Rs.10

JIMA

Volume 68 (RNI) ♦ Number 03 ♦ MARCH 2024 ♦ KOLKATA

JOURNAL *Of the* INDIAN MEDICAL ASSOCIATION

Official Publication of the Indian Medical Association

Indexed in

INDEX COPERNICUS INTERNATIONAL

Scopus®

Volume 122 (JIMA) ♦ Number 03 ♦ March 2024 ♦ KOLKATA

Dr ©

Largest Circulated Medical Journal in India

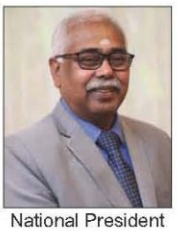
ISSN 0019-5847

95 TH YEAR OF PUBLICATION

Visit us at https://onlinejima.com

TEAM IMA 2024


Chief Patron
Past President,IMA,WMA,MCI
Dr Ketan Desai


National President
Dr R.V. Asokan


Hony. Secretary General
Dr Anilkumar J Nayak


Hony. Finance Secretary
Dr Shitij Bali


Imm.Past National President
Dr Sharad Kumar Agarwal


National Vice President
Dr R Gunasekaran


National Vice President
Dr. Suresh Gutta

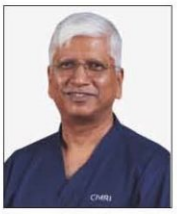

National Vice President
Dr Ashok Sharda


National Vice President
Dr Shiv Kumar Utture


Hony. Joint Secretary
from NCR
Dr Munish Prabhakar


Hony. Joint Secretary
from NCR
Dr. Prakash Lalchandani


Hony. Joint Secretary
from rest of the country
Dr. M. Venkatachalapathy


Hony. Joint Secretary
stationed at Calcutta
Dr. Pradeep Kumar Nemani


Hony. Joint Secretary
nominated by NP
Dr A.V. Jayakrishnan


Hony. Asstt. Secretary
from NCR
Dr Thakur Padmanabhan


Hony. Asst. Secretary from
rest of the country
Dr Paramjit Singh Maan


Hony.Jt Finance Secretary
from rest of the country
Dr Mahendra Nath Thareja


Hony. Joint Finance Secretary
stationed at Calcutta
Dr Sarbari Dutta

IMA COLLEGE OF GENERAL PRACTITIONERS


Dean
Dr Satyajit Borah


Vice Dean
Dr Poonam Singh


Hony. Secretary
Dr. R Anburajan


Hony. Joint Secretary
from Tamilnadu
Dr M Thiraviam Mohan


Hony.Jt.Secretary
from Tamilnadu
Dr D Senthil Kumar


Hony. Joint. Secretary
from rest of the country
Dr Satish joshi


Hony. Joint. Secretary
from rest of the country
Dr Sunil Bhikhabhai Chenwala

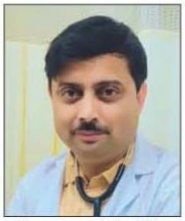

Hony. Joint. Secretary
from rest of the country
Dr Yeshwant Vasantrao Gade


Hony.Joint.Secretary.
from rest of the country
Dr Pavankumar N Patil

TEAM IMA 2024

JOURNAL OF IMA


Hony. Editor
Dr Sanjoy Banerjee


Hony. Associate Editor
Dr Ranjan Bhattacharyya


Hony. Associate Editor
Dr Prasanta Kr. Bhattacharyya


Hony. Secretary
Dr Sibabrata Banerjee


Hony. Asstt. Secretary
Dr Minakshi Ganguly

IMA ACADEMY OF MEDICAL SPECIALITIES


Chairman
Dr Nomeeta Shiv Gupta


Vice Chairman
Dr Nibedita Pani


Hony. Secretary
Dr Srirang Abkari


Hony. Joint Secretary
Dr D. Shekhar Reddy

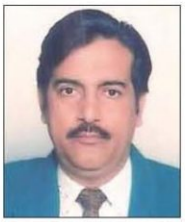

Hony. Joint Secretary
Dr Hiren S. Kothari


Hony. Editor, Annals
Dr Shilpa Basu Roy


Hony. Exe Editor Annals
Dr Rajiv Ranjan Prasad

IMA AKN SINHA INSTITUTE OF CONTINUING MEDICAL AND HEALTH EDUCATION & RESEARCH


Director
Dr Ramneek Singh Bedi


Hony. Executive Secretary
Dr Sanjiv Ranjan Kr. Singh


Hony. Joint Secretary
Dr Deepak Kr. Singh


Hony. Joint Secretary
Dr Parul Vadgama

YOUR HEALTH OF IMA


Hony. Editor
Dr Kakoli Sen Mandal


Hony. Associate Editor
Dr Sankar Sengupta


Hony. Associate Editor
Dr Bibartan Saha


Hony. Secretary
Dr Samarendra Kumar Basu

