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ABOUT THE JOURNAL

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AIMS & SCOPE:

The Green Life Medical College Journal is an english language scientific papers dealing with clinical medicine, basic sciences, epidemiology, diagnostic, therapeutics, public helath and healthcare in relation to concerned specialities. It is an official journal of Green Life Medical College and is published bi-annually.

This Joural is recognized by Bangladesh Medical & Dental Council (BM&DC).

The Green Life Medical College Journal of Bangladesh intends to publish the highest quality material on all aspects of medical science. It includes articles related to original research findings, technical evaluations and reviews. In addition, it provides readers opinion regarding the articles published in the journal.

INSTRUCTION TO AUTHORS:

Papers:

The Green Life Medical College Journal (published bi-annually) accepts contributions from all branches of medical science which include original articles, review articles, case reports, and letter to the Editor.

The articles submitted are accepted on the condition that they must not have been published in whole or in part in any other journal and are subject to editorial revision. The editor preserves the right to make literary or other alterations which do not affect the substance of the contribution. It is a condition of acceptance that the copyright becomes vested in the journal and permission to republish must be obtained from the publisher. Authors must conform to the uniform requirements for manuscripts submitted to biomedical journals (JAMA 1997; 277: 927-34).

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In preparing the manuscript, use double spacing throughout, including title, abstract, text, acknowledgement, references, table and legends for illustrations and font type and size 'Times New Roman 12'. Begin each of the following sections on a separate paper. Number pages consecutively.

The standard layout of a manuscript:

- Title page
- Abstract, including Keywords
- Introduction
- Methods
- Results
- Discussion
- Acknowledgements
- Funding
- List of references
- Tables & Figures
- Illustrations

The pages should be numbered in the bottom right-hand corner and the title page being page one, etc. Start each section on a separate page.

Title page:

A separate page which includes the title of the paper. Titles should be as short and concise as possible (containing not more than 50 characters). Titles should provide a

reasonable indication of the contents of the paper. This is important as some search engines use the title for searches. Titles in the form of a question, such as 'Is drinking frequent coffee a cause of pancreatic carcinoma?" may be acceptable.

The title page should include the name(s) and address(es) of all author(s). Details of the authors' qualifications and post (e.g., professor, consultant) are also required. An author's present address, if it differs from that at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript numbers ([1, 2, 3] etc.) If the address to which proofs should be sent is not that of the first author, clear instructions should be given in a covering note, not on the title page.

Abstract:

The 'Abstract' will be printed at the beginning of the paper. It should be on a separate sheet, in structured format (Introduction/Background; Methods; Results; and Conclusions) for all Clinical Investigations and Laboratory Investigations. For Reviews and Case Reports, the abstract should not be structured. The Abstract should give a succinct account of the study or contents within 350 words. The results section should contain data. It is important that the results and conclusion given in the 'Abstract' are the same as in the whole article. References are not included in this section.

Keywords:

Three to six keywords should be included on the summary page under the heading Keywords. They should appear in alphabetical order and must be written in United Kingdom English spelling.

Introduction:

The recommended structures for this section are:

- Background to the study/Introduction
- What is known/unknown about it
- What research question / hypothesis you are interested in
- What objective(s) you are going to address

The introduction to a paper should not require more than about 300 words and have a maximum of 1.5 pages double-spaced. The introduction should give a concise account of the background of the problem and the object of the investigation. It should state what is known of the problem to be studied at the time the study was started. Previous work should be quoted here but only if it has direct bearing on the present problem. The final paragraph should clearly state the primary and, if applicable, secondary aims of the study.

Methods:

The title of this section should be 'Methods' - neither 'Materials and methods' nor Patients and methods'. The Methods section should give a clear but concise description of the process of the study. Subjects covered in this section should include:

- Ethics approval/license
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- Conduct of the study
- Data handling
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- Cognitive Task Analysis (CTA)

Ethical clearance:

Regardless of the country of origin, all clinical investigators describing human research must abide by the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki, and adopted in October 2000 by the World Medical Association. This document can be found at: http://ohsr.od.nih.gov/guidelines/helsinki.html. Investigators are encouraged to read and follow the Declaration of Helsinki. Clinical studies that do not meet the Declaration of Helsinki criteria will be denied peer review. If any published research is subsequently found to be non-compliant to Declaration of Helsinki, it will be withdrawn or retracted. On the basis of the Declaration of Helsinki, the Green Life Medical Journal requires that all manuscripts reporting clinical research state in the first paragraph of the 'Methods' section that:

- The study was approved by the appropriate Ethical Authority or Committee.
- Written informed consent was obtained from all subjects, a legal surrogate, or the parents or legal guardians for minor subjects.

Human subjects should not be identifiable. Do not disclose patients' names, initials, hospital numbers, dates of birth or other protected healthcare information. If photographs of persons are to be used, either take permission from the person concerned or make the picture unidentifiable. Each figure should have a label pasted on its back indicating name of the author at the top of the figure. Keep copies of ethics approval and written informed consents. In unusual

circumstances the editors may request blinded copies of these documents to address questions about ethics approval and study conduct.

The methods must be described in sufficient detail to allow the investigation to be interpreted, and repeated if necessary, by the reader. Previously documented standard methods need not be stated in detail, but appropriate reference to the original should be cited. However, any modification of previously published methods should be described and reference given. Where the programme of research is complex such as might occur in a neurological study in animals, it may be preferable to provide a table or figure to illustrate the plan of the experiment, thus avoiding a lengthy explanation. In longitudinal studies (case-control and cohort) exposure and outcome should be defined in measurable terms. Any variables, used in the study, which do not have universal definition should be operationalised (described in such terms so that it lends itself to uniform measurement). Where measurements are made, an indication of the error of the method in the hands of the author should be given. The name of the manufacturer of instruments used for measurement should be given with an appropriate catalogue number or instrument identification (e.g. Keyence VHX-6000 digital microscope). The manufacturer's town and country must be provided, in the case of solutions for laboratory use, the methods of preparation and precise concentration should be stated.

Single case reports:
Single case reports of outstanding interest or clinical relevance, short technical notes and brief investigative studies are welcomed. However, length must not exceed 1500 words including an unstructured abstract of less than 200 words. The number of figures/tables must not be more than 4 and references more than 25.

Animal studies:
In the case of animal studies, it is the responsibility of the author to satisfy the board that no unnecessary suffering has been inflicted on the animal concerned. Therefore, studies that involve the use of animals must clearly indicate that ethical approval was obtained and state the Home Office License number or local equivalent.

Drugs:
When a drug is first mentioned, it should be given by the international non-proprietary name, followed by the chemical formula in parentheses if the structure is not-well known, and, if relevant, by the proprietary name with an initial capital letter. Dose and duration of the drug should be mentioned in sufficient details. If the drug is already in use (licensed by appropriate licensing authority), generic name of the drugs should preferably be used followed by proprietary name in brackets.

Present the result in sequence in the text, table and figures. Do not repeat all the data in the tables and/or figures in the text. Summarize the salient points. Mention the statistics used for statistical analysis as footnote under the tables or figures. Figures should be professionally drawn. Illustration can be photographed (Black and White glossy prints) and numbered.

Discussion:
Do not repeat the data in detail, already given in the results. Give implications of the findings, their strengths and limitations in comparison to other relevant studies. Avoid un-qualified statements and conclusions which are not supported by the data. Avoid claiming priority.

Conclusion:
Comments on the observation of the study and the conclusion derived from it. New hypothesis or implications of the study may be labeled as recommendations.

References:
References should be written in Vancouver style, numbered with arabic numerals in the order they appear in the text. The reference list should include all information, except for references with more than six authors, in which case give the first six names followed by et al.

Examples of correct forms of references:
Dorababu M, Prabha T, Priyambada S, Agrawal VK, Aryaa NC, Goel RK. Effect of Azadirachta indica on gastric ulceration and healing of bacopa monnierang in experimental NIDDM rats. *Indian J Exp. Biol 2004; 42: 389-397.*

Chapter in a book:
Hull CJ. Opioid infusions for the management of postoperative pain. In: Smith G, Covino BG, eds. Acute Pain. London: Butterworths. 1985,1 55-79.

All manuscripts for publication should be addressed to the executive editor.

LETTER TO THE EDITOR:
Any reader can provide feedback regarding published articles by writing letter to editor. The reader can also share any opinion in relation to medical science.

Prof. Dr. ABM Bayezid Hossain
Editor-in-chief
Green Life Medical College Journal and
Principal
Green Life Medical College

ABOUT THE COLLEGE

INTRODUCTION

In 2005, about fifty distinguished physicians of the country started a hospital to give specialized care in the private sector. They named it Green Life Hospital and it turned out to be a great success. So in 2009, they decided to establish a medical college which will be a non-government, non-profit, self-financing project and will serve the humanity.

This College came into existence in 2009. The college commences its activities with the enrollment of 51 students in the 1st batch in 2010. Since inception, the college has undergone tremendous development and became a splendid centre for learning and development. At present we are enrolling 110 students each year. Among them, numbers of seats are reserved for overseas students.

We continue to evaluate and improve our programme to ensure the best medical education for the students. Our educational strategy is to create a conducive learning environment and to steer our students to acquire adequate knowledge, skills and temperament to practice medicine and be a competent health care professional group.

Green Life Medical College (GMC) is approved by the Ministry of Health and Family Welfare (MOHFW), Government of Bangladesh and Bangladesh Medical and Dental Council (BMDC) and affiliated to the University of Dhaka.

AIMS AND OBJECTIVES OF THE COLLEGE

Aims:

To create a diverse and vibrant graduate scholars in medical discipline and to create highly competent and committed physicians for the country.

Objectives:

- To provide an appropriate learning environment where medical students can acquire a sound theoretical knowledge and practical skills with empathetic attitude to the people.
- To carry out research in medical sciences to scale up the standard of medical education in the country.

LOCATION

The campus is located at 31 and 32, Bir Uttom K. M. Shafiullah Sarak (Green Road), Dhanmondi, Dhaka. The location is at the heart of the mega city Dhaka and is facilitated with very good communication networks.

The Medical College and the Hospital complexes have been raised in a multistoried fully air-conditioned building with an arrangement of approximately 500 patients. The building is equipped with state-of-the-art infrastructure, excellent with an out-patient department and adequate in-patient facilities.

EDITORIAL

Heat-Related Illnesses: A Call to Action

Global warming is not a fiction any more, it's a reality. Worldwide extreme temperature events are observed to be increasing in their frequency, duration, and magnitude, and Bangladesh is no exception. Hot ambient conditions and associated heat stress can lead to increased morbidity and mortality; increased adverse pregnancy outcomes and effect on mental health; reduced physical work capacity and motor-cognitive performances, and increase the risk of occupational health problems.[1,2,3]

Heat-related illnesses encompass a spectrum of conditions, ranging from minor discomfort to life-threatening emergencies. Heat oedema, heat rash, heat cramps, heat tetany, heat syncope, heat exhaustion, and heat stroke are the most common manifestations, each characterized by distinct symptoms and severity. While heat cramps typically involve muscle spasms and dehydration, heat exhaustion manifests as profuse sweating, weakness, nausea, and dizziness. Heatstroke, the most severe form, can lead to organ damage, neurological impairment, and death if left untreated.[4]

The risk of heat-related illness results from a combination of individual susceptibility, endogenous and exogenous heat exposure, and sociocultural factors that affect the ability to adapt.

Extreme heat can affect anybody. Those most at-risk include people over 65 years, infants and young children, pregnant women, people with acute and chronic health problems or disabilities, outdoor workers, athletes, people living in lower income households or homeless and who are socially isolated.[3,4] People on certain medications such as diuretics, beta-blocker, drugs with anticholinergic properties, and central nervous system stimulants are also at-risk of heat related problems.

Preventing heat-related illnesses requires a multifaceted approach involving public awareness, policy interventions, and individual actions.

Public health campaigns should educate communities about the signs and symptoms of heat-related illnesses, the importance of hydration, and the need to seek shade and cool environments during periods of extreme heat. Employers should implement heat safety protocols to protect outdoor workers, including scheduled breaks, access to shade, and proper hydration.[2,5]

Policy initiatives, such as urban planning strategies to mitigate heat islands and regulations mandating heat safety measures in workplaces, can further reduce the burden of heat-related illnesses.

Individuals must also take proactive measures to protect themselves and their loved ones, including staying hydrated, wearing lightweight and breathable clothing, and avoiding strenuous outdoor activities during peak heat hours.[1,2,5,6] Drinks of choice include water and sports water drinks; avoid alcohol and fluids with caffeine, such as tea, coffee, and cola, as these can lead to dehydration.

As temperatures continue to rise due to climate change, the incidence of heat-related illnesses is expected to increase, placing individuals and communities at greater risk. By raising awareness, promoting preventive measures, and advocating for systemic changes, we can safeguard public health and reduce the burden of heat-related morbidity and mortality. It is imperative that healthcare providers, policymakers, employers, and individuals collaborate to implement comprehensive strategies for preventing and mitigating the impact of heat-related illnesses.

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References:

1. Rahman, M.A., Afridi, S., Hossain, M., et al. Nexus between heatwave, food security and human health (HFH): Developing a framework for livelihood resilience in Bangladesh. Environmental Challenges 2024; 14: 100802. DOI: 10.1016/j.envc.2023.100802
2. Sharma A, Andhikaputra G, Wang Y-C. Heatwaves in South Asia: Characterization, Consequences on Human Health, and Adaptation Strategies. Atmosphere. 2022; 13(5):734 DOI: 10.3390/atmos13050734
3. Adnan MSG, Kabir I, Hossain MA, Enan ME, Chakma S, Tasneem SN et al. Heatwave vulnerability of large metropolitans in Bangladesh: an evaluation. 2023 Jun 29 DOI: 10.21203/rs.3.rs-3093933/v1.
4. Kristie L Ebi, et al. Hot weather and heat extremes: health risks. Lancet 2021; 398: 698–708
5. Lubna KF, et al. Study on Heat Wave and its Thermodynamic features over Bangladesh using Numerical Weather Prediction Model (NWPM). International Journal of Science and Business 2020; 4(6): 44-52 DOI: https://doi.org/10.5281/zenodo.3839997
6. Protecting Children from Heat Stress: A technical note; © United Nations Children's Fund, May 2023 https://www.unicef.org/media/139926/file/Protecting-children-from-heat-stress-A-technical-note-2023.pdf

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ORIGINAL ARTICLE

Role of vitamin D3 supplementation in reducing pain intensity in Rheumatoid Arthritis Patients: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Introduction: Vitamin D deficiency is now widely recognized as a problem in Rheumatoid Arthritis patients. The aim of this study was to assess how supplementing vitamin D3 with conventional synthetic DMARDs in reducing pain in RA patients.

Methods: This study was a randomized, double-blind, placebo-controlled trial conducted in the Department of Pharmacology, BSMMU in collaboration with the Rheumatology Rehabilitation Clinic of the Department of Physical Medicine and Rehabilitation, BSMMU. The study enrolled fifty-eight RA patients in the induction phase, with fifty-two eligible for analysis. Twenty-three received placebo capsules for eight weeks with csDMARDs, while twenty-nine received 40,000 IU vitamin D3 capsules weekly orally for eight weeks with csDMARDs. Pain intensity was assessed using the Visual Analog Scale at baseline and after eight weeks.

Results: After eight weeks of treatment, VAS scores decreased significantly (p-value < 0.05) in both placebo and intervention arms. However, the reduction was significantly lower in the intervention arm than in the placebo arm while serum vitamin D levels increased significantly (p-value < 0.05) in the intervention arm in comparison to the baseline.

Conclusion: This was revealed interestingly that all of the RA patients were vitamin D deficient. Therefore, vitamin D3 supplementation along with csDMARDs has additional benefits in reducing the intensity of pain in patients with Rheumatoid Arthritis.

Keywords: Rheumatoid Arthritis, csDMARD, Visual Analogue Scale

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Introduction:

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by the progressive destruction of synovial-lined joints as well as some extra-articular symptoms.[1,2] Women and countries with higher incomes were more likely to have RA, which affects 0.3–1.0 percent of the world's population.[3,4] In Bangladesh, the prevalence of RA was 1.6%.[5] It was affected about 0.7% of rural adults, 0.4% of urban slums, and 0.2% of Bangladesh's urban affluent population.[6]

Females were 2–3 times more likely than males to develop Rheumatoid Arthritis.[4,7] Genetics influenced RA progression.[8]

The use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) in combination with

targeted synthetic (ts) DMARDs or biologic (b) DMARDs has revolutionized RA treatment. Methotrexate can be used as a monotherapy or in a step-up approach with other csDMARDs, bDMARDs, and tsDMARDs. It can also be used as an initial combination therapy with other csDMARDs. bDMARDs and tsDMARDs. MTX is the most widely used first-line treatment for RA in the world.[9,10,11,12,13]

Vitamin D has immunomodulatory properties, works as an anti-osteoporotic agent, and helps in the pain management of RA patients.[14] Vitamin D3 deficiency in the RA population was found in some studies.[14,15,16,17,18] Vitamin D3 supplementation as adjuvant therapy for RA patients resulted in a decline in pain severity.[14,15]

All vitamin D deficient patients should be treated with 50,000 IU of vitamin D3 once a week for 8 weeks, or the equivalent of 6000 IU of vitamin D3 daily, followed by maintenance therapy of 1500–2000 IU/d to maintain a blood level of 25(OH)D above 30 ng/ml.[19]

Vitamin D3 has an immunomodulatory and anti-inflammatory effect. Some recent trials attempted to assess the role of oral supplementation of vitamin D3 in decreasing pain intensity. The present study was designed to observe the effect of oral administration of vitamin D3 as adjuvant therapy in Rheumatoid Arthritis patients.

