational practice-based clinical study. Int Endod J. 52: 569–578. doi: 10.1111/iej.13040.
Kosmac T, Dakskobler A, Oblak C, Jevnikar P. (2007) The strength and hydrothermal stability of Y-TZP ceramics for dental applications. Int J Appl Ceram Technol; 4 (2): 164-74.
Libman WJ, Nicholls JI. (1995) Load fatigue of teeth restored with cast posts and cores and complete crowns. Int J Prosthodont; 8: 155-61.
Nissan J, Parson A, Barnea E, Shifman A, Assif D. (2007) Resistance to fracture of crowned endodontically treated premolars restored with ceramic and metal post systems. Quintessence Int.; 38: 120-123.
Nothdurft PF., Pospiech RP. (2006) Clinical evaluation of pulpless teeth restored with conventionally cemented zirconia posts: A pilot study. J Prosthet Dent.; 95: 311-4.
Oblak C, Jevnikar P, Kosmac T, Funduk N, Marion Lj. (2004) Fracture resistance and reliability of new zirconia posts. J Prosthet Dent; 91: 342-8.
Ozkurt Z, Iseri U, Kazazoglu E. (2010) Zirconia ceramic post systems: a literature review and a case report. Dental Materials Journal. 29 (3): 233-245.
Pereira JR, Valle AL, Shiratori FK, Ghizoni JS, Melo MP. (2009) Influence of intraradicular post and crown ferrule on the fracture strength of endodontically treated teeth. Braz Dent J. 20 (4): 297-302.
Qudaih AM, Yousief SA, Allabban NM, Nejri AM, Elmarakby AM. (2020) Effect of Two Different Surface Treatments on Retention of Cosmopost with Two Different Core Materials. Clinical, Cosmetic and Investigational Dentistry. 12
Sarkis-Onofre R., Amaral Pinheiro H. et al. (2020) Randomized controlled trial comparing glass fiber posts and cast metal posts J Dent. May: 96:103334. doi: 10.1016/j.jdent.2020.103334.
Sawant A, Chunawalla Y, Morawala A, Kanchan NS, Jain K, Talathi R. (2017) Evaluation of novel glass fiber-reinforced composite technique for primary anterior teeth with deep carious lesions: a 12-month clinical study. Int J Clin Pediatr Dent. ;10: 126–130. doi: 10.5005/jp-journals-10005-1421.
Sorensen JA, Engelman MJ. (1990) Ferrule design and fracture resistance of endodontically treated teeth. J Prosthet Dent 1990; 63: 529-36.
Sorensen JA, Martinoff JT. (1984) Intracoronal reinforcement and coronal coverage: a study of endodontically treated teeth. J Prosthet Dent; 51: 780-784.
Stankiewicz N, Wilson P. (2008) The ferrule effect. Dent Update 35: 222-4.3is article
Shuny Ying, Song Chen, Siyuan Wang, Lingli Xu, Xiaofeng Wang, Fuming He, and Wei Liu (2022) Outcome of teeth restored with CAD/CAM zirconium dioxide post-cores: a retrospective study with a follow-up period of 3–6 years. BMC Oral Health. 2022; 22: 236.
Toksavul Suna, Türkün Murat, Toman Muhittin. (2004) Esthetic enhancement of ceramic crowns with zirconia dowels and cores: a clinical report. https://doi.org/10.1016/j.prosdent.2004.03.032
Tulbah HI. (2019) Zirconia ceramic post-and-core systems. An updated literature review of some clinical-related issues. Int J Med Dent. 23: 591–598.