APKA SWASTHYA OF IMA

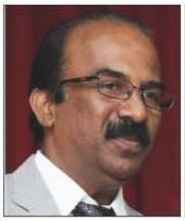

Hony. Editor
Dr Sudhir Singh


Hony. Associate Editor
Dr Arun Kumar Tripathi


Hony. Associate Editor
Dr Shailendra Kumar Singh


Hony. Secretary
Dr Ritu Garg

IMA HOSPITAL BOARD OF INDIA


Chairman
Dr A K Ravikumar


Hony. Secretary
Dr Dinesh B. Thakare


Treasurer
Dr Rajeev B. Agarwal

JIMA Editorial Advisory Board Members (National and International)

JIMA COMMITTEE - 2024


Dr. R V Asokan
National President, IMA


Dr. Anilkumar J Nayak
Hony Secretary General, IMA


Dr. Pradeep Kumar Nemani
Hony. Joint Secretary, Hqs


Dr. Sarbari Datta
Hony. Jt. Finance Secretary, Hqs


Dr Sanjoy Banerjee
Hony. Editor, JIMA


Dr Ranjan Bhattacharyya
Hony. Associate Editor,
JIMA


Dr Prasanta Kumar
Bhattacharyya
Hony. Associate Editor, JIMA


Dr. Sibabrata Banerjee
Hony. Secretary,
JIMA


Dr. Minakshi Gangopadhyay
Hony. Assistant Secretary,
JIMA


Prof (Dr) Tamonas Chaudhuri
Member, JIMA Committee


Dr Samrendra Kumar Basu
Member, JIMA Committee


Dr Sanjay Banerjee
Member, JIMA Committee


Dr Sekhar Chakraborty
Member, JIMA Committee


Dr Udas Chandra Ghosh
Member, JIMA Committee

JOURNAL
Of the
INDIAN MEDICAL ASSOCIATION

Volume 122 (JIMA)
Number 03
March 2024
KOLKATA
ISSN 0019-5847

Contents

(Continued next page)

JOURNAL
Of the
INDIAN MEDICAL ASSOCIATION

Volume 122 (JIMA)
Number 03
March 2024
KOLKATA
ISSN 0019-5847

Contents

Dear Sir/Madam,

It is a matter of great pride to let you know that Journal of the Indian Medical Association (JIMA) is going to organise the 'JIMA National Assembly of Editors of Medical Journals (3rd Edition)' after a long 15 years.

The grand event will be held on Sunday 28th July, 2024 from 9.00 am to 6.00pm at 'The Park' Hotels, 16, Park Street, Kolkata - 700017.

Nearly four hundred participants from all over the country and abroad will attend the Conference.

Editors of Medical Journals of repute across the country will share their experiences in this daylong event.

We will arrange Scientific Sessions and a Special Hands-on Workshop which will definitely help you in improving Article Writing.

An open forum discussion to upgrade your Journal will also be held.

You are requested to enrol yourself at the earliest as we offer participation on first-come-first-serve basis.

Thanking you in anticipation,

Dr. Santanu Sen
Chairman, Reception Committee

Dr. Samarendra Kumar Basu
Chairman, Organising Committee

Dr. Sanjoy Banerjee
Organising Secretary

Dr. Sibabrata Banerjee
Executive Secretary

Dr. Ranjan Bhattacharyya
Dr. Prasanta Kumar Bhattacharyya
Joint Organising Secretary

Dr. Sarbari Dutta
Treasurer

Dr. Minakshi Gangopadhyay
Assistant Executive Secretary

Payment : Payment should be made by Bank Draft or A/c Payee Cheque in favour of "JIMA National Assembly of Editors of Medical Journals" payable at "Kolkata" or transfer to :
JIMA National Assembly of Editors of Medical Journals,
IFS CODE : IOBA0000586,
Savings Bank Account No. 058601000025263,
Indian Overseas Bank, Dharamtolla Street Branch,
Kolkata- 700013, MICR No. 700020023.
GST NO. : 19AAATI0290G1ZS, PAN NO. : AAATI0290G