Methods:

This study was a randomized, double-blind, placebo-controlled study. It was conducted in the Rheumatology Rehabilitation Clinic of the Department of Physical Medicine and Rehabilitation, Bangabandhu Sheikh Mujib Medical University (BSMMU) and Department of Pharmacology, Bangabandhu Sheikh Mujib Medical University (BSMMU) between March 2020 to January 2022. The study was carried out among patients with Rheumatoid Arthritis according to the 2010 ACR/EULAR criteria for Rheumatoid Arthritis.[20] The ethical committee approved the clinical trial (BSMMU/2021/3958) and registered it with www.clinicaltrials.gov (Identifiers NCT05078502). Informed written consent was taken from all study participants.

Study participants:

Patients who met 2010 ACR/EULAR criteria for Rheumatoid Arthritis, 18 years or above age group, and both gender were enrolled.

Sample size:

Total sample size was one eighty and ninety patients in each arm.[14]

Outcome measures:

Patients were assessed by Questionnaire for Socio-Demographic Data and Visual Analogue Scale (VAS) 0-10 cm[14,15,21]. The Laboratory Parameters of the study were serum vitamin D3 level at baseline and after 8 weeks. The primary outcome measure was the Visual Analogue Scale (VAS) score change from baseline to 8 weeks and the secondary outcome measure was serum 25(OH) D level change from baseline to 8 weeks.

Study Procedure:

Procurement of medicine and placebo:

Medicines and placebo were purchased from the manufacturer at the original market price. The capsule placebo was identical to vitamin D3 (Cholecalciferol) 40,000IU and supplied in the same container.

Packaging of Medicine and Placebo:

Vitamin D3 and placebo capsules were packaged in boxes and masked with stickers. Placebo capsules were coded as 'P', while medicine capsules were coded as 'M'. Each strip contained 8 capsules. Packages were sealed, 'M' & 'P' codes were removed, and patient ID numbers were labeled on stickers.

Storage of Packages:

Medicine and placebo-containing packages were stored in a temperature within 15 to 30 degrees centigrades.

Randomization:

Patients were randomly allocated into two arms using online graph pad software, which generated two distinct sets of numbers based on sample size and enrollment. A competent third person, a Professor from the University's Microbiology Department, conducted the process.

Blinding:

Immediately after randomization, random numbers of the two sets were assigned as patient code numbers. One set was designated as an intervention group and another set was a placebo group. Then the set of code numbers that belong to the intervention group was written as patient ID numbers on the packages containing vitamin D3 capsules. On the other hand, the set belonging to the placebo group were designated as patient ID numbers on the packages containing placebo capsules. Thus, the participants,

caregiver, outcome assessor, and analyst, were effectively blinded.

Allocation Concealment:
To prevent selection bias, concealment of allocation was done. Third-person allocated two distinct sets of random numbers into the intervention group and placebo group. This allocated code was written in two paper documents, preserved in two separate pen drives, and sealed in two different envelopes. The sealed envelopes were preserved by another two distinguished Professors. So intervention allocation was not known to any person involved in the research.

Recruitment of the patients for the present study:
All the patients diagnosed as RA according to 2010 ACR/ EULAR criteria by a competent Physiatrist were recruited in this study.

Consent Procedure:
All the recruited patients were evaluated according to inclusion and exclusion criteria. Patients were also informed that their participation was voluntary and they had every right to refuse to participate or to withdraw at any time without compromising their medical care. Patients who were convinced and agreed after adequate understanding only took part in the study with written consent.

Enrollment of patients for the present study:
The patients were recruited, enrolled, treatment allocated, follow-up, and finally analyzed after dropout according to the principle of CONSORT. In total, 58 patients were enrolled after giving informed written consent from the Rheumatology Rehabilitation Clinic of Physical Medicine and Rehabilitation Department, BSMMU.

Treatment of the Patients:
Patients with Rheumatoid arthritis received conventional synthetic DMARDs and one capsule of vitamin D3 40000IU orally weekly for 8 weeks, determined by a physiatrist of the Physical Medicine and Rehabilitation department. The patient received oral placebo capsules in the same manner, schedule, and time frame.

Data collection Procedure:
A total of 58 patients were enrolled after giving informed written consent. At the baseline, the present researcher assessed the VAS, and 5ml blood was collected for the baseline estimation of vitamin D. Then patients gave capsules of vitamin D3 with cs DMARDs and placebo capsules with cs DMARDs. After 8 weeks, the RA patients were assessed by the VAS and again 5ml blood was collected for estimation of vitamin D levels. The total procedure took approximately 20-30 minutes for each patient on each visit.

Estimation of serum vitamin D3 level:
In this study, HPLC methodology was used in the Department of Pharmacology, BSMMU for the detection and quantification of vitamin D3 in serum.

Patient Evaluation in the Follow-up Visit:
Patients were assessed by a physiatrist with a VAS score who was completely unaware of the study. All the questionnaires answered by the patients were collected and documented after the follow-up session in particular patient files. The follow-up visits were done and follow-up samples were collected after 8 weeks of enrollment (± 4 days).

Unblinding:
Eight weeks of intervention and follow-up were completed, then unblinding was done by the Professor of the Microbiology Department. At first, the envelope was opened and documented paper where the code number was written and signed by the Professor. Then pen drive was given.

Data interpretation:

To facilitate the use of computers a special spreadsheet prepared by the researcher was used in this study.

Statistical analysis:

Statistical analysis was done by Microsoft Office Excel 2007. A chi-square test was done to see the association between the intervention and the placebo arm. An unpaired ‘t-test was done to compare a score of the two arms. Paired t-test was done to compare the score before and after the intervention. A significant p-value is < 0.05.

Results:
Total fifty-eight patients were enrolled based on the eligibility criteria from June 2021 to October 2021 for study. Of which, after decoding, thirty (30) patients were found to receive this intervention, and twenty-eight (28) patients received placebo. Six (6) patients were dropped out during the research due to discontinued intervention (n=4), unable to travel (n=2) in this pandemic situation. The dropout cases were excluded from per-protocol analysis. At the end of the study, a total of fifty- two (52) patients were assessed and evaluated.

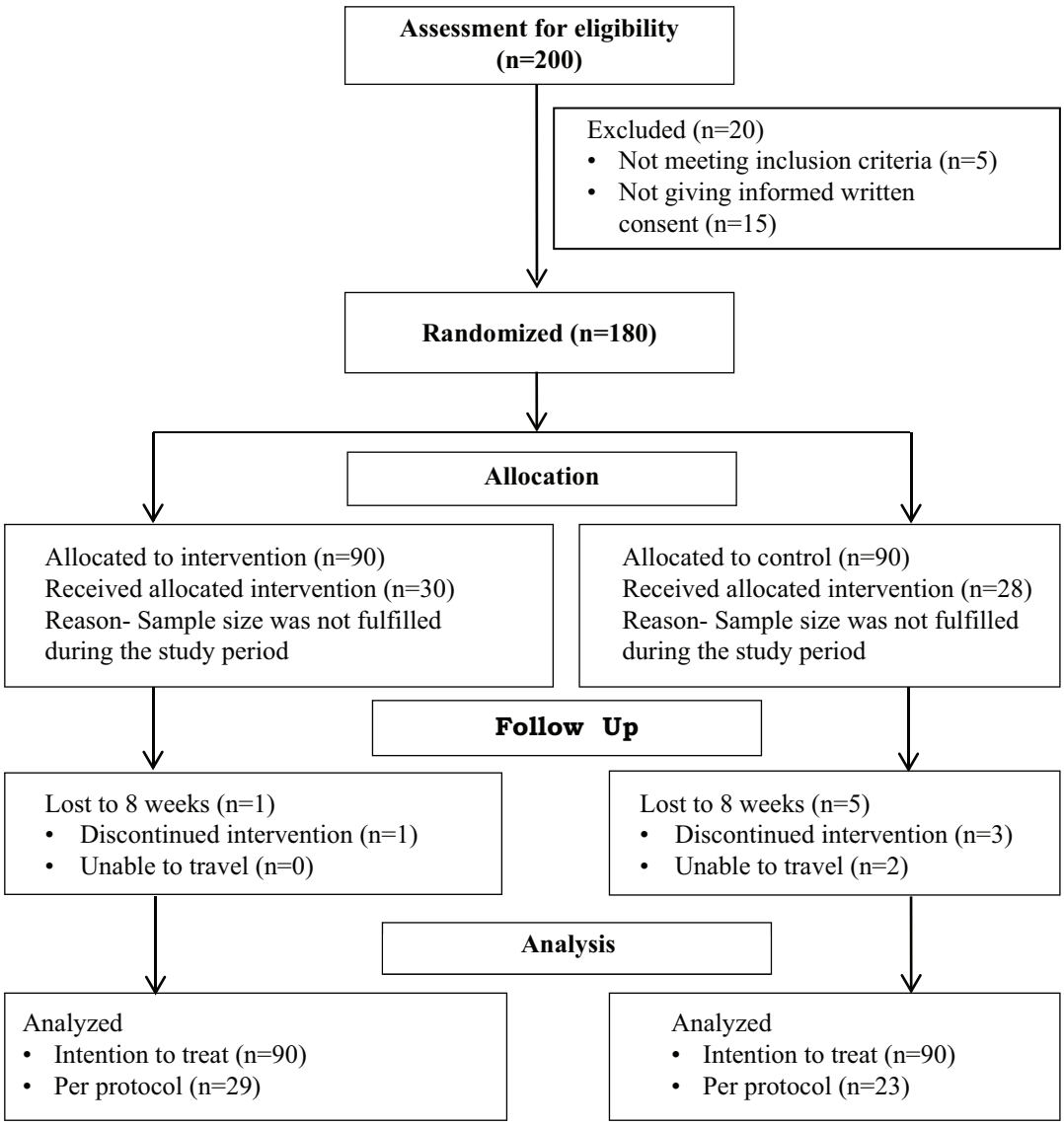

Figure 1: *Flowchart of Consolidated Standards of Reporting Trials (CONSORT)*[14,15]

Table-I showed, The mean age and SD of patients were 47.83 ± 10.70 in the placebo arm and 41.93 ± 11.26 in the intervention arm and the difference was not statistically significant (p = 0.06).

Table-II showed, at baseline the mean score of VAS was 6.35 ± 0.78 in the placebo arm compared to 6.52 ± 0.63 in the intervention arm with no significant difference (p = 0.40). After 8 weeks, VAS scores significantly decreased in both groups [(placebo- 4.52 ± 0.73; $p < 0.05$); (intervention- 3.24 ± 1.18; $p < 0.05$)] and these were also shown in figure 2. The intervention arm reported 21% higher in reducing pain intensity (50% vs 29%; $p < 0.05$).

Table-III showed, that at baseline, the mean serum vitamin D levels were 6.55 ± 4.38 ng/ml in the placebo arm compared

Table I

Demographic characteristics of the patients (n=52) at baseline[14,15]

Variables	Placebo[a](n=23)	Intervention[b](n=29)	P - value
Age (years)			
Mean ± SD	47.83 ± 10.70	41.93 ± 11.26	0.06[x]
Range, 95% CI	43.20-52.45	37.65-46.21	

x Unpaired t-test was done

Table-II

Comparison of Intensity of Pain Assessed by VAS Score of the patients in the Placebo and Intervention Arm (at baseline and after 8 weeks of treatment)[14,15]

VAS Score	Placebo[a] (n=23) Mean ± SD	Intervention[b] (n=29) Mean ± SD	P - value
At Baseline	6.35 ± 0.78	6.52 ± 0.63	0.40[x]
Range, 95% CI	6.01-6.68	6.28-6.76	
After 8 weeks of treatment	4.52 ± 0.73	3.24 ± 1.18	0.00[x]
Range, 95% CI	4.21-4.84	2.79-3.69	
P - value	0.00[y]	0.00[y]	

[x]Unpaired t-test was done
[y]Paired t-test was done

Table-III

Comparison of Patients According to serum vitamin D levels in the Placebo and Intervention Arm (at baseline and after 8 weeks of treatment)

Vitamin D level	Placebo (n=23) Mean ± SD	Intervention (n=29) Mean ± SD	P – value
At Baseline	6.55 ± 4.38	6.22 ± 3.99	0.84[x]
Range,95% CI	4.02-9.09	3.81-8.63	
After 8 weeks of treatment	3.21 ± 1.35	10.57 ± 8.72	0.01[x]
Range, 95% CI	2.43-3.99	5.30-15.84	
P - value	0.01[y]	0.03[y]	

[x]Unpaired t-test was done
[y]Paired t-test was done

to 6.22 ± 3.99 ng/ml in the intervention arm. The difference was not statistically significant (p = 0.84). After 8 weeks, the serum vitamin D levels were significantly decreased in the placebo arm in comparison to baseline [placebo-3.21 ± 1.35; $p < 0.05$]. The serum vitamin D levels were significantly increased in the intervention arm in comparison to baseline [intervention-10.57 ± 8.72; $p < 0.05$] and also the serum vitamin D levels were significantly higher ($p < 0.05$) in the intervention arm than in the placebo arm.

Discussion:

The present study was designed to explore the potential of vitamin D3 supplementation to be helpful for patients with Rheumatoid Arthritis in reducing pain. The study had started blindly but when unblinding was done, there was no significant difference between the two groups in sociodemographic characteristics.

After 8 weeks of treatment, the VAS scores were significantly decreased than the baseline both in the intervention and placebo arm. However, the reduction was significantly lower in the intervention arm than in the placebo arm. It indicated that this intervention significantly improved the particular parameter. Supplementation of vitamin D3 with csDMARDs significantly reduced pain in Rheumatoid Arthritis patients. These studies had similar age, ethnicity, occupation, and standard of care as the present study.[14,19]

Serum vitamin D levels were significantly increased in the intervention arm after 8 weeks of treatment. On the other hand, the serum vitamin D levels were significantly decreased in the placebo arm in comparison to baseline, after 8 weeks of treatment. Those who were in the placebo arm might have problems with vitamin D synthesis or they were not taking vitamin D-containing foods, or vitamin D3 supplements from outside. More newly recruited patients who had not yet started full-dose csDMARDs were in the placebo arm. These were the possible causes of decreased levels of vitamin D in the placebo arm after 8 weeks. There

was a significant increase in serum vitamin D3 levels in Rheumatoid Arthritis Patients in the intervention arm, but there was no change in the serum vitamin D3 levels in the placebo arm after 3 months. This study had similar age, the standard of care but the ethnicity, study duration, and vitamin D3 dose were not the same in comparison to the present study.[22]

The whole study population of the present study was vitamin D deficient. In contrast to the present study, vitamin D deficiency was also found in few studies[14,16,17,18,19], but the percentages were different. Although the study population of these studies was similar to the present study population in terms of age, the standard of care, and occupation. Even the ethnicity was similar in the three studies[14,18,19] though was not similar in the two studies.[16,17]The study design was different in these studies.[16,17,18]

The above-mentioned findings of the study reiterated the fact that the addition of vitamin D3 with csDMARD in RA patients contributes to significant improvement in different parameters. These clinical findings might have some important clinical implications in the management of Rheumatoid Arthritis.

Study Limitation:

The main limitations of the study are inadequate number of patients and short time frame. Rheumatoid Arthritis disease activity score was not assessed.

Conclusion:

Vitamin D3 supplementation is effective as an adjuvant therapy to reduce pain in patients with conventional synthetic Disease-Modifying Antirheumatic Drugs (csDMARD) treated Rheumatoid Arthritis patients. It might be beneficial to do additional research with a large number of patients over an extended period of time.