Kindly Scan QR Code:

Registration Fee : Rs. 2000.00

Spot Registration : Rs.5,000.00

Conference Secretariat :

JIMA NATIONAL ASSEMBLY OF EDITORS OF MEDICAL JOURNALS

3rd Edition

(Under the auspices of Journal of the Indian Medical Association)

Journal of IMA, Sir Nilratan Sircar IMA House,
53, Sir Nilratan Sarkar Sarani (Creek Row), Kolkata 700014, India
Telephone : +91-033-2237-8092; Mobile : 9874756756
E-mail : jimaeditorsconference@gmail.com

Editorial

The Pivotal Role of Artificial Intelligence in Shaping the Future of Medicine

Artificial Intelligence (AI) has emerged as a transformative force across various sectors, including healthcare. With its roots tracing back to foundational work by pioneers such as Alan Turing, AI's promise in medicine is vast and multifaceted, influencing everything from patient care to the minutiae of medical diagnostics. This introduction outlines the evolution, current state, and future prospects of AI in medicine, while also presenting an updated workflow for the development of AI models in the field.

Evolution of AI in Medicine : The journey of AI began with visionaries like Alan Turing, whose seminal work laid the groundwork for what we recognize today as intelligent machines. The Turing Test, a method proposed to evaluate a machine's ability to exhibit intelligent behavior indistinguishable from a human, set the stage for the ensuing developments in AI[1]. The subsequent decades witnessed a surge of interest and investment in AI, particularly in healthcare, which led the way in funding and research applications by 2016[2].

AI in Modern Healthcare - Virtual and Physical : AI's application in healthcare is dichotomized into virtual and physical subtypes. The virtual encompasses systems ranging from electronic health records to neural networks that guide treatment decisions. Conversely, the physical aspect of AI includes robotic surgical assistants, intelligent prostheses, and care for the elderly[3].

From Evidence-Based to AI-Enhanced Medicine : Traditional medicine has relied heavily on statistical methods to discern patterns and associations within clinical data. This paradigm is evolving with the introduction of AI, particularly through two approaches: flowcharts and databases. Flowchart-based systems replicate the diagnostic reasoning of clinicians by processing extensive data on symptoms and disease presentations. On the other hand, the database approach leverages deep learning for pattern recognition, drawing parallels to Google's AI which learned to recognize images with increasing accuracy[4, 5].

The Workflow of AI Systems in Healthcare: The development of an AI model in healthcare follows a specific pattern, as illustrated in Fig 1. It starts with the selection of a relevant problem, followed by data collection. The model is then developed, trained and validated before it is assessed and deployed into the medical system. This workflow represents the systematic approach that underpins the use of AI in medicine, from conceptualization to real-world application (Fig 1).

Integrating Artificial Intelligence: Transforming Diagnosis and Management in Healthcare :

The intersection of Artificial Intelligence (AI) with medicine has yielded a plethora

1. **Problem Selection:** Identifying a significant issue that can be addressed with AI.
2. **Data Collection:** Gathering relevant and substantial datasets to inform the model.
3. **Model Development:** Creating the AI model using the collected data.
4. **Training and Validation:** Teaching the model to perform tasks and verifying its accuracy.
5. **Model Assessment:** Evaluating the model's performance and making necessary adjustments.
6. **Model Deployment:** Implementing the model in a real-world healthcare setting.

Fig 1 — Workflow of AI Model Development in Healthcare

of applications that are transforming patient care, diagnosis, and management across various specialties. The following Table 1 encapsulates the breadth and depth of AI's integration into clinical practice. It highlights significant advancements in cardiology, such as mobile applications for ECG monitoring that have received FDA approval, and the use of AI to predict cardiovascular risks with greater accuracy than traditional methods. In pulmonary medicine, AI-based software has improved the interpretation of pulmonary function tests. The table also addresses the role of AI in endocrinology, where