References:

1. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. Jama. 2018 Oct 2;320(13):1360-72. doi:10.1001/jama.2018.13103
2. Grassi W, De Angelis R, Lamanna G, Cervini C. The clinical features of rheumatoid arthritis. European journal of radiology. 1998 May 1;27:S18-24. https://doi.org/10.1016/S0720-048X(98)00038-2
3. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bulletin of the world health organization. 2003 Sep;81(9):646-56.
4. Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, Williams B, Gabriel S, Lassere M, Johns N, Buchbinder R. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Annals of the rheumatic diseases. 2014 Jul 1;73(7):1316-22. http://dx.doi.org/10.1136/annrheumdis-2013-204627
5. Zahid-Al-Quadir A, Zaman MM, Ahmed S, Bhuiyan MR, Rahman MM, Patwary I, Das BB, Hossain SA, Paul S, Shahin A, Rahman M. Prevalence of musculoskeletal conditions and related disabilities in Bangladeshi adults: a cross-sectional national survey. BMC rheumatology. 2020 Dec;4(1):1-4.
6. Haq SA, Darmawan J, Islam MN, Uddin MZ, Das BB, Rahman F, Chowdhury MA, Alam MN, Mahmud TA, Chowdhury MR, Tahir M. Prevalence of rheumatic diseases and associated outcomes in rural and urban communities in Bangladesh: a COPCORD study. The Journal of rheumatology. 2005 Feb 1;32(2):348-53.
7. Kvien TK, Uhlig T, Ødegård S, Heiberg MS. Epidemiological aspects of rheumatoid arthritis: the sex ratio. Annals of the New York academy of Sciences. 2006 Jun;1069(1):212-22. https://doi.org/10.1196/annals.1351.019
8. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955–2007. Arthritis & Rheumatism. 2010 Jun;62(6):1576-82. https://doi.org/10.1002/art.27425
9. Fraenkel L, Bathon JM, England BR, St. Clair EW, Arayssi T, Carandang K, Deane KD, Genovese M, Huston KK, Kerr G, Kremer J. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis & Rheumatology. 2021 Jul;73(7):1108-23. https://doi.org/10.1002/art.41752
10. Drosos AA, Pelechas E, Voulgari PV. Treatment strategies are more important than drugs in the management of rheumatoid arthritis. Clinical Rheumatology. 2020 Apr;39(4):1363-8.
11. Burmester GR, Pope JE. Novel treatment strategies in rheumatoid arthritis. The Lancet. 2017 Jun 10;389(10086):2338-48. DOI: https://doi.org/10.1016/S0140-6736(17)31491-5
12. Bansback N, Phibbs CS, Sun H, O'Dell JR, Brophy M, Keystone EC, Leatherman S, Mikuls TR, Anis AH, CSP 551 RACAT Investigators*. Triple therapy versus biologic therapy for active rheumatoid arthritis: a cost-effectiveness analysis. Annals of internal medicine. 2017 Jul 4;167(1):8-16.
13. Taylor PC, Balsa Criado A, Mongey AB, Avouac J, Marotte H, Mueller RB. How to get the most from methotrexate (MTX) treatment for your rheumatoid arthritis patient?—MTX in the treat-to-target strategy. Journal of clinical medicine. 2019 Apr 15;8(4):515. https://doi.org/10.3390/jcm8040515
14. Gopinath K, Danda D. Supplementation of 1, 25 dihydroxy vitamin D3 in patients with treatment naive early rheumatoid arthritis: a randomised controlled trial. International journal of rheumatic diseases. 2011 Oct;14(4):332-9. https://doi.org/10.1111/j.1756-185X.2011.01684.x
15. Mukherjee D, Lahiry S, Thakur S, Chakraborty DS. Effect of 1, 25 dihydroxy vitamin D3 supplementation on pain relief in early rheumatoid arthritis. Journal of Family

Medicine and Primary Care. 2019 Feb;8(2):517. doi: 10.4103/jfmpc.jfmpc_446_18

16. Haque UJ, Bartlett SJ. Relationships among vitamin D, disease activity, pain and disability in rheumatoid arthritis. Clin Exp Rheumatol. 2010 Sep 1;28(5):745-.

17. Rossini M, Maddali Bongi S, La Montagna G, Minisola G, Malavolta N, Bernini L, Cacace E, Sinigaglia L, Di Munno O, Adami S. Vitamin D deficiency in rheumatoid arthritis: prevalence, determinants and associations with disease activity and disability. Arthritis research & therapy. 2010 Dec;12:1-7.

18. Meena N, Chawla SP, Garg R, Batta A, Kaur S. Assessment of vitamin D in rheumatoid arthritis and its correlation with disease activity. Journal of natural science, biology, and medicine. 2018 Jan;9(1):54. doi: 10.4103/jnsbm.JNSBM_128_17

19. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. The Journal of clinical endocrinology & metabolism. 2011 Jul 1;96(7):1911-30. DOI: 10.1210/jc.2011-0385

20. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham III CO, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis & rheumatism. 2010 Sep;62(9):2569-81. https://doi.org/10.1002/art.27584

21. Arifina R, Parveen M, Rahman MS. Cross-Cultural Translation and Validation of Selected Tools to Evaluate Patients Satisfaction Level in Different Pain Management Settings. BJPain. 2021;3(1):11-17

22. Buondonno I, Rovera G, Sassi F, Rigoni MM, Lomater C, Parisi S, Pellerito R, Isaia GC, D'Amelio P. Vitamin D and immunomodulation in early rheumatoid arthritis: A randomized double-blind placebo-controlled study. PLoS One. 2017 Jun 5;12(6):e0178463. https://doi.org/10.1371/journal.pone.0178463

ORIGINAL ARTICLE

Status of Magnesium in Type 2 Diabetic Mellitus Patients with or without Diabetic Nephropathy: Experience from a Tertiary Care Hospital in Bangladesh

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Abstract

Introduction: *Diabetes mellitus (DM) is one of the most significant public health challenges in both developed and developing countries. Diabetic nephropathy (DN) is one of the major causes of morbidity and mortality among patients with DM worldwide. Alteration in mineral status has been found to be associated with impaired insulin release, insulin resistance and dysglycemia. Disturbances in magnesium (Mg) metabolism were observed in type 2 DM patients. There is now growing evidence that Mg deficiency is implicated in type 2 diabetes and its complications. Our aim of study was to evaluate serum magnesium levels in type 2 diabetic patient with or without diabetic nephropathy.*

Methods: *This cross-sectional study was done in BIRDEM General Hospital from January 2019 to December 2019. 150 respondents were taken according to inclusion and exclusion criteria and were divided into three groups, 50 respondents above 30 years with type 2 DM, 50 respondents with DN and another 50 without DM. After taking informed written consent from each subject, a structured questionnaire was filled up for necessary information. Relevant biochemical parameter serums Mg levels were estimated and included in the questionnaire along with other measurements. We used ANOVA, Chi-square test and Pearson's correlation coefficient. All the statistical tests were considered at 5% level of significance at SPSS.*

Results: *In this study we collected data from 150 subjects, 50 subjects in each group. Male and female were 41.3% and 58.7% respectively. The mean± SD of HbA_1c were 10.33± 2.07, 8.33± 2.16 and 5.72±.53 in DM patients with nephropathy, DM patients without nephropathy and healthy control respectively. It was found that serum magnesium was significantly ($p<0.001$) lower in Type 2 diabetes patients compare with healthy control.*

Conclusion: *This study concluded that serum magnesium levels are significantly low in type 2 diabetes mellitus patients with diabetic nephropathy compared with type 2 diabetes mellitus patients without diabetic nephropathy.*

Keywords: *Serum magnesium, T2DM, HbA1c, Diabetic nephropathy, eGFR*

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Introduction:

Diabetes mellitus (DM) is a major metabolic and noncommunicable disease. It is one of the most significant public health challenges of 21st century. The number of the people with DM has turned into more than double globally, over the past three decades.[1] The International Diabetes Federation (IDF) Diabetes Atlas estimated that in 2012, more than 371 million people had DM and half of the people with diabetes were undiagnosed.[2]

Diabetic nephropathy (DN) is one of the major micro-vascular complications of diabetes and the leading cause of end stage renal disease (ESRD) globally, causing high morbidity and mortality in patients with diabetes.[3] In DN there are structural and functional changes in kidneys. These changes result in a clinical presentation that is characterized by proteinuria, hypertension and progressive reductions in kidney function. The

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pathophysiologic changes in diabetic nephropathy include hyperfiltration and microalbuminuria followed by worsening of renal function associated with cellular and extracellular derangement.[4]

Most important and abundant intracellular ion is magnesium (Mg) which plays a vital role in insulin secretion and activity. Insulin is involved in the transport of Mg through the cellular membrane and in the intracellular supply.[5] It is claimed that there is an inverse relationship between Mg intake and incidence of DM.[6] Mg deficiency is common in diabetic patients. The incidence of hypomagnesaemia varies between 11 and 47.7%.[7] Cellular Mg deficiency can alter the membrane bound sodium potassium-adenosine triphosphate which is involved in the maintenance of glucose transport. Studies have shown that Mg deficiency has a negative effect on the post receptor signaling of insulin which leads to insulin resistance.[8] Insulin deficiency and resistance can effect tubular reabsorption of Mg.[9]

Concomitant use of diuretics and hypolipidemic agents also increase urinary Mg loss.[10] On the other hand, some studies suggested that glycemic control did not affect serum Mg level.[11]

Sakaguchi et al reported that, hypomagnesemia independently predicts the progression to ESRD in patients with advanced DN and serum Mg levels were significantly lower in DN patients when compared to diabetic patients without complications. Hypomagnesemia was signifiantly associated with progression of ESRD in patients with DN but not in those with nondiabetic CKD (chronic kidney disease).[12]

On the other hands Zargar et al found that, glycemic control did not affect serum Mg level.[11] In this background, the aim of this study was to evaluate Mg levels among patients with type 2 DM with or without DN.

Methods:

This cross-sectional study was done in BIRDEM General Hospital from January 2019 to December 2019. 150 respondents were taken according to inclusion and exclusion criteria and were divided into three groups, 50 respondents above 30 years with type 2 DM, 50 respondents with DN and another 50 without DM. The data was collected through a questionnaire which included their gender, residence, education, physical exercise and treatment of DM. DN was diagnosed by the attending consultant at the Nephrology Department based on the previous reports of the patient's biochemical tests of urine albumin, serum creatinine, eGFR, BP, and clinical assessment. Those patients undergoing dialysis or renal transplantation, hepatic disorders, malignancies, acute infection, drugs that alter magnesium levels (diuretics, aminoglycosides, amphotericinB) malabsorption or diarrhea, chronic alcoholic, vitamin or mineral supplements, pregnancy and lactation were excluded from study. Estimating glomerular filtration rate (eGFR) was calculated using the modified diet in renal disease equation by the USA National Kidney Foundation with a reference range of normal glomerular filtration rate (GRF) values in young individuals is from 80 to 130 mL/min, 1/1.73 m2, declining at <"10 mL/min/decade after 50 years of age.

Sample collection

At first identity of the patient is confirmed. With proper counselling and consent, privacy is ensured. Then 6 ml blood sample was collected from each study subject. From this blood sample, 2 ml was delivered in EDTA tube for HbA_1C and 4ml was delivered in a plain tube for estimation of fasting blood glucose and serum magnesium.

Statistical Analysis

Statistical analysis was performed with the help of SPSS 22 version. Descriptive statistics were presented as mean±SD score for normally distributed data and median (interquartile range or range) for skewed data. Continuous data were compared using parametric test ANOVA, Chi square test and skewed data using the nonparametric Pearson's correlation coefficient test. Statistical tests were considered significant at the level of <5% and considered as test of significance when $p<0.05$.

Results:

This cross-sectional study was carried out at Bangladesh Institute of Research and Rehabilitation for Diabetes, Endocrine and Metabolic Disorder (BIRDEM), during the period of January 2019 to December 2019. In this study 150 participants were taken from outpatient Department of Nephrology according to the inclusion criteria. Among them 50 previously diagnosed diabetic nephropathy patients were selected as group I(a), 50 previously diagnosed Diabetic patients without Nephropathy were selected as group I(b) and 50 healthy individuals were selected as group II. Of the total participants male and female were 41.3% and 58.7% respectively.

Table I showed duration of DM 0-5 years, 6-10 and >10 years were 50%, 30% and 20% respectively in case of T2DM without DN and 0.0%, 18%, 82% respectively in case of DM with DN.

Table II showed that, the Mean± SD of HbA_1c (%) of diabetic patient with nephropathy was 10.88± 2.07 (%), in

case of DM without DN was 8.33± 2.16(%) respectively, in healthy controls was and 5.72± .53 (%) respectively. We observed the mean value of HbA1c of DN patients were higher in comparison with other two groups and the differences were statistically significant (p<0.001).

Table III showed the comparison of functional status of kidney among the groups. This table IV showed the mean± SD of s. creatinine and eGFR of DN were 3.16± .99mg/dl and 18.32± 6.19ml/min/m^2 respectively, in case of DM without DN 0.92± .13 mg/dl and 82.10± 13.27ml/min/m^2 respectively and in case of healthy control 0.75± .09 mg/dl and 93.52± 13.27 ml/min/m^2 respectively. Table showed that the mean value of s. creatinine of diabetic nephropathy patients was higher in comparison with other two groups and the differences were statistically significant (p<0.001). We observed that mean value of eGFR of diabetic nephropathy patients were lower in comparison with other two groups and the differences were statistically significant (p<0.001).

Table IV showed the comparison of biochemical variables among three groups (Diabetic patients with nephropathy, type 2 diabetic patients without nephropathy and healthy control).

This table also showed the mean± SD of S. Mg was 0.68± 0.08 respectively in case of DM with DN; 0.76± 0.08 respectively in case of DM without DN and 0.82± .06 respectively in case of healthy control.

Table showed that, S. Mg levels were decreased in T2DM with DN in comparison with other two groups.

Table V showed correlation between eGFR and other variables in three groups. There was positive correlation of S. Mg with eGFR in T2DM patients with DN (group Ia).

Table I

Association between duration of diabetes and DN

Duration of Diabetes	Group I(b)		Group I(a)		p value
(Years)	Frequency	Percentage	Frequency	Percentage	
0-5	25	50.0	0	0.0	<0.001
6-10	15	30.0	9	18.0	
>10	10	20.0	41	82.0	
Total	50	100	50	100	

Statistical analysis was done by chi square test

Table II

Comparison of age and HbA1c among the groups

Variables	Group I(a) (n=50) Mean± SD	Group I(b) (n=50) Mean± SD	Group II (n=50) Mean± SD	p value
HbA1c (%)	10.33± 2.07	8.33± 2.16	5.72± .53	<0.001***
Range	6.50 -14.20	5.10-14.50	5.88-4.70	
Age (years)	57.02±5.34	56.94±4.15	55.42±3.39	0.122
Range	48-65	50-69	44-64	

Statistical analysis was done by ANOVA test to compare among groups. Values are expressed as the mean± SD. *= significant. *$p \leq 0.05$, **p<0.01, ***p<0.001.

Table III

Comparison of and functional status of kidney among the groups

Variables	Group I(a) (n=50) Mean± SD	Group I(b) (n=50) Mean± SD	Group II (n=50) Mean± SD	p value
S. creatinine (mg/dl)	3.16± .99	0.92± .13	0.75± .09	<0.001***
Range	1.90-5.70	0.60-1.20	0.60-1.0	
eGFR (ml/min/m^2)	18.32± 6.19	82.10± 13.27	93.52± 13.27	<0.001***
Range	7.0-31.0	64.0-108.0	67.0-129.0	

Statistical analysis was done by ANOVA test to compare among groups. Values are expressed as the mean± SD. *= significant. *$p \leq 0.05$, **p<0.01, ***p<0.001.

Table IV

Comparison of biochemical variables among the groups

Variables	Group I (a) (n=50) Mean± SD	Group I (b) (n=50) Mean± SD	Group II (n=50) Mean± SD	*p* value
Serum Mg (ml/mol)Range	0.68± 0.080.54-0.81	0.76± 0.080.60-0.90	0.82± .060.70-0.90	<0.001***

Statistical analysis was done by ANOVA test to compare among groups. Values are expressed as the mean± SD. *= significant. **p* d"0.05, ***p*<0.01, ****p*<0.001.

Table V

Correlation of eGFR with HbA1c and serum magnesium among study subjects

Correlations

Groups			HbA1c(%) mmol/l	S. Mg
DM with DN	eGFR	r- value	+0.086	+0.287
		p- value	0.552	0.043
DM without DN	eGFR	r- value	+0.123	+0.106
		p- value	0.393	0.464
Healthy Control	eGFR	r- value	-0.125	+0.196
		p value	0.386	0.174

Statistical analysis was done by Pearson correlation test. Values are expressed as the r: Pearson correlation coefficient. *= significant. **p* ≤0.05, ***p*<0.01, ****p*<0.001.

Discussion:

This study is a cross sectional study which evaluates serum magnesium levels among patients with type 2 diabetes mellitus with or without diabetic nephropathy. In this study the baseline characteristics of the study population are also analyzed. The total study subjects were 150 including both sexes. The study population was divided into three groups. Group I (a) type 2 diabetic patients with nephropathy, group I(b) type 2diabetic patients without nephropathy and group II healthy controls. 150 subjects are equally divided in three groups and each group contains 50 subjects individually.

The mean HbA_1C of the study subjects in type 2 diabetic patient with nephropathy was 10.33± 2.07%, type 2 diabetic patient without nephropathy was 8.33± 2.16 and healthy control 5.72±.53%. The HbA_1C of three groups showed statistically significant difference (p< 0.001) which reflect the finding of Renuka and Vasanta, 2016. HbA_1C in type 2 diabetic patient with nephropathy, type 2 diabetic patient without nephropathy and healthy control group were 9.89± 0.06%, 6.7± 0.11% and 5.4± 0.56.[13]

Serum creatinine in group I(a), group I(b) and group II were 3.16± .99mg/dl,0.92± 0.13mg/dl and 0.75± .09 mg/dl respectively. It was significantly different among 3 groups (p< 0.001). Mohammed et al. (2013) found serum creatinine was 2.65± 0.21mg/dl, 0.72± 0.16mg/dl and 0.79± 0.18 mg/dl in type 2 diabetic patient with nephropathy, type 2 diabetic patient without nephropathy and healthy control respectively with a significant difference among groups (p< 0.025).[14] Another study also detected similar finding.[15]

In the present study it was found that eGFR was significantly lower (p< 0.001) in group I(a) than group I(b) and group II (18.32± 6.19,82.10± 13.27 and 93.52± 13.27 respectively). Mohammed et al. (2013) also demonstrated that eGFR was significantly differed (p<0.027) among type 2 diabetic patients with nephropathy, type 2 diabetic patients without nephropathy and healthy control (51.1± 39.3, 113.4± 26.3 and 101.0± 39.4 ml/min/1.73m^2 respectively).[14] Similar finding was shown in another study.[15]

Serum magnesium in group I(a), group I(b) and group II was 0.68± 0.08,0.76± 0.08 and 0.82± .06 mmol/l respectively. It was significantly different among 3 groups (p< 0.001). Renuka et al. (2016) found serum magnesium was 0.57± 0.11, 0.62± 0.09 and0.78± 0.07 mmol/l in type 2 diabetic patient with nephropathy, type 2 diabetic patient without nephropathy and healthy control respectively with a significant difference among groups (p< 0.001).[13] Kumar

et al, 2018 found average serum magnesium was 0.625 mmol/l in diabetic nephropathy patients.[16] In this study positive correlation of S. Mg with eGFR. This can be possibly explained as low magnesium in diet, osmotic diuresis causing high renal excretion of magnesium, insensitivity to insulin affecting intracellular magnesium transport and thereby causing increased loss of the extracellular magnesium, and reduced tubular reabsorption due to insulin resistance. On the other hands Zargar et al found that, glycemic control did not affect serum Mg level. They conclude that Mg levels are not altered in DM. It may be for their dietary habit and concern for disease.[11]

Limitation:

This study was done in a limited period of time which was done only in one tertiary care hospital of Bangladesh, hence may not represent the whole population of the country. Detailed dietary habit could not be considered and effect of other antioxidants and trace materials on diabetic nephropathy did not measured.