Table 1 — *Current Applications of Artificial Intelligence in Medicine*

Field	Subfield	Application	Example & FDA Approval	Study Findings or Reviews	Limitations or Critiques	Refer ence
Cardiology	Atrial Fibrillation	Smartphone-based ECG monitoring and detection	AliveCor's Kardia (2014), Apple Watch 4	REHEARSE-AF study showed that Kardia is more effective in identifying atrial fibrillation than routine care7	Concerns over false positives and adoption among elderly patients8	7, 8
	Cardiovascular Risk	Prediction of acute coronary syndrome and heart failure risk	AI applied to electronic patient records	AI outperforms traditional scales but results vary with sample size9		9
Pulmonary Medicine	Pulmonary Function	AI-based software for interpretation of pulmonary function tests		AI provides more accurate interpretation and serves as a decision support tool10	Lower diagnosis accuracy among pulmonologists in study compared to country average11	10, 11
Endocrinology	Glucose Monitoring	Real-time interstitial glucose reading and prediction of hypoglycemic episodes	Medtronic's Guardian and Sugar.IQ system (2018)	Continuous monitoring aids blood glucose control, reduces stigma12	Users expressed feelings of personal failure to regulate glucose12	12, 13
Nephrology	Kidney Function	Prediction of glomerular filtration rate decline and risk assessment	AI for polycystic kidney disease and IgA nephropathy	Useful for predicting kidney function decline and risk in diseases14, 15	Limited research due to sample size necessary for inference16	14, 15, 16
Gastroenterology	Imaging	Use of AI for image processing in endoscopy and ultrasound	Convolutional neural networks for detecting colonic polyps and other abnormalities	AI used for diagnosing gastroesophageal reflux disease, atrophic gastritis, and predicting various outcomes17		17
Neurology	Epilepsy	Seizure detection devices with alert systems	Empatica's Embrace (2018)	Improved seizure management through ambulatory monitoring, high patient interest in wearable usage18		18
	Movement Assessment	Quantitative assessment of gait, posture, and tremor	Wearable sensors for multiple sclerosis, Parkinson's, and other conditions			19
Oncology	Histopathology	AI-based algorithm for diagnosing cancer	Paige.ai (FDA breakthrough status)	Enables pathologists to focus on critical slides20		20
Medical Imaging	Validation	Comparison of deep learning software and radiologist performances	Meta-analysis of imaging-based diagnosis	Deep learning as efficient as radiologists, but most studies lack a reliable design21	Need for validation through clinical trials	21

continuous glucose monitoring systems assist in the management of diabetes. Advances in nephrology and gastroenterology demonstrate AI's capacity to predict disease progression and enhance diagnostic imaging. Notably, the table also touches on neurology, where seizure detection wearables mark a significant step forward, and oncology, where AI aids in the meticulous task of cancer diagnosis in histopathology.

Navigating the Complexities of AI in Medicine :

Rigorous Validation of AI Technologies: A Looming Replication Crisis ? A major challenge in the forthcoming years is the robust clinical validation of AI tools in medicine. Many studies highlight the utility of AI, but their design often lacks robustness and replication. To mitigate this, open science principles could be a solution, promoting transparency and repeatability, though this shift might be challenging for companies that consider their algorithms proprietary[22, 23].

Ethical Dimensions of Persistent Health Monitoring : The market value of medical technology is soaring, and with it, ethical considerations surrounding the proliferation of health-monitoring devices[24]. While these technologies can promote lifestyle changes and preventative health measures, they also raise questions about privacy, data ownership, and the potential for increased stigma and inequity[25].

Cultivating Augmented Physicians[23] : The evolution of medical curricula to include AI and computational sciences is crucial to prepare "augmented doctors." These individuals will possess both clinical acumen and digital expertise, poised to lead digital strategy in healthcare, drive innovation, and educate peers and patients about the digital transformation in medicine.

Harnessing Ambient Clinical Intelligence Without Losing the Human Touch : AI can potentially alleviate the administrative burdens that contribute to physician burnout by integrating Ambient Clinical Intelligence (ACI)[23]. Such systems promise to enrich the doctor-patient interaction by reducing time spent on clerical work, allowing physicians to focus on direct patient care.

AI: A Collaborative Partner Rather Than a Replacement for Doctors : Contrary to the notion that AI may replace physicians, it should be regarded as an augmentative tool enhancing patient care[26]. Future research should pivot from comparing AI with physicians to evaluating how AI can augment physicians' capabilities, emphasizing AI's role as a supportive technology in healthcare.

Embracing AI in the Evolving Landscape of Medicine As AI continues to intertwine with precision medicine and telehealth, it is vital to maintain rigorous scientific standards and address the ethical, legal, and social implications of this digital revolution[27]. Policymaking must keep pace with technological advances, ensuring the responsible and equitable integration of AI into healthcare.