Conclusion:

In this study serum magnesium was significantly lower in type 2 diabetes mellitus patients with diabetic nephropathy compared with type 2 diabetes mellitus patients without diabetic nephropathy. It was also observed that, there is positive correlation of serum magnesium with eGFR.

References:

1. Najeeb Q, Aziz R, Hamid S. To evaluate the levels of glycated hemoglobin, serum calcium, magnesium, phosphate, uric acid and microalbuminuria in patients with newly diagnosed type 2 diabetes mellitus. Int J Res Med Sci. 2014;2(4):1462-5.
2. International Diabetes Federation, What we do: Epidemiology and Prevention: Diabetes Atlas: Update 2013.
3. Giunti S, Barit D, Cooper ME. Mechanisms of diabetic nephropathy: role of hypertension. Hypertension. 2006;48(4):519-26.
4. Reddy GK. AGE-related cross-linking of collagen is associated with aortic wall matrix stiffness in the pathogenesis of drug-induced diabetes in rats. Microvascular research. 2004;68(2):132-42.
5. de Valk HW. Magnesium in diabetes mellitus. The Netherlands journal of medicine. 1999;54(4):139-46.
6. Kim DJ, Xun P, Liu K, Loria C, Yokota K, Jacobs Jr DR, He K. Magnesium intake in relation to systemic inflammation, insulin resistance, and the incidence of diabetes. Diabetes care. 2010;33(12):2604-10.
7. Dasgupta A, Sarma D, Saikia UK. Hypomagnesemia in type 2 diabetes mellitus. Indian journal of endocrinology and metabolism. 2012;16(6):1000-3.
8. Riduara RL, Stamfer MJ, Willet WC. Magnesium intake and risk of type 2 diabetes mellitus in men and women. Diabetes care. 2004;27:134-40.
9. Mandon BE, Siga E, Chabardes D, Firsov D, Roinel N, De Rouffignac C. Insulin stimulates Na+, Cl-, Ca2+, and Mg2+ transports in TAL of mouse nephron: cross-potentiation with AVP. American Journal of Physiology-Renal Physiology. 1993;265(3):F361-9.
10. Badyal A, Sodhi KS, Pandey R, Singh J. Serum magnesium levels: A key issue for diabetes mellitus. JK science. 2011;13(3):132.
11. Zargar AH, Bashir MI, Masoodi SR, Laway BA, Wani AI, Khan AR, Dar FA. Copper, zinc and magnesium levels in type-1 diabetes mellitus. Saudi Med J. 2002;23(5):539-42.
12. Sakaguchi Y, Shoji T, Hayashi T, Suzuki A, Shimizu M, Mitsumoto K, Kawabata H, Niihata K, Okada N, Isaka Y, Rakugi H. Hypomagnesemia in type 2 diabetic nephropathy: a novel predictor of end-stage renal disease. Diabetes care. 2012;35(7):1591-7.
13. Renuka P, Vasantha M. Study of the serum levels of iron, ferritin and magnesium in diabetic complications. Int. J. Pharm. Clin. Res. 2016;8:254-9.
14. Mohammed MK, Abdrabo AA. Evaluation of serum bone minerals level in diabetic type 2 Sudanese patients. Sudanese Journal of Public Health. 2013;8:25-28.
15. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nature reviews endocrinology. 2012;8(4):228-36.
16. Kumar CA, Kolli SG, Katta S, Katta S. Serum magnesium levels in type 2 diabetes patients and its relation with diabetic nephropathy. Int J Med Res Health Sci. 2018;7(7):90-4.

ORIGINAL ARTICLE

Renoprotective Effect of Trimetazidine in Diabetic Nephropathy-an Experimental Study in Drug Induced Diabetic Rats

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Abstract

Introduction: Malondialdehyde (MDA) level and limits membrane damage caused by reactive oxygen species (ROS) that inhibited by Trimetazidine (TMZ). It also has cytoprotective effect and limit the production of trimethylamine N-Oxide (TMAO) and provide the renoprotective effect.This study was done to see the renoprotective effect of Trimetazidine.

Methods: This experimental trial was conducted in Animal rat house of Pharmacology Department at BSMMU, Dhaka, Bangladesh. For this experimental study sixty-six rats (66) were divided into eight groups. Group I& II received no medication. Three groups (IIIa, IVa&Va) of rats were induced diabetic nephropathy by streptozotocin (STZ). Parallel to these groups, three combined treatment groups (IIIb, IVb&Vb) treated by trimetazidine concomitant with STZ.IIIa&IIIb were sacrificed on 22nd day to detect incidence of nephropathy, groupsIVa&IVb were sacrificed on 43rd day to detect onset of nephropathy and groups Va&Vb were sacrificed on 57th day to detect progression of nephropathy. Biochemical indices like the status of oxidative stress was assessed by renal cortical MDA levels.

Results: In streptozotocin treated groups, renal MDA was significantly ($p<0.01$) higher when compared to control. In TMZ treated group, whereas renal MDA was significantly ($p<0.01$) lower when compared with STZ induced nephropathy groups of rats.

Conclusion: It may be assumed from the present study that trimetazidine has nephroprotective effects because of its special antioxidant effects, which can delay the onset, severity and progression of nephropathy induced by STZ in rats.

Keywords: Trimetazidine (TMZ), Diabetic Nephropathy (DN), Streptozotocin (STZ), Malondialdehyde (MDA)

Journal of Green Life Med. Col. 2023; 8(2): 42- 45

Introduction:

Diabetic nephropathy is one of the most common complication of diabetes mellitus. It is produced by several hemodynamic alterations, ischemic reperfusion injury that generated oxidative free radicals, which causes cell death and broadly produces impaired renal function and progress to end stage renal disease (ESRD).[3] The incidence of nephropathy is increasing in Bangladesh due to diabetes.

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Till now, many researches have been conducted to prevent the progression and treat nephropathy but only a little of them could reach to any conclusive recommendation which are not adequate. Trimetazidine (TMZ) is anti-ischemic drug, used to treat ischemic heart disease with or without heart failure.[2] This medicine has established safety record without producing significant adverse effects. Moreover, as this medicine is well tolerated and cheap and therefore would not become an economic burden for the patients. Consequently, investigating possible protective effect of Trimetazidine against Streptozotocin (STZ) induced diabetic nephropathy in rats can be a good opportunity to find a way of treatment for the patients suffering from diabetic nephropathy.[11]The aim of this study to see thattrimetazidine has nephroprotective effects because of its special antioxidant effects.[4,5] which can delay the onset, severity and progression of nephropathy induced by STZ in rats.

Methods:

We conducted one year experimental study done in animal rat house of Pharmacology department at BSMMU from March 2017-March 2018.Proper ethical permission was taken from concern authority.

Drugs:

Streptozotocin (STZ)

This drug was brought from Sisco Research Laboratory Pvt. Ltd (SRL). It was stored at 4ºC temperature and wrapped in aluminium foil to retain its biological activity.[6,1] It was administration by single intraperitoneal injection at a dose of 50mg/kg body weight.

Trimetazidine (TMZ)

This medicine was brought from local market as tablet Metacard 35 mg MR (trade name of Aristopharma Limited). It was given at 20mg/kg/day in liquid form by mixed with distilled water.[6,9]

Chemicals and reagents used for estimation of renal MDA:

- Tyrode's (Physiological) solution- Made in laboratory of department of Pharmacology, BSMMU.
- 0.5% Thiobarbituric acid- Sigma Aldrich ChemieGmbh, Germany.
- 25% Tricloroacetic acid– Sigma Aldrich ChemieGmbh, Germany.
- 1,1,3,3, Tetraethoxy Propane (MDA standard)- Sigma Aldrich Chemic Gmbh, Germany

Animals

Sixty-six (66) [According to the formula] adult male Long Evan's Norwegian rats were obtained from the animal house of BSMMU. The rats were 8-12 weeks old and weight between 190-230 gm. The environment of the animal house was properly maintained because it was essential for animal's well-being, the quality of animal research and also the health and safety of the investigator. Standard laboratory conditions where the dark/light cycle 12/12 hours, temperature 25-30ÚC and humidity 65±5% were maintained and the polypropylene plastic cages were used for keeping the rats, each cage was properly labeled for identification of different groups and the cage was cleaned regularly during the experimental period. Rats were given diet and water ad libitum. Standard rat diet is prepared according to the guideline of the I.A.T (The Institute of Animal Technician).[10]

Experimental design

The rats were divided into eight groups as follows:

I ⟺Control group received normal diet ad libitum (C1) and sacrificed on 22nd day , II ⟺ Received distilled water (1ml/rat/single I/P injection) and sacrificed on 22nd day (C2), IIIa Received Streptozotocin (50mg/kg single I/P injection) and sacrificed on 22nd day (STZ1), IIIb Streptozotocin induced diabetic rats received Trimetazidine (20mg/kg/day orally for 21 days) and sacrificed on 22nd day (STZ+TMZ), Iva Received Streptozotocin (50mg/kg single I/P injection) and sacrificed on 43rd day (STZ2), IVb Streptozotocin induced diabetic rats received Trimetazidine (20mg/kg/day orally from 22nd day to 42nd day) and sacrificed on 43rd day (STZ+TMZ), Va ReceivedStreptozotocin (50mg/kg single I/P injection) and sacrificed on 57th day (STZ3), Vb Streptozotocin induced diabetic rats received Trimetazidine (20mg/kg/day orally from 22nd day to 56th day) group and sacrificed on 57th day (STZ+TMZ).

Here,

C1 = Control normal healthy rats group

C2 = Control heathy rat received distilled water intra peritonealy (I/P)

STZ = Streptozotocin induced DN rats group

TMZ = Trimetazidine treated rats groups

Estimation of renal cortical MDA (/l)level by TBARS method[3]

MDA is formed as a result of lipid peroxidation and reacts with thiobarbituricacid at 90° -100°c temp. The reaction yields pink MDA-TBA products, which will be measured at 532 nm. The content will be expressed as mol/L.

2TBA+ MDA MDA-TBA adduct +2

Results:

Effect of TMZ on STZ induced changes in MDA contents

Malondialdehyde (MDA) levels in kidney homogenates are shown in (Table 1). The concentration of MDA in animals treated with STZ was significantly increased in homogenates of kidney.The mean SD of renal MDA concentration was in Group I (control) was 0.73 0.14 (Table I).

Table I

Renal cortical MDA levels of experimental and control rat's groups

Value expressed	Group							
in mol/L	I	II	IIIa	IIIb	IVa	IVb	Va	Vb
Mean	0.73	0.97	1.76	1.12	2.25	1.47	3.26	1.80
SD	0.14	0.08	0.20	0.18	0.13	0.16	0.42	0.10
P value	-	0.00637	0.00001	0.00002	0.00001	0.00015	0.00001	0.00001

In Group II (D/W sacrificed on 22nd day), the mean SD of MDA concentration was 0.97 0.08. This was significant (p=0.00637) elevation when compared to that Group I (Table I), indicating nephrotoxicity in distilled water group.

In Group IIIa (STZ group, sacrificed on 22nd day), the mean SD of the renal MDA of 6 rats out of 8 was 1.76 0.20. This was a significant (p= 0.00001) elevation when compared to that of Group I, indicating nephrotoxicity in Group IIIa rats (Table I).

In Group IIIb (STZ+TMZ group, sacrificed on 22nd day), the mean SD of the renal MDA concentration of 6 rats out of 8 was 1.12 0.17. This was significant (p= 0.0002) reduction of renal MDA level in Group IIIb when compared to that Group IIIa (Table I), indicating nephroprotective effect in Group IIIb.

In Group IVa (STZ group, sacrificed on 43rd day), the mean SD of the renal MDA was 2.25 0.16. This was a significant (p=0.00001) elevation when compared to that of Group I, when the level of renal MDA of Group IVa compared to Group IIIa, there was also significant elevation (p=0.00015) of renal MDA level in Group IVa, indicating nephrotoxicity in Group IVa rats.

In Group IVb (STZ+TMZ group, sacrificed on 43rd day), the mean SD of renal MDA concentration of 7 rats out of 9 was 1.5 0.16 . This was significant (p=0.00015) reduction of renal MDA level in Group IVb when compared to that Group IVa, when the level of renal MDA level of Group IVb compared to Group IIIb, there was also significant reduction (p=0.00321) of MDA level in Group IVb (Table I), indicating nephroprotective effect in Group IVb rats.

In Group Va (STZ group, sacrificed on 57th day), the mean SD of the renal MDA of 7 rats out of 10 was 3.26 0.42. Thiswas a significant (p=0.00001) elevation when compared to that of Group I, when the level of renal MDA of Group Va compared to Group IVa, there was also significant elevation (p=0.00002) of renal MDA level in Group Va (Table I) indicating nephrotoxicity in Group Va rats.

In Group Vb (STZ+TMZ group, sacrificed on 57th day), the mean SD of the renal MDA concentration of 7 rats out of 10 was 1.8 0. This was significant (p=0.00001) reduction of MDA level in Group Vb when compared to that Group Va, when the level of MDA of Group Vb compared to Group IVb, there was also significant reduction (p=0.00069) of MDA level in Group Vb (Table I), indicating nephroprotective effect in Group Vb rats.

Discussion:

The present study revealed that trimetazidine has significant effect of nephro-protection in Streptozotocin induced diabetic nephropathy in rats. This study is important for this field of research, because Hell PM[4]was reported that as in every year, average 7.64 persons out of 1000 are suffering from ESRD due to gradual loss of renal function caused by diabetic nephropathy.[4]The diabetes mellitus was induced in adult male rats through the administration of streptozotocin (STZ) at recommended route and dosage.[1]Three different durations were studied (21, 42 and 56 days) in order to demonstrate any difference in incidence, severity and progression of diabetic nephropathy in trimetazidine (TMZ) treated and untreated groups among the STZ induced diabetic rats. Effort was made to find any significant effect of TMZ to delay the incidence, severity and progression of diabetic nephropathy on different duration. Nephropathy and nephro-protective effects were estimated by biochemical observations.

In present study, where renal cortical MDA concentration (p<0.01)of IIIb (STZ+TMZ group, sacrificed on 22nd day)was significantly lower[8] found renoprotective effect of TMZ on diabetic nephropathy and showed that renal MDA of TMZ group was significantly (p<0.01) lower when compared to diabetic control groupin a study of 6 weeks duration.

Trimetazidine also decreased renal MDA concentration in all trimetazidne treated groups when compared with the untreated diabetic nephropathy groups, possibly because trimetazidinehas special antioxidant property, Dezsi CA

was reported TMZ increased superoxide dismutase and glutathione peroxidase that decrease MDA (end product of lipid peroxidation) level.[11]

In present study trimetazidine also significant ($p<0.05$) improved body health then the diabetic groups induced by STZ, because Ussher et al, reported that TMZ inhibited 3-ketoacyl-CoA thiolase which reduced anti-oxidative effect thus improve insulin sensitivity to the muscle and increase lipogenesis thus improved heath.[7]

From the above discussion, it appears that trimetazidine played a positive role ofrenoprotectionin diabetic nephropathy, which may be beneficial in preventing ESRD to renal failure.

Conclusion:

The observation and results of the present study showed that Trimetazidine (TMZ) was able to produced considerable protection and alleviation of kidney from nephropathy induced by Streptozotocin in rats. TMZ occurred possibly by inhibition of lipid peroxidation due to its antioxidant activity, from biochemical observations showed that trimetazidine lead to delay the onset, severity and progress of diabetic nephropathy. So, it can be used in the treatment of diabetic nephropathy in human.Trimetazidine is already prescribed medicine for treatment of ischemic heart disease (IHD) in human. In present study showed it protected kidney from nephropathy induced by streptozotocin. So, it can be used in the treatment of diabetic nephropathy in human.

References:

1. Choi YE, Ahn SK,Lee WT,Lee JE, et al. Soybeans Ameliolate Diabetic Nephropathy in Rats, Hindawi, 2008; vol. 7, no. 4, pp. 433-40.
2. Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The Antianginal Drug Trimetazidine Shifts Cardiac Energy Metabolism from Fatty Acid Oxidation to Glucose Oxidation by Inhibiting Mitochondrial Long-Chain 3-Ketoacyl Coenzyme a Thiolase, American Heart Association, 2000; vo. 86, pp. 580-8.
3. Placer ZA, Cushman LL, Johnson BC. Estimation of product of lipid peroxidation (malonyldialdehyde) in biochemical systems, Analytical Biochemistry, 1966, vol. 16, no. 2, pp. 359-64.
4. Hall PM,Prevention of Progression in Diabetic Nephropathy', Diabetes Spectrum, 2006, vol. 19, no. 1, pp. 18-24.
5. Soetikno V,Sari FR,Veeraveedu PT, et al. Curcumin ameliorates macrophage infiltration by inhibiting NF- B activation and proinflammatory cytokines in streptozotocin induced-diabetic nephropathy, BioMed Central, 2011; pp. 1-11.
6. Rodea ASDL,Shanzer SK, Hartigh JD, et al. 'Anomer-Equilibrated Streptozotocin Solution for the Induction of Experimental Diabetes in Mice, The American Association for Laboratory Animal Science, 2010; vol. 49, no. 1, pp. 40-4.
7. Ussher JR, Keung W, Fillmore N, et al. Treatment with the 3-Ketoacyl-CoA Thiolase Inhibitor Trimetazidine Does Not Exacerbate Whole-Body Insulin Resistance in Obese Mice, The Journal of Pharmacology and Experimental Therapeutics, 2014; vol. 349, pp. 487-96.
8. Wang L, Zhang L, Yu Y, et al. The Protective Effects of Taurine against Early Renal Injury in STZ-Induced Diabetic Rats, Correlated with Inhibition of Renal LOX-1- Mediated ICAM-1 Expression, Informa Health Care, 2009; vol. 30, pp. 763-71.
9. Parini M, Harpey C. Effect of trimetazidine on membrane damage induced by oxygen free radicals in human red cells, British Journal of Pharmacology, 1985. vol. 20, pp. 148-51.
10. Yamabe N, Yokozawa T, Oya T, et al. Therapeutic Potential of (-)-Epigallocatechin 3-O-Gallate on Renal Damage in Diabetic Nephropathy Model Rats, The Journal of Pharmacology and Experimental Therapeutics, 2006; vol. 319, no. 1, pp. 228-36.
11. Dezsi CA, Trimetazidine in Practice: Review of the Clinical and Experimental Evidence, American Journal of Therapeutics2016, vol. 23, pp. 871-9.

REVIEW ARTICLE

Postmenopausal Osteoporosis

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Abstract

Postmenopausal osteoporosis is the most common cause of fragility fractures in women leading to significant morbidity and mortality. It is recommended to do dual-energy x-ray absorptiometry (DXA) of the spine and hip (T-score ≤-2.5 means osteoporosis) for postmenopausal women ≥65 years of age and younger than 65 who have risk factors. Selection of therapy depends on the risk stratification which is based on the T-score, presence of fractures and fracture risk assessment tool (FRAX). Treatment is aimed at reducing risk of fractures and improving bone mineral density (BMD). Bone turnover markers (BTM) may also predict fracture risk and monitor treatment. Before initiating definite therapies for osteoporosis, calcium and vitamin-D level in blood must be normalized. Antiresrorptives (reduce osteoclastic activity) include bisphosphonates (alendronate, risedronate, ibandronate and zoledronate), RANK ligand inhibitor (denosumab), conjugated equine estrogen (CEE), and selective estrogen-receptor modulator (raloxifene and bazedoxifene). Anabolics (enhance bone formation) include parathyroid hormone receptor agonists (teriparatide and abaloparatide). Sclerostin inhibitor romosozumab acts as anabolic-antiresorptive agent. CEE is approved for the prevention of postmenopausal osteoporosis. Ibandronate is not effective to reduce the risk of hip fracture. Bisphosphonates and denosumab are the preferred antiresorptives for "high risk" of fracture group and, initial use of anabolics for 2 years or romosozumab for 1 year followed by antiresorptives are considered for "very high risk" of fracture group. It is recommended to repeat DXA 1-2 years after initiating or changing therapy. Reassessment of fracture risk is done in 3-5 years and 5-10 years interval for bisphosphonates and denosumab, respectively. Bisphosphonates are usually continued for 5-10 years and followed by the drug-free years depending on stable BMD and fracture risk. Such "drug holidays" is important to prevent atypical femur fractures in long-term bisphosphonate therapy. Several emerging anti-osteoporotic drugs are in different stages of clinical development as well.

Keywords: Postmenopausal osteoporosis, Dual-energy x-ray absorptiometry (DXA), Bone turnover markers (BTM), Antiresorptives, Anabolics, Drug holidays

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Introduction:

Globally, more than 200 million women are suffering from osteoporosis.[1] Postmenopausal state, due to oestrogen deficiency causing loss of bone mineral density (BMD), becomes the most vulnerable to develop osteoporosis particularly in the years immediately before and after menopause.[2] BMD starts to reduce 3 to 5 years prior to menopause and bone loss continues even 5 years after cessation of menopause at an average rate of 1 to 2% yearly[3] which worsens with advancing age (figure 1). Postmenopausal osteoporosis is the most prevalent cause of osteoporosis worldwide which leads to fragility fractures of spine, hip, forearm, humerus and pelvis as a consequence.[3] Such sequalae, resulting into significant burden of morbidity and mortality. About one-third women over 50 years of age will experience an osteoporotic fracture in their lifetime.[4] Hip fractures are

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the most serious consequences having mortality of 12 to 20% within 2 years and more than 50% of survivors bear lifelong morbidity due to fractures.[3] Almost 50% of all postmenopausal women with an osteoporosis-related fracture over their lifetime are susceptible to develop a spine deformity and a hip fracture in 25% and 15% cases, respectively. By 2050, Asia is expected to account for half of all hip fractures worldwide.[5] Dual-energy x-ray absorptiometry (DXA) of the spine and hip is recommended in postmenopausal women ≥65 years of age or ≤65 years of age who have risk factors to check the status of BMD. Osteoporosis is diagnosed if DXA T score is ≤-2.5 or on the basis of fragility fractures. Forearm BMD predicts fracture. Each standard deviation reduction below a T score of 0 is associated with doubling or tripling in the fracture risk.[2] Pharmacologic approach is based on the risk stratification of fracture which is done by using DXA and FRAX (fracture risk assessment tool) score. Several bone turnover markers (BTM) can be considered to diagnose and monitor the treatment of osteoporosis.[6] Management approach of postmenopausal osteoporosis is individualized, depending on the patient profile and suitability of the medications to that particular case. Multiple therapeutic options are available which are used by balancing their pros and cons. Drug monitoring should also be done accordingly.

Methods:

This review article is based on the information, recent updates and evidences obtained from multiple sources such as Google Scholar, Science Direct, UpToDate, Wiley Online Library, PubMed, BMC, MEDLINE, Cochrane databases, Medscape and William's Textbook of Endocrinology using the terms postmenopausal osteoporosis, bone mineral density, bone turnover markers, fragility fractures, predictors of postmenopausal osteoporosis, bisphosphonates, antiresorptive therapies, anabolic agents, newer drugs for osteoporosis, guidelines for the diagnosis and treatment of postmenopausal osteoporosis, drug holidays, atypical femur fracture, and pipeline drugs for postmenopausal osteoporosis. However, searching articles focusing on the details of postmenopausal osteoporosis was supported by the literatures, guidelines, consensus and chapters related to this topic available from January 2001 to January 2024.

Pathogenesis and risk factors for postmenopausal osteoporosis and fracture

Pathogenesis:

Oestrogens play a pivotal role in bone mass maintenance and its deficiency leading to bone loss is most pronounced after menopause.[7] A lack of oestrogen causes an increase in osteoblast death and, through many mechanisms, inhibits osteoblast development. It has been demonstrated that osteoblast development is suppressed when oestrogen receptor-α (ER-α) expression is inhibited. Furthermore, it has been observed that oestrogens suppress the generation of many pro-inflammatory cytokines, including interleukins IL-1, IL-4, IL-6, and IFN-γ, which are crucial for osteoclast development and bone resorption.[8] Additionally, oestrogens promote the production of osteoprotegerin (OPG) by osteoblasts and lymphocytes while suppressing the production of receptor activator of nuclear factor kappa-B (NF-κB) ligand (RANKL). This maintains the RANKL/OPG ratio required for balanced bone remodelling.[9-11] Numerous studies have shown the critical role that IL-17 activated in oestrogen deprivation plays in the development of osteoporosis. Innate immune cells secrete more RANKL, TNF-α, and IL-1 when exposed to IL-17, which promotes bone resorption.[12] Osteoporosis in postmenopausal women is associated with increased serum levels of IL-17A, RANKL, and OPG as well as increased peripheral blood CD4+ T-cells that produce IL-17.[13,14] The activation mechanism of bone tissue resorption linked to an increase in reactive oxygen species (ROS) during a reduction in oestrogen levels has been extensively addressed in the last decade.[15] According to data from transcriptomic and biochemical analyses, parathyroid cells and C-cells of the thyroid gland, which have receptors for oestrogen and alter parathyroid hormone and calcitonin secretion in response to its level, may be a non-immunological component of oestrogen-dependent bone loss.[16,17] Multiple genes contribute to the physiological traits that result in the osteoporotic phenotype, and a family history of osteoporotic fractures is often regarded as a substantial risk factor for osteoporosis. 85% of osteoporotic fractures are thought to be caused by genetic causes, according to various estimates.[18] Osteoporosis is not regarded as a hereditary disorder despite its high heritability because it is controlled by a number of metabolic, dietary, and other variables, including vitamin D levels.[7] Thus, oestrogen deficiency at menopause results in low bone mineral density, deteriorated bone microarchitecture, decreased bone strength, and increased risk of fragility fractures.[2]

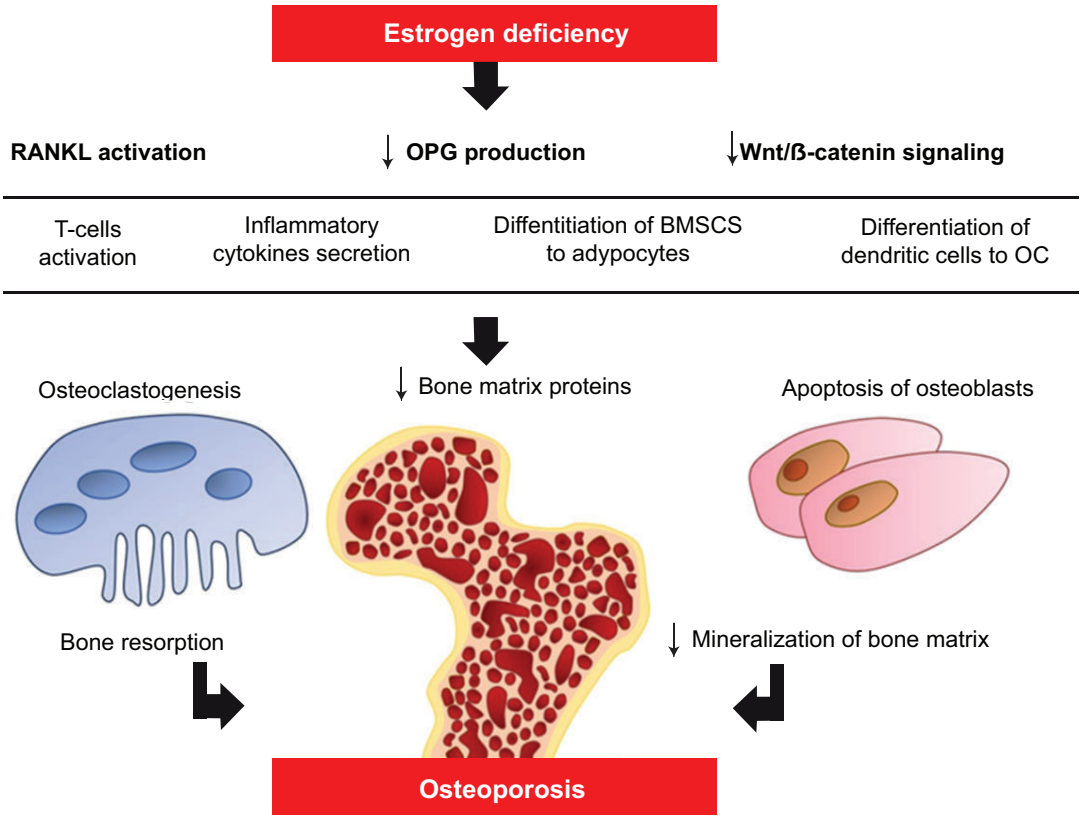

Figure 1: *The role of oestrogen deficiency in the pathogenesis of osteoporosis. RANKL (receptor activator of nuclear factor kappa-B ligand), BMSCs (bone marrow mesenchymal stem cells), OPG (osteoprotegerin), Wnt/β-catenin (wingless integrated type-1/ β-catenin), (OC (osteoclast), ↓(decrease).*[7]

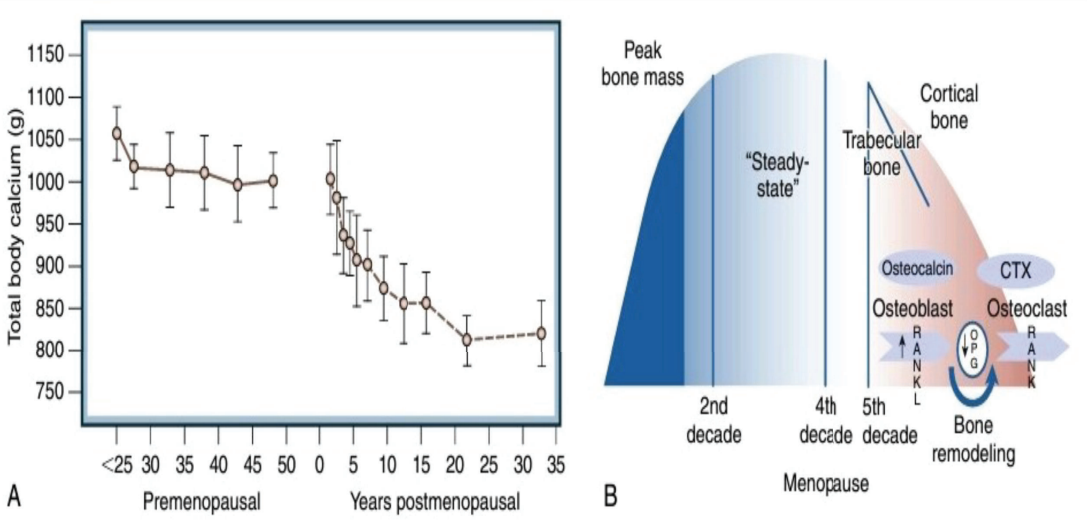

Figure 2: *a) The decline in total body calcium with years since menopause b) Bone mass development, maintenance and loss: trabecular bone loss is earlier and more intense than in cortical bones.*[19]

Risk Factors[2]:

- Older age
- Low weight (<58 kg) or low body mass index[3] (BMI <20 kg/m^2)
- Previous fracture during adulthood (particularly hip, spine, or wrist); recent fracture (within past one year) indicates a higher risk
- Parental history of hip fracture

- Current or past glucocorticoid treatment (>5 mg prednisolone daily or equivalent for ≥3 months)
- Other medications that cause bone loss (such as aromatase inhibitors, suppressive doses of thyroid hormone, chemotherapy, cyclosporine, unfractionated and low-molecular-weight heparins, antidepressants, thiazolidinediones, selected anticonvulsant drugs, and proton-pump inhibitors)
- Current smoking
- Excess alcohol intake
- Causes of secondary osteoporosis (such as organ transplantation, primary hyperparathyroidism, chronic kidney disease, type 1 and type 2 diabetes, anorexia nervosa, hypopituitarism, malabsorption, bariatric surgery, immobility, untreated hyperthyroidism, chronic pulmonary disease, human immunodeficiency virus infection, Cushing's disease, osteogenesis imperfecta, Gaucher's disease, and Marfan syndrome)
- Rheumatoid arthritis
- Premature menopause (<40 years of age) or hypogonadism
- Frequent falls

Epidemiology and disease burden of postmenopausal osteoporosis

In the United States, 20% women >50 years and 30% women ≥65 years of age are diagnosed with osteoporosis among which White, Asian, and Hispanic females are more susceptible.[20,21] Moreover, an additional 40% postmenopausal women in the U.S. have low bone mass (osteopenia). About 50% of postmenopausal women will have osteoporosis-related fractures (fragility fractures) and among which, 20% of institutionalized cases (black women are more prone to develop) of hip fractures bear doubled risk of death within 1 year.[22,23] The health care cost per annum due to fragility fractures in the U.S. is projected to exceed $95 billion by 2040 from the $57 billion at present.[24] Osteoporotic fractures are a major source of medical care costs as well as a common cause of disability and death among the elderly in Asia-pacific (AP) region as well.[25,26] In most Asian countries, the number of hip fractures has increased by two to three times in the last three decades.[25,27] Hip fractures are expected to rise 2.28 times annually from 1.12 million in 2018 to 2.56 million in 2050.[25] Osteoporosis is significantly underdiagnosed and undertreated in Asian countries, regardless the risk of fractures. Consequently, the AP region will face increasing threats to postmenopausal osteoporosis in the coming decades, which calls for the development of the best possible diagnostic and monitoring tools to reduce this risk.[5]

Diagnosis and Evaluation of postmenopausal osteoporosis

It may remain asymptomatic until the fracture appears clinically. Such fragility (low-trauma) fractures of the spine, hip, distal forearm, proximal humerus and pelvis in the absence of other metabolic bone disease and even independent of the BMD value (T-score) are diagnostically significant.[3]