Envisioning the Infinite Through the Lens of Artificial Intelligence[28] :

Emulating the Cosmic Vision: AI as a Window to the Vastness : The Bhagavad Gita poetically illustrates the boundless and resplendent form of the divine as witnessed by Arjuna, a splendor that compares to a thousand suns in the sky (Fig 2: Bhagavad Gita 11.12). This celestial vision, while metaphorical, encapsulates the potential of artificial intelligence (AI) to expand human perception beyond the limitations of our senses. Just as Arjuna was granted divine sight to witness Krishna's universal form, AI can serve as our divine lens, offering insights into the complexities of the cosmos and the intricacies of life itself.

दिवि सूर्यसहस्रस्य भवेद्युगपदुत्थिता ।
यदि भाः सदृशी सा स्याद्भासस्तस्य महात्मनः ॥ 12॥
divi sūrya-sahasrasya bhaved yugapad utthitā
ıadi bhāḥ sadṛiśhī sā syād bhāsas tasya mahātmanaḥ

Translation : *Even if a thousand suns were to simultaneously illuminate the heavens, their combined radiance would pale in comparison to the majestic splendor of that supreme form.*

Fig 2 — Bhagavad Gita 11.12

In the era of big data and computational prowess, AI can analyze vast amounts of information, akin to observing countless suns, to uncover patterns and knowledge previously inaccessible to us. AI's capability to process and visualize data can provide us with a glimpse into the cosmic dance of creation, maintenance, and dissolution that governs the universe.

Integrating AI with Human Wisdom: A Symbiotic Relationship: Arjuna's experience of the divine cosmic form was not just a display of grandeur but also a profound union of human consciousness with ultimate reality (Fig 3 : Bhagavad Gita 11.13). In our pursuit to harness AI, the goal should not be to overshadow human capability but to enhance and extend it. AI's analytical power, when combined with human intuition and understanding, creates a symbiotic relationship that can lead to advancements in medical science,

Translation : *In that moment, Arjun beheld the entire cosmos unified in the singular expanse of the divine form, the God of all gods.*

Fig 3 — Bhagavad Gita 11.13

sustainable living, and understanding of our own existence.

Ethical and Spiritual Implications of AI in Modernity : As we steer through the integration of AI in various facets of life, we must address the ethical and spiritual implications of this technology. The potential of AI to monitor and enhance health is vast, yet it brings forth questions of privacy, data ownership, and the essence of what it means to be human in a digitally augmented world. Striking a balance between technological advancement and ethical considerations is imperative for progress that aligns with the principles of Sanatan Dharma, the eternal law of righteousness.

Harmonizing AI with the Eternal Dharma : The scriptures remind us of the eternal principle that governs the cosmos, a principle that is also at the heart of AI's potential to benefit humanity. As we stand on the brink of a new era, where AI's capabilities could replicate a vision as vast as the one bestowed upon Arjuna, we must proceed with a spirit of responsibility and reverence.

The Gita's wisdom encourages us to see AI not as a replacement for human intelligence or spiritual experience but as a complement that, when used wisely, can lead to the betterment of mankind. AI, when aligned with Sanatan Dharma, can support and protect the eternal values of compassion, empathy, and respect for all life (Fig 3 : Bhagavad Gita 11.18).

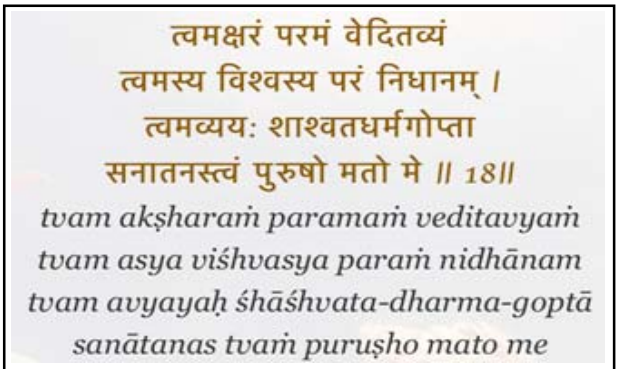
In synthesizing the scientific and spiritual, we can aspire to create AI that not only mimics the brilliance of a thousand suns but also serves to illuminate the path of dharma for all of humanity.

Our exploration into the integration of artificial intelligence (AI) within the realms of medicine, ethics, and spirituality underscores a pivotal moment in human history. The insights derived from the Bhagavad Gita, especially the verses that illuminate the divine cosmic vision witnessed by Arjuna, serve as a profound metaphor