Vertebral compression fractures- Most common, frequently painful and cause height loss >1.5 inches (>3.8 cm) but, may remain asymptomatic. If suspected, vertebral fracture analysis or spine radiography should be performed.[2]

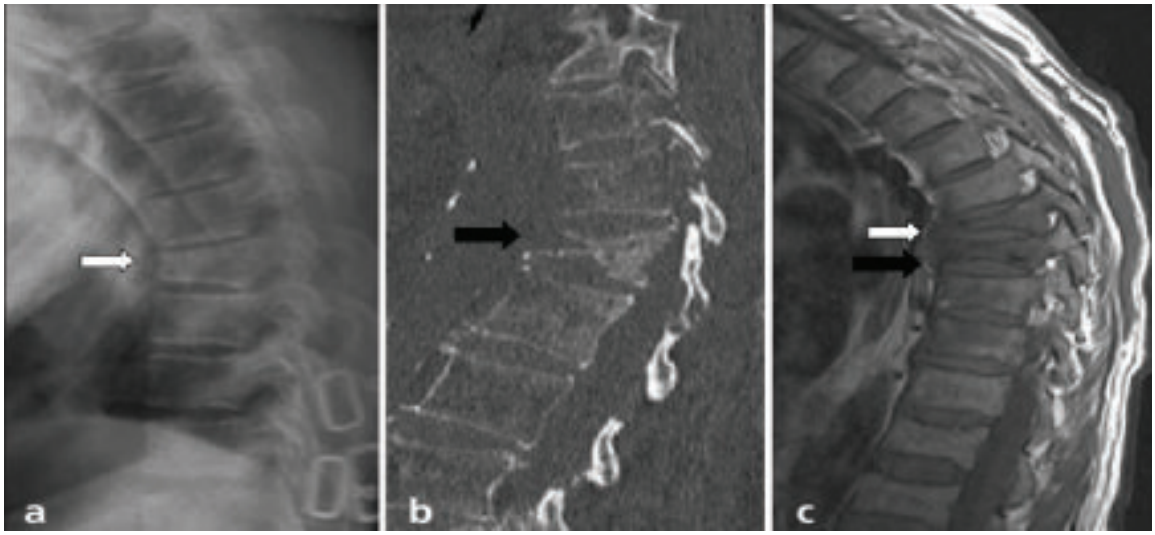

Figure 3: *a) X-ray images of vertebral compression fracture with anterior wedging (white arrow) b) CT (computed tomography) scan of biconcave vertebral compression fracture (black arrow) c) T2 weighted MRI (magnetic resonance images) of wedge vertebral compression fracture (white arrow), and biconcave vertebral compression fracture (black arrow).*[28]

Evaluation of osteoporosis risk should be done for all postmenopausal women aged ≥50 years. A detailed history, physical examination, and clinical fracture risk assessment with fracture risk assessment tool (FRAX®) or other fracture risk assessment tool should be included in the initial evaluation for osteoporosis.[3]

Testing of bone mineral density (BMD as expressed by T score) is the gold standard for diagnosing osteoporosis.[3] Normal level is considered when T-score is -1.0 or above. Dual-energy x-ray absorptiometry (DXA) is recommended in all postmenopausal women ≥65 years of age or <65 years of age who have risk factors.[2]

2020 AACE diagnostic criteria of postmenopausal osteoporosis:[3]

1. T-score −2.5 or below in the lumbar spine, femoral neck, total proximal femur, or 1/3 radius
2. Low-trauma spine or hip fracture (regardless of BMD)
3. T-score between −1.0 and −2.5 (low bone mass or osteopenia) along with a fragility fracture of proximal humerus, pelvis, or distal forearm
4. T-score between −1.0 and −2.5 (i.e. osteopenia) and high FRAX® (or if available, TBS-adjusted FRAX®) fracture probability based on country-specific thresholds

(AACE-American Association of Clinical Endocrino-logists, FRAX®-fracture risk assessment tool, TBS-trabecular bone score).

FRAX® integrates the contribution of BMD and other clinical risk factors and calculates an individual's probability of fracture over 10 years. Over 80% of fragility fractures occur in women with BMD in the osteopenia range.[3] TBS is a textural index that measures pixel gray-level differences in the lumbar-spine DXA image to provide an indirect index of trabecular microarchitecture and predicts fracture risk independent of BMD.[29] Age substantially alters the impact of TBS on FRAX® estimated risk in determining TBS-adjusted FRAX assessment. TBS adjustment of FRAX® has been validated in 14 prospective international cohorts.[30]

Evaluation includes risk stratification into "high risk" and "very high risk" groups to categorize patients for specific pharmacologic approaches.[2,3]

- High-risk:
  - Osteopenia and a history of fragility fracture of the hip or spine
  - Osteoporosis of spine, femoral neck, total hip, or 1/3 radius
  - Osteopenia and FRAX 10-year probability for major osteoporotic fracture ≥20%, hip fracture ≥3%
- Very high-risk:
  - A recent fracture, fractures while on approved osteoporosis therapy, multiple fractures, fractures while on drugs causing skeletal harm
  - Very low T-score (less than -3.0)
  - High risk for falls or history of injurious falls
  - FRAX probability for major osteoporosis fracture >30%, hip fracture >4.5%

Measurement of bone microstructure and strength by means of high-resolution peripheral quantitative CT (HRpQCT) predicts fracture risk regardless BMD, but is not FDA-approved for diagnosis.[31] Recent data indicate that measuring bone turnover markers (BTM) as an alternative non-invasive test might have a role in the prediction of fracture risk and monitoring treatment, but they have multiple drawbacks and low specificity. BTM are peptides, produced by osteoblasts, osteocytes, and osteoclasts which are released into the circulation during the process of bone remodelling.[6] Bone formation markers reflecting osteoblast activity such as procollagen type N-terminal propeptide, and bone resorption markers are the products of collagen degradation such as serum C-terminal crosslinking telopeptide.[32]

Management of postmenopausal osteoporosis

Aim of the treatment is to prevent fractures in postmenopausal women, as primary or secondary prevention. Lifestyle modifications are applicable to all the cases. Pharmacologic options are directed according to the individual patient status and fracture risk stratification.[2,3]

Lifestyle measures-

- Adequate intake of calcium and vitamin D (1000-1200mg of calcium and 400-1000 IU of vitamin D daily).[2] Source of calcium is preferably from diet, but supplementations of calcium and vitamin D can be taken if required. Daily requirements of calcium and vitamin D for women ≥50 years of age are 1200 mg/day and 1000-2000 IU/day, respectively.[3] Serum vitamin D levels are recommended to be adjusted, at least ≥20 ng/ml prior to initiating the drug treatment.[3,33] All patients should maintain adequate ongoing calcium and vitamin D intake while on treatment.

- Prohibition of smoking, excessive alcohol (≤2 units/ day is allowed) and limited intake of caffeine.
- Adequate protein intake (0.8 gm/kg daily) and consuming a balanced diet.
- Performing regular weight-bearing and balance exercises (at least 3-4 days weekly).
- Measures to be taken for prevention of falls.

Pretreatment evaluation

Hypocalcaemia, vitamin D deficiency, and renal impairment must be assessed by measuring serum calcium, 25-hydroxyvitamin D (25[OH]D) and creatinine.

Pharmacologic approaches-

The threshold for starting therapy as well as the choice and duration of treatment may vary in different guidelines. But generally, the recommendations are consistent with the guidelines of the Endocrine Society and the Bone Health and Osteoporosis Foundation.[2,3] Antiresorptive therapies (mitigates bone resorption by osteoclasts) and anabolic (enhances bone formation by osteoblasts) agents for postmenopausal osteoporosis: -

a) Antiresorptive drugs:
   - Bisphosphonates (BP)
   - RANK ligand inhibitor- Denosumab
   - Conjugated equine oestrogen (CEE)
   - Selective oestrogen receptor modulator (SERM)

b) Anabolic agents: Parathyroid hormone (PTH) receptor agonists.
   - PTH analogue- Teriparatide (PTH 1-34)
   - PTH-rP analogue- Abaloparatide

c) Anabolic-antiresorptive therapy:
   - Sclerostin inhibitor- Romosozumab

Required information regarding these medications, their role and efficacy in the management of postmenopausal osteoporosis are briefly discussed below.

√ Bisphosphonates (BP) -

Nitrogen-containing BP (2nd and 3rd generation) are more potent and efficient than the simple BP to improve the bone mineral density (BMD), hence, used the most for treating osteoporosis.[34] They bind to bone hydroxyapatite, engulfed by osteoclasts leading to their apoptosis and therefore, inhibit bone resorption (particularly at sites of active bone remodelling). Thus, it can help to strengthen bones and reduce the risk of bone breaking. Oral bisphosphonates include alendronate (70mg/week or 10mg/day), risedronate (35mg/week or 150 mg/month), ibandronate (150mg monthly) and intravenous (IV) infusion of zoledronic acid (5mg/year) are the recommended options for postmenopausal osteoporosis. Alendronate, risedronate, and zoledronate reduce the risk of hip, spine and other nonvertebral fractures; whereas, ibandronate is effective mostly in reducing vertebral fractures.[35-37] Bisphosphonates reduce bone turn over, improve BMD and are considered as initial therapy for high-risk fracture group.[2,3] Serum calcium and vitamin D must be normalized prior to starting BP. Using BP is contraindicated in severe renal impairment (eGFR <30 ml/ min for risedronate and ibandronate or <35 ml/min for alendronate and zoledronate).

Bioavailability of oral BP is usually <1-2%, 50% of which exerts action and 50% is excreted unmetabolized in the urine.[34] Empty stomach ensures its maximum absorption; therefore, it must be taken alone on an empty stomach first thing in the morning with at least 240 ml of water and the patient should avoid any food, drink, medications, or supplements and remain upright for at least 30 minutes (alendronate, risedronate) or 1 hour (ibandronate). Half-life of BP is about one hour. Enteric-coated, delayed-release risedronate can be taken immediately after breakfast with 120 ml of water.[38] GI irritation can occur with oral bisphosphonates. Oral BP should not be given if any active upper gastrointestinal disease, oesophagitis, oesophageal varices or dysmotility is present. IV zoledronic acid has the highest bioavailability, potency and efficacy as used in postmenopausal osteoporosis. It can be considered as an alternative when oral BP are not tolerated or contraindicated. Creatinine clearance should be calculated before zoledronate infusion. It is given as slow infusion for at least 15 minutes, can be extended up to 45-60 minutes to avoid flu-like symptoms and can be treated with acetaminophen or ibuprofen.[39] Infusion may cause such acute-phase reaction in 30% patients at first dose.[3] Patient needs to be adequately hydrated while taking the infusion. Osteonecrosis of jaw (ONJ) and atypical femur fracture (AFF) are rare complications in usual dose of BP used in osteoporosis. However, 70% AFF of subtrochanteric region reported prodromal groin/thigh pain; hence, any patient having BP therapy with such presentation warrants immediate interruption of the drug.

Monitoring of treatment is done by doing a baseline DXA and then, 1-2 yearly while on treatment. Duration of therapy should be individualized based upon patient characteristics and preferences as well as clinical risk of

subsequent fractures. Usually, treatment is continued for 3 years (treated with IV zoledronate) to 5 years (treated with oral BP) for the patients having high risk of fracture, and, 6 years (with IV zoledronate) to 10 years (with oral BP) for women having very high risk of fracture.[3] Durability of antiresorptive effect beyond their period of use due to prolonged binding to mineral matrix and strong affinity to calcium ions leading to the 'recycling' potential (Zoledronate>Alendronate>Risedronate) is a unique feature of bisphosphonates.[4]

Bisphosphonate drug holidays- It is recommended for long-term treatment with BP and aims to reduce the risk of atypical femur fractures (AFF) while maintaining durability potential of BP in the prevention of fragility fractures. Duration-dependent association between BP use and AFF is seen recently.[40] This temporary treatment break is considered generally after 3-5 years of BP therapy, if BMD is stable.[2] Zoledronate after 6 annual infusions and 5 years of weekly alendronate showed much reduction in fractures for longer duration following discontinuation of the drug (residual therapeutic effect of BP), whereas faster (low BMD at total hip after 1-year holiday) offset of antiresorptive effect of risedronate results in more frequent fractures.[4] Although several studies showed fracture detection within 6 months of drug holiday, but the decline of BMD was found most significant after 3 years of drug holiday.[3,4] DXA of hip, lumbar spine and distal radius is usually done during drug holidays. Bone turnover markers (BTM) can also be considered to assess the length of drug holidays; include serum procollagen type I N-propeptide (P1NP) as the marker of bone formation and C-terminal telopeptide of type I collagen (CTX) as marker for resorption. However, they could not predict loss of bone density in women undertaking a drug holiday in a UK cohort.[41] Risk-factors for holiday-related fractures include older age, low hip BMD, underweight, low medication adherence, and incident fractures.[4] Resumption of bisphosphonates following drug holidays should be considered if there is reproducible bone loss (approximately 5%) on at least 2 DXA (dual-energy x-ray absorptiometry) measurements taken at least 2 years interval, using the same make and model DXA scanner; or, significant decline of BMD on single DXA measurement both at the spine and hip; or, evidence of bone loss on one DXA measurement at either site along with a rising resorption marker (fasting CTX >600 pg/ml). Thus, duration of drug holidays is variable and individualized.

ONJ has been reported at a rate of 1 to 69 per 100,000 person-yr and 0 to 90 per 100,000 person-yr with oral and IV bisphosphonates, respectively. AFF has been reported at a rate of 1.78 per 100,000 person-yr with <2 years of getting BP, increasing to 113.1 per 100,000 person-yr after 8-10 years of BP therapy.[42] The risk of AFF is likely to be higher among Asian women than among White women.[40]

√Denosumab-

Human monoclonal antibody that binds to receptor activator of nuclear factor-κB ligand (RANKL) which reversibly inhibits osteoclast formation, function and

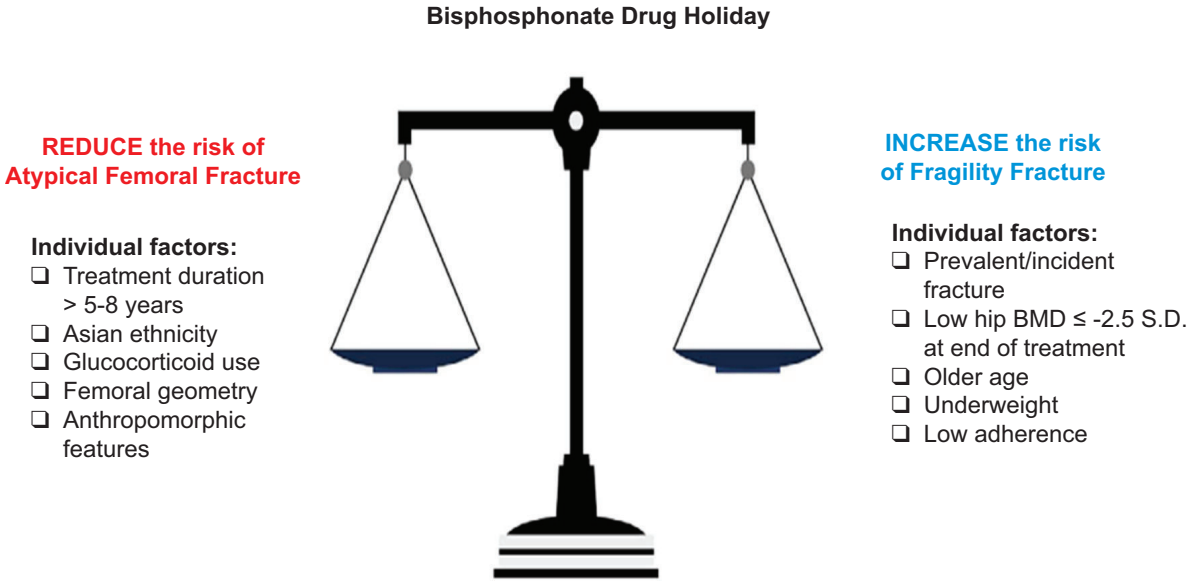

Figure 4: *Weighing up the risk of fragility fracture versus AFF*[4]

survival. It is more effective than bisphosphonates to some extent in improving BMD as well as reducing vertebral, hip and non-vertebral fracture risk.[1-3] Therefore, considered as initial therapy in both high-risk and very-high risk fracture group. It is given as 60 mg 6 monthly subcutaneous injection and contraindicated in hypocalcemia and vitamin D deficiency. Unlike bisphosphonates, it can be given in renal impairment; also preferred in the conditions where bisphosphonates are intolerable.[3] Rebound bone loss and fractures occur after stopping the drug is a major concern.[2] Hence, it must be continued indefinitely or requires transition to bisphosphonates 6 months following the last dose of denosumab to maintain stable BMD, but switching to teriparatide should be avoided owing to bone loss.[3] Reassessing fracture risk after 5-10 years of denosumab is suggested.[2]

√ Teriparatide and Abaloparatide-

These anabolic agents act as PTH receptor agonists to increase bone formation and results faster gain of BMD in DXA scan; hence, recommended as initial therapy for very high-risk fracture group.[3] They significantly reduce vertebral and non-vertebral fracture risk, but role in risk reduction of hip fracture is not established.[2] It is contraindicated in hypercalcaemic conditions. Abaloparatide is not available in Bangladesh yet. They are given as daily subcutaneous injection (20μg Teriparatide, 80μg Abaloparatide) for 2 years in lifetime as longer use may cause increased risk for osteosarcoma in some cases.[2] Therefore, treatment completion with anabolic agents requires to be followed by any antiresorptive therapy (Bisphosphonates/Denosumab) to maintain further BMD. Good response leads to increase bone formation markers. Treatment with teriparatide combined with bisphosphonates or denosumab to gain BMD is not recommended.[2]

√ Romosozumab-

Human monoclonal antibody against sclerostin acts by decreasing bone resorption and increasing bone formation leading to improve bone mass. It is the newest FDA-approved therapeutic for postmenopausal osteoporosis, given as 210 mg monthly subcutaneous injection for 12 months in lifetime. Then, treatment must be followed by antiresorptive therapy (BP/Denosumab);[2] duration of romosozumab therapy is limited to 12 months due to its cardiovascular risks and recommended only for the very high-risk for fracture patients. It is contraindicated in individual with cardiovascular risk profile, recent stroke/MI, hypocalcemia and vitamin D deficiency. In a head-to-head comparison of teriparatide and romosozumab for 1 year, it was revealed that romosozumab has more potency and faster anabolic effect with less occurrence of hypercalcaemia.[32] In the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME), romosozumab could cause much reduction in the risk of vertebral and non-vertebral fractures at 12 months of therapy as compared with placebo as well as in another trial, it was found that romosozumab for 1 year followed by alendronate for 1 year significantly reduced vertebral, non-vertebral and hip fractures compared to alendronate alone for 2 years.[2]

√ Other antiresorptive agents-

Oestrogens (CEE) decrease osteoclastic bone resorption and reduce vertebral, hip, non-vertebral fracture risk; are given as 0.625 mg daily orally. It is approved for the prevention of postmenopausal osteoporosis; avoided in history of breast cancer, active liver disease and venous thromboembolic (VTE) conditions. Hormone replacement therapy (HRT) can be used in women <60 years of age or within 10 years of menopause having vasomotor symptoms.[2,3]

Selective oestrogen receptor modulator (SERM) having weak oestrogen agonist activity that reduces bone resorption at given dose of 60 mg daily orally (Raloxifene). Bazedoxifene 20 mg plus conjugated oestrogen 0.45 mg once daily orally is approved for prevention of postmenopausal osteoporosis. SERM can reduce the risk of vertebral fractures only; hence, considered appropriate only when other therapeutic options are not available or contraindicated. It must be avoided if history of VTE is present.[2]

Calcitonin is a very weak anti-resorptive agent causing minimal increase of BMD in the spine only, when used >5 years after menopause onset.[3] It can be given as intranasal spray (200 IU/day) or subcutaneous injection (100 IU/day).[19] Calcitonin is rarely recommended for postmenopausal osteoporosis and preferred to be chosen if all the other therapeutic options become inappropriate, or significant adverse effects occur with each of the drugs discussed above.[2]

Drugs in pipeline

Multiple drugs are emerging for the treatment of postmenopausal osteoporosis which are at different stages of clinical trials at present, as briefly mentioned below.[43]

HLX14, a recombinant anti-RANKL human monoclonal antibody injection having denosumab biosimilar properties which can decrease bone resorption to improve bone mass

and strength in both cortical and trabecular bones. Currently, it is in Phase III stage of clinical trial evaluation. CMAB807 is a denosumab, a human IgG2 monoclonal antibody with affinity and specificity for inhibition of human RANKL is currently undergoing phase III clinical trial. EBP05 or EB613 is the first and most advanced oral, daily tablet (6mm diameter) formulation teriparatide, a parathyroid hormone analogue. EB613 is positioned as the first potential anabolic drug which could provide a patient friendly, once daily, oral, bone building capacity. SHR-1222 is a novel humanized monoclonal antibody against sclerostin, currently is being evaluated in Phase II clinical trial for the treatment of postmenopausal osteoporosis.

Conclusion:

Postmenopausal osteoporosis is a chronic condition affecting millions of women worldwide. It occurs due to oestrogen deficiency and results in fragility fractures. In conjunction with non-pharmacologic strategies, several drugs are available for the management of this condition according to the fracture risk stratification and individual patient characteristics. Multiple newer agents in treating osteoporosis have shown their efficacy as well. But, cost-effectiveness and side-effects of these traditional as well as newer therapies for osteoporosis management should be kept in mind to determine the drug of choice, dose and duration of treatment. Since postmenopausal osteoporosis is getting to be much prevalent among Asian countries in coming decades; it requires rightly taken approaches directed to its diagnosis, appropriate measures and monitoring of treatment in order to reduce the disease burden.

References:

1. Long G, Liu C, Liang T, et al. Predictors of osteoporotic fracture in postmenopausal women: a meta-analysis. J Orthop Surg Res. 2023 Aug 5;18(1):574-83.
2. Walker MD, Shane E. Postmenopausal Osteoporosis. N Engl J Med. 2023 Nov 23;389(21):1979-91.
3. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis-2020 Update. Endocr Pract. 2020 May;26(1):1-46.
4. Wang M, Wu YF, Girgis CM. Bisphosphonate Drug Holidays: Evidence From Clinical Trials and Real-World Studies. JBMR Plus. 2022 May 24;6(6):e10629.
5. Huang CF, Chen JF, Reid IR, et al. Asia-pacific consensus on osteoporotic fracture prevention in postmenopausal women with low bone mass or osteoporosis but no fragility fractures. J Formos Med Assoc. 2023;122(1):S14-S20.
6. Tournis S, Makris K. Clinical Use of Bone Turnover Markers in Osteoporosis. Biomedical Sciences. 2018. Available at: https://doi.org/10.1016/B978-0-12-801238-3.99538-2
7. Zhivodernikov IV, Kirichenko TV, Markina YV, et al. Molecular and Cellular Mechanisms of Osteoporosis. International Journal of Molecular Sciences. 2023;24(21): 15772.
8. Vrachnis N, Zygouris D, Vrachnis D, et al. Effects of Hormone Therapy and Flavonoids Capable on Reversal of Menopausal Immune Senescence. Nutrients. 2021;13(7):2363.
9. Cheng C-H, Chen L-R, Chen K-H. Osteoporosis Due to Hormone Imbalance: An Overview of the Effects of Estrogen Deficiency and Glucocorticoid Overuse on Bone Turnover. International Journal of Molecular Sciences. 2022;23(3):1376.
10. Wang L-T, Chen L-R, Chen K-H. Hormone-Related and Drug-Induced Osteoporosis: A Cellular and Molecular Overview. International Journal of Molecular Sciences. 2023;24(6):5814.
11. Tian H, Jiang, T, Yang, K, et al. á-Asarone Attenuates Osteoclastogenesis and Prevents Against Oestrogen-Deficiency Induced Osteoporosis. Front. Pharmacol. 2022;13:780590.
12. Zhang J, Fu Q, Ren Z, et al. Changes of Serum Cytokines-Related Th1/Th2/Th17 Concentration in Patients with Postmenopausal Osteoporosis. Gynecol. Endocrinol. 2015;31:183-90.
13. Molnár I, Bohaty I, Somogyiné-Vári É. IL-17A-Mediated SRANK Ligand Elevation Involved in Postmenopausal Osteoporosis. Osteoporos. Int. 2014;25:783-86.
14. Zhao R, Wang X, Feng F. Upregulated Cellular Expression of IL-17 by CD4+ T-Cells in Osteoporotic Postmenopausal Women. Ann. Nutr. Metab. 2016;68:113-18.
15. Bonaccorsi G, Piva I, Greco P, et al. Oxidative Stress as a Possible Pathogenic Cofactor of Post-Menopausal Osteoporosis: Existing Evidence in Support of the Axis Oestrogen Deficiency-Redox Imbalance-Bone Loss. Indian J. Med. Res. 2018;147:341-51.
16. Filipovi´c B, Šoši´c-Jurjevi´c B; Ajd•anovi´c V, et al. The Effects of Sex Steroids on Thyroid C Cells and Trabecular Bone Structure in the Rat Model of Male Osteoporosis. J. Anat. 2013;222:313-20.
17. Haglund F, Ma R, Huss M, et al. Evidence of a Functional Estrogen Receptor in Parathyroid Adenomas. J. Clin. Endocrinol. Metab. 2012;97:4631-39.
18. Sabri SA, Chavarria JC, Ackert-Bicknell C, et al. Osteoporosis: An Update on Screening, Diagnosis, Evaluation, and Treatment. Orthopedics. 2023;46:e20-e26.
19. Paula FJAD, Black DM, Rosen CJ. Osteoporosis: Basic and Clinical Aspects. In: Melmed S, Auchus RJ, Goldfine AB (Eds). Williams Textbook of Endocrinology. 14th ed. Philadelphia: Elsevier Publishing; 2020. P1256-1297.
20. Looker AC, Sarafrazi Isfahani N, Fan B, Shepherd JA. Trends in osteoporosis and low bone mass in older US adults, 2005-

2006 through 2013-2014. Osteoporos Int. 2017;28: 1979-88.

21. Sarafrazi N, Wambogo EA, Shepherd JA. Osteoporosis or low bone mass in older adults: United States, 2017–2018. NCHS data brief. No 405. Hyattsville, MD: National Center for Health Statistics, 2021.
22. Dyer SM, Crotty M, Fairhall N, et al. A critical review of the long-term disability outcomes following hip fracture. BMC Geriatr. 2016;16:158.
23. LeBlanc ES, Hillier TA, Pedula KL, et al. Hip fracture and increased short-term but not long-term mortality in healthy older women. Arch Intern Med. 2011;171:1831-37.
24. Lewiecki EM, Ortendahl JD, Vanderpuye-Orgle J, et al. Healthcare policy changes in osteoporosis can improve outcomes and reduce costs in the United States. JBMR Plus. 2019;3(9):e10192.
25. Cheung CL, Ang SB, Chadha M, Chow ES, Chung YS, Hew FL, et al. An updated hip fracture projection in Asia: the Asian Federation of Osteoporosis Societies study. Osteoporos Sarcopenia. 2018;4(1):16-21.
26. Pisani P, Renna MD, Conversano F, et al. Major osteoporotic fragility fractures: risk factor updates and societal impact. World J Orthoped. 2016;7(3):171-81.
27. Dhanwal DK, Dennison EM, Harvey NC, et al. Epidemiology of hip fracture: worldwide geographic variation. Indian J Orthop. 2011;45(1):15-22.
28. Alexandru D, So W. Evaluation and management of vertebral compression fractures. Perm J. 2012;16(4):46-51.
29. Silva BC, Leslie WD, Resch H, et al. Trabecular bone score: a noninvasive analytical method based upon the DXA image. J Bone Miner Res. 2014;29:518-30.
30. McCloskey EV, Odén A, Harvey NC, et al. A meta-analysis of trabecular bone score in fracture risk prediction and its relationship to FRAX. J Bone Miner Res. 2016;31:940-48.
31. Samelson EJ, Broe KE, Xu H, et al. Cortical and trabecular bone microarchitecture as an independent predictor of incident fracture risk in older women and men in the Bone Microarchitecture International Consortium (BoMIC): a prospective study. Lancet Diabetes Endocrinol. 2019;7:34-43.
32. Shoback D, Rosen CJ, Black DM, et al. Pharmacological management of osteoporosis in postmenopausal women: an endocrine society guideline update. J Clin Endocrinol Metab. 2020;105:587-94. Available at doi: 10.1210/clinem/dgaa048
33. LeBoff MS, Greenspan SL, Insogna KL, et al. The clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2022;33:2049-102.
34. Ruggiero A, Triarico S, Romano A, et al. Bisphosphonates: From Pharmacology to Treatment. Biomed Pharmacol J. 2023;16(1).
35. Crandall CJ, Newberry SJ, Diamant A, et al. Comparative effectiveness of pharmacologic treatments to prevent fractures: an updated systematic review. Ann Intern Med. 2014;161:711.
36. Barrionuevo P, Kapoor E, Asi N, et al. Efficacy of Pharmacological Therapies for the Prevention of Fractures in Postmenopausal Women: A Network Meta-Analysis. J Clin Endocrinol Metab. 2019;104:1623.
37. Freemantle N, Cooper C, Diez-Perez A, et al. Results of indirect and mixed treatment comparison of fracture efficacy for osteoporosis treatments: a meta-analysis. Osteoporos Int. 2013;24:209.
38. McClung MR, Balske A, Burgio DE, et al. Treatment of postmenopausal osteoporosis with delayed-release risedronate 35 mg weekly for 2 years. Osteoporos Int. 2013;24:301.
39. Wark JD, Bensen W, Recknor C, et al. Treatment with acetaminophen/paracetamol or ibuprofen alleviates post-dose symptoms related to intravenous infusion with zoledronic acid 5 mg. Osteoporos Int. 2012;23:503.
40. Black DM, Geiger EJ, Eastell R, et al. Atypical femur fracture risk versus fragility fracture prevention with bisphosphonates. N Engl J Med. 2020;383(8):743-53.
41. Roberts J, Castro C, Moore AE, et al. Changes in bone mineral density and bone turnover in patients on 'drug holiday' following bisphosphonate therapy: real-life clinic setting. Clin Endocrinol (Oxf). 2016;84(4):509-15.
42. Siu A, Allore H, Brown D, et al. National Institutes of Health pathways to prevention workshop: research gaps for long-term drug therapies for osteoporotic fracture prevention. Ann Intern Med. 2019;171:51-57.
43. Postmenopausal osteoporosis - Pipeline Insight, Nov 2023. Available at:

CASE REPORT

Oral Ulcers: A Case Series

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Abstract

Mouth ulcers, most generally aphthous ulcers, are quite common in all age groups. They can be linked to several conditions, such as a blunt injury due to acute trauma, sharp edges of a tooth, or an autoimmune disease. The underlying causes of recurrent aphthous stomatitis remain poorly understood. Oral difficulties can result from improper medication use, weakened immunity, local and systemic inflammation, and negligence of oral hygiene as seen during COVID-19 treatment. Diagnosis is usually made after clinical oral examination. Management of these mouth ulcers depends on the clinical presentation and symptoms and comprises a range of topical medications, including antibiotics. A clinician's approach to oral health care and clinical oral examinations will be beneficial for treatment and recovery. The objective of this study was to evaluate the pathophysiology, prevention, and treatment of oral mucosal ulcers.

Keywords: Aphthous stomatitis, Clinical oral examination, Mouth ulcers

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Introduction:

Recurrent aphthous stomatitis, affecting the oral mucosa, is characterized by recurrent single or multiple, discrete, painful ulcers that routinely heal within 7–14 days.[1]

The pathogenesis is indistinct and is reasonably multifactorial with some evidence to aid the idea of immune dysregulation resulting in an exaggerated pro-inflammatory process, or a relatively weak anti- inflammatory response.[2]

A number of types of oral mucosal lesions, including lichen planus and recurrent aphthous stomatitis, have been reported in patients having diabetes mellitus. Not all study results have presented this association, and these are moderately frequent disorders that are seen in patients who do not have diabetes.[3,4]

The most common signs of COVID-19 were fever, cough, dyspnea, and in severe cases, even death. Cases of COVID-19 extrapulmonary symptoms, including oral signs have been reported.[5,6, 7.]

Patients with oral mucosal signs present with a variety of oral pathologies. The most common continuous lesions accounted for 73.85%, including ulcer 55.38%, aphthous lesions 12.31%, erosion 6.15%, followed by macula 6.15%, petechiae 4.61%, plaque 4.61%, bullae 3.08%, the least is gingival abnormalities. Among the patients with oral mucosal lesions, the most common site is tongue (52.56%), followed by palate and lip (16.67%), gingival (7.69%), buccal mucosa (3.85%), and connective site (2.56%).[8]

Other than the immunosuppressive drugs in COVID-19 patients, the prolonged prone positioning and mechanical ventilation devices are primary risk factors for the oral complications in post-COVID patient. Maintenance of oral hygiene was found to be effective in preventing ventilator-associated pneumonia in critically ill patients.[9] The majority of the patients reportedly experienced oral mucosal lesions within 10 days of COVID infection.[10, 11]

Elderly, long-term hospitalized, unhygienic or diabetic people tend to have oral mucosal lesions, and these individuals are more likely to have more severe, long-lasting, and wide-ranging oral lesions.[12] In addition, it had been stated that aphthous-like lesions, herpes-like lesions, fungal infections (candidiasis and mucormycosis), herpes simplex virus (HSV) reactivation-related ulcers, oral herpes zoster and gingivitis are frequently seen.[10, 12, 13]

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Our case series is emphasized on the clinical characteristics and underlying mechanisms of oral ulcers, in order to help clinicians diagnose patients exhibiting oral symptoms.

Case series

Case Report no. 1

We report the case of a 64 year old female diabetic patient.

On oral examination, we found out minor aphthous ulcer at the floor of the mouth and dental caries. Patient also complains of hyposalivation and burning sensation in the mouth and tongue.

Non-invasive treatment was carried out. She was treated with chlorhexidine oral gel applied on affected areas twice daily for seven days. Additionally, povidone iodine mouthwash was prescribed thrice daily for seven days. Vitamin B complex supplements were also advised.

The patient was followed up with disappearance of aphthous ulcer seven days later.

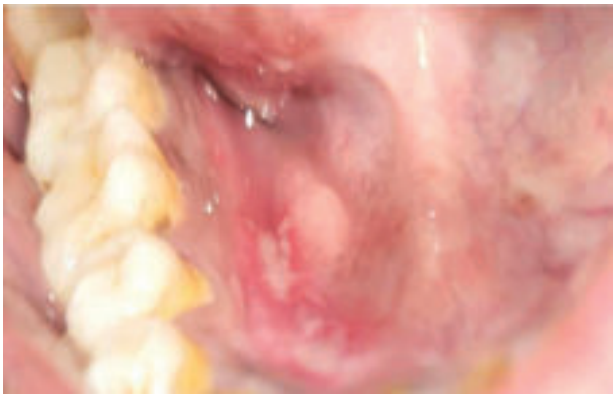

Figure-1: *Aphthous ulcer at the floor of the mouth*

Case Report No. 2

A 60 year old male reported to the outdoor department of Dentistry of our hospital with the complaints of oral ulcers on the lips and aphthous stomatitis lasting for one week. He had a burning sensation in the mouth, which was present on intake of hot and spicy food. There was no history of previous episodes of oral ulceration. Fever and malaise accompanied the oral lesions.

The intraoral examination yielded painful lesions located mainly along the upper and lower lip. Aphthous stomatitis was also present on the hard palate, causing difficulty to eat.

He was advised povidone iodine mouthwash thrice daily for seven days and vitamin B complex supplements.

After 7 days, there was satisfactory improvement of the oral lesions.

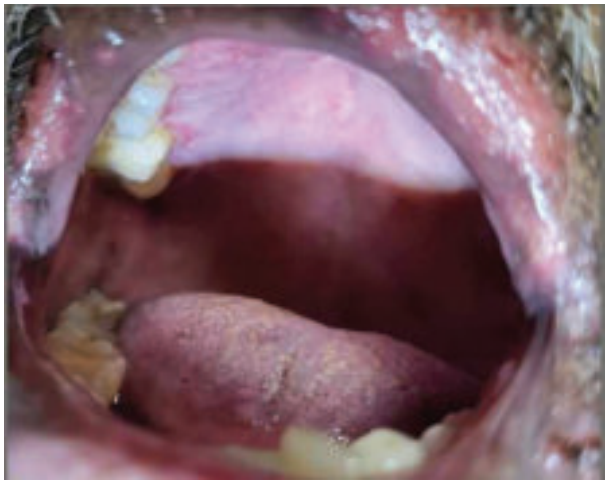

Figure-2: *Erythematous ulcer with irregular margins on the lips*

Case Report No. 3

On examination of the oral mucus membrane of a 27 year old male doctor, there were multiple aphthous ulcers on the inner aspect of upper and lower lips, buccal mucosa and dorsal tongue. The recurrent ulcers depict an erythematous halo with a white pseudomembrane.

He was treated by rinsing with 250 mg tetracycline powder mixed with water thrice a day for 3 days and povidone iodine solution as mouthwash. He was also prescribed vitamin B complex supplements.

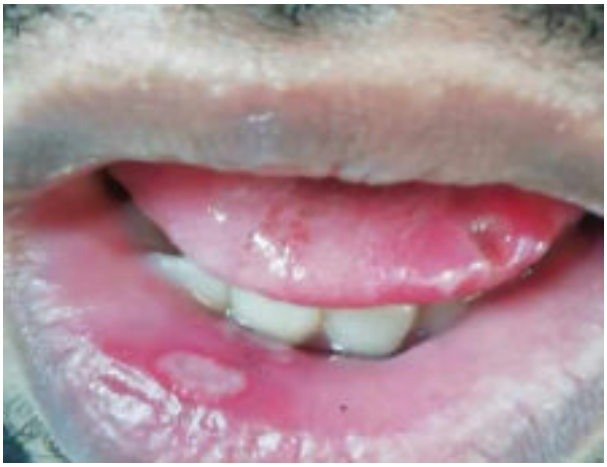

Figure.-3: *Ulcer lesions on the inferior labial mucosa and dorsal lingua*

Case Report No. 4

A 66-year-old female patient admitted in medicine department, with a history of post COVID-19-related

pneumonia needed a dental consultation. She had taken systemic steroids during her COVID treatment.

On clinical examination we found out oral lesions at the dorsal surface of her tongue, specifically in the middle third, in the form of painful haemorrhagic ulceration and fissure. Severe oral ulcer was associated with exudate at the circumvallate papillae of dorsum tongue. Unilateral reddish lesion at the labial commisure indicated the presence of angular stomatitis. Since she could not eat due to pain, she used the chlorhexidine oral gel that was prescribed on affected areas on her gum and tongue twice daily for seven days. Povidone iodine mouthwash was also prescribed thrice daily for seven days.

The patient was followed up with disappearance of the hemorrhagic ulceration without scarring seven days later. The patient felt better and only complained of burning on her tongue while eating hot food.

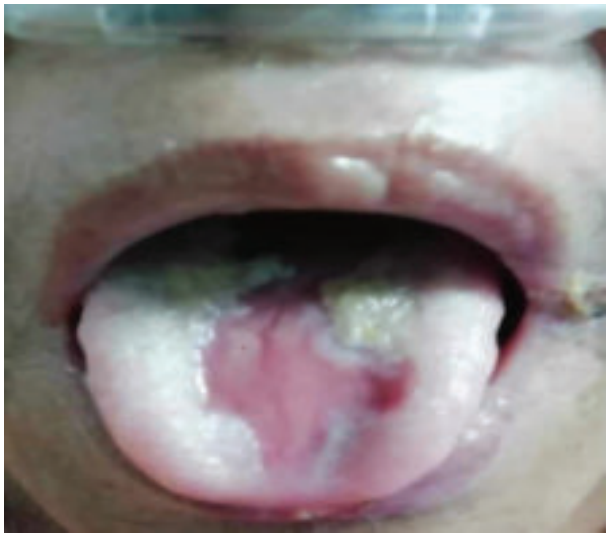

Figure-4: *Depapillated area on the dorsal surface and purulent exudate on the posterior part of the tongue.*

Discussion:

There are four phases in the development of recurrent aphthous stomatitis, the first of which takes place during the first 24 hours following the development of a recurrent aphthous stomatitis lesion and initially manifests as a burning mouth feeling in the patient. Oedema starts to form and the pre-ulceration stage follows. This lasts between 18 to 72 hours (3 days). During this period, discomfort becomes intense. Papules and macules with erythematous borders form at the affected location. Papules and macules ulcerate in the ulcerative stage, which persists for 1 to 16 days, and these ulcers are then covered by a fibro membranous layer. Only then will there be a decrease in pain intensity. Typically, the lesions heal without leaving any scars in 10 to 21 days. The epithelium covers the ulcer.[14]

Because of its uncertain etiology and various clinical presentations, aphthous stomatitis remains a challenge for the oral and maxillofacial health care professionals. Most patients with recurrent aphthous stomatitis need no treatment because of the mild nature of the disease. Some manage with maintenance of good oral hygiene.[15]

In the first case report of our study, we found aphthous ulcers in the diabetic female patient. A case-control study reported a prevalence of 22% for ulcerative lesions in the oral cavity among patients with diabetes type 2.[16] Other lesions (angular cheilitis and fissured tongue) found in the study facilitate the emergence of opportunistic infections such as candidiasis.[17]

Burning sensation or dysesthesia in the oral cavity of diabetic patients is attributed to poor glycemic control, metabolic alterations in oral mucosa, angiopathy, candida infection, and neuropathy.[18]

Some oral mucosa alterations such as coated and fissured tongue, geographic tongue, recurrent aphthous stomatitis, and some premalignant lesions including lichen planus can be associated with diabetes.[18-21]

Viral and bacterial infections, systemic diseases, hormonal imbalance, mechanical trauma and stress are examples of factors that alter the immune responses in recurrent aphthous stomatitis.[22, 23]

Some cases of recurrent aphthous stomatitis are caused by psychological stress that can cause recurrent ulcers in the oral cavity. Recurrent aphthous stomatitis in the patient of our third case report was brought on by psychological stress situations caused by familial problems and gastritis.

For the hypothalamus to release CRH (corticotropic releasing hormone), psychosocial stress stimulates the central nervous system. The pituitary gland is then stimulated by CRH to produce the hormone ACTH (adrenocorticotropic hormone). Aldosterone is produced in the glomerular zone by the adrenal cortex when ACTH stimulates it. Aldosterone helps maintain the body's electrolyte balance by acting on NA+ and K+, and it also causes the vascular zone to create cortisol. IgA, IgG, and neutrophil activities are suppressed by glucocorticoids found in cortisol. IgA functions to bind viruses and bacteria, preventing them from sticking to the mucosa. Stress causes IgA to work less efficaciously, which make it easier for micro-organisms to bind to the mucosa and invade, increasing susceptibility to infection.[14]

In order to enact phagocytosis, which involves the killing and removal of micro-organisms, neutrophils are required. As a result, when there is a decrease in neutrophils, phagocytosis and the capacity to kill microorganisms are also reduced.[14] When under stress, the adrenal cortex releases cortisol, which alters the balance of type 1/type 2 cytokines toward a type 2 response by lowering the production of IFN-ã (type 1 cytokine) and multiplying the production of IL-10 (type 2 cytokine).[24] In recurrent aphthous stomatitis, there are a number of immune responses that occur in effect, including a reduction in the number of CD4 lymphocytes and a change in the CD4:CD8 ratio, a reduction in CD4-CD25 Treg regulatory activity, an elevation in the number of B lymphocytes and T cells, an increase in the complement system, a rise in the number of NK cells, a reactivation and hyperreactivity of neutrophils, pro-inflammatory cytokines generated by Th1 and IL-2, IL-12, IFN gamma, and TNF- were expressed more frequently than anti-inflammatory cytokines produced by Th2 and TGF.[25]

Multivitamins and minerals serve a purpose by repairing the immune system, stimulating faster wound healing, and forming connective tissue. Thiamine, riboflavin, and niacin are vitamins that help with carbohydrate metabolism. Pyridoxine helps with protein and glycogen metabolism. Vitamins B12 (cobalamin), folic acid, and pantothenic acid help with red blood cell formation and DNA synthesis. Zinc has roles in glucose metabolism, cell regeneration, hastening the regeneration of injured tissue, and promoting wound healing.[25]

In addition to systemic treatment according to the symptoms felt by the patient, counseling and psychotherapy can be employed to treat individuals with recurrent aphthous stomatitis linked with psychological stress.[26]

The critically ill patients suffering from COVID-19 and admitted to the intensive care units (ICUs) are susceptible to a wide array of complications of which oral mucocutaneous problem is one of the important complications. Yet the oral complication is often being neglected. In the fourth case report, we described the clinical characteristics of the oral lesions in a post COVID-19 patient. A multidisciplinary approach to oral health care and clinical oral examinations for COVID-19 patients will be beneficial for treatment and recovery.[27]

Conclusions:

Everyone with diabetes should have good oral hygiene and regular dental checkup.

Eliminating the stress-causing variables is one of the basic therapies for aphthous stomatitis linked with psychological stress.

A multidisciplinary approach is strongly advocated for the monitoring and management of COVID-19 patients.

This paper highlights the importance of integrating dermatology and stomatology into the treatment of improving the oral health and rehabilitation of patients with oral mucosal complications.

References:

1. Edgar NR, Saleh D, Miller RA. Recurrent aphthous stomatitis: A review. *J ClinAesthetDermatol*. 2017;10:26-36
2. Slebioda Z, Szponar E, Kowalska A. Etiopathogenesis of recurrent aphthous stomatitis and the role of immunologic aspects: Literature review. *Arch ImmunolTherExp (Warsz)*. 2014;62:205-15
3. Yuen HK, Wolf BJ, Bandyopadhyay D, Magruder KM, Salinas CF, London SD. Oral health knowledge and behavior among adults with diabetes. Diabetes Res ClinPract. 2009 Dec;86(3):239-46. doi: 10.1016/j.diabres.2009.09.010.
4. MasoodMirza K, Khan AA, Ali MM, Chaudhry S. Oral health knowledge, attitude, and practices and sources of information for diabetic patients in Lahore, Pakistan. Diabetes Care. 2007 Dec;30(12):3046-7.
5. Chen, N., Zhou, M., Dong, X., et al. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 395, 507–513. doi: 10.1016/S0140-6736(20)30211-7
6. Rodriguez-Morales, A. J., Cardona-Ospina, J. A., Gutiérrez-Ocampo, E., et al. (2020). Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med. Infect. Dis. 34:101623. doi: 10.1016/j.tmaid.2020.101623
7. da Rosa Mesquita, R., Francelino Silva Junior, L. C., Santos Santana, F. M., et al. (2021). Clinical manifestations of COVID-19 in the general population: Systematic review. Wien. Klin. Wochenschr. 133, 377–382. doi: 10.1007/s00508-020-01760-4
8. Egido-Moreno S., Valls-Roca-Umbert J., Jané-Salas E., López-López J., Estrugo-Devesa A. (2021). COVID-19 and Oral Lesions, Short Communication and Review. *J. Clin. Exp. Dent* 13, e287–e294. 10.4317/jced.57981
9. Zhao, T.; Wu, X.; Zhang, Q.; Li, C.; Worthington, H.V.; Hua, F. Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia. *Cochrane Database Syst. Rev.* 2020, *12*, CD008367
10. Amorim dos Santos, J., Normando, A. G. C., Carvalho da Silva, R. L., et al. (2021a). Oral manifestations in patients with COVID-19: A living systematic review. J. Dent. Res. 100, 141–154. doi: 10.1177/0022034520957289

11. Brandão, T. B., Gueiros, L. A., Melo, T. S., et al. (2021). Oral lesions in patients with SARS-CoV-2 infection: Could the oral cavity be a target organ? Oral Surg.Oral Med. Oral Pathol. Oral Radiol. 131, e45–e51. doi: 10.1016/j.oooo.2020.07.014

12. Iranmanesh, B., Khalili, M., Amiri, R., Zartab, H., and Aflatoonian, M. (2021). Oral manifestations of COVID-19 disease: A review article. Dermatol. Ther. 34, e14578–e14578. doi: 10.1111/dth.14578

13. Orilisi, G., Mascitti, M., Togni, L., Monterubbianesi, R., Tosco, V., Vitiello, F., et al. (2021). Oral manifestations of COVID-19 in hospitalized patients: A systematic review. Int. J. Environ. Res. Public Health 18:12511. doi: 10.3390/ijerph182312511

14. Bankvall M. Recurrent Aphthous Stomatitis A study, with emphasis on host genetics, oral microbiota composition, and immunoregulatory networks. 1st ed. Maria Bankvall 2017, editor. Department of Oral Medicine and Pathology Institute of Odontology Sahlgrenska Academy at University of Gothenburg. Gothenburg, Sweden: John Wiley and Sons Ltd; 2017. 14–16 p.

15. CASIGLIA JM. Recurrent aphthous stomatitis: Etiology, diagnosis and treatment. Gen Dent. 2002; 50:157-166.

16. Bajaj S, Prasad S, Gupta A, Singh VB. Oral manifestations in type-2 diabetes and related complications. Indian J EndocrinolMetab. 2012;16:777-9.

17. Vernillo AT. Dental considerations for the treatment of patients with diabetes mellitus. J Am Dent Assoc. 2003;134:24S-33S

18. Cicmil S, Mladenoviæ I, Kruniæ J, Ivanoviæ D, Stojanoviæ N. Oral Alterations in Diabetes Mellitus. Balk J Dent Med. 2018;22:7-14.

19. Al-Maskari AY, Al-Maskari MY, Al-Sudairy S. Oral Manifestations and Complications of Diabetes Mellitus: A review. Sultan QaboosUniv Med J. 2011;11:179-186. [PubMed]

20. Mauri-Obradors E, Estrugo-Devesa A, Jané-Salas E, Viñas M, López-López J. Oral manifestations of DiabetesMellitus. A systematic review. Med Oral Patol Oral Cir Bucal. 2017;22:e586-e594.

21. Khan T. Oral manifestations and complications of diabetes mellitus: A review. Int J Med Health Res. 2018;4:50-52.

22. Chavan M, Jain H, Diwan N, Khedkar S, Shete A, Durkar S. Recurrent aphthous stomatitis: A review. J Oral Pathol Med. 2012;41(8):577–83.

23. Chiang CP, Yu-Fong Chang J, Wang YP, Wu YH, Wu YC, Sun A. Recurrent aphthous stomatitis – Etiology, serum autoantibodies, anemia, hematinic deficiencies, and management. J Formos Med Assoc. 2019;118(9):1279–89. Available from: https://doi.org/10.1016/j.jfma.2018.10.02

24. Brinkmann V, Kristofic C 1995 Regulation by corticosteroids of Th1 and Th2 cytokine production in human CD4+ effector T cells generated from CD45RO- and CD45RO+ subsets. *J Immunol* 155:3322-3328.

25. Sari RK, Ernawati DS, Soebadi B. Recurrent Aphthous Stomatitis Related To Psychological Stress, Food Allergy and Gerd. ODONTO Dent J. 2019;6:45.

26. Verma S, Srikrishna K, . S, et al. (February 13, 2023) Recurrent Oral Ulcers and Its Association With Stress Among Dental Students in the Northeast Indian Population: A Cross-Sectional Questionnaire-Based Survey. Cureus 15(2): e34947. doi:10.7759/cureus.34947

27. Song W, Bo X, Patil S, Zeng J. Oral health interventions: Is it important for COVID-19 patients? *Asia Pac J Public Health*. 2022; 34(8):860-863.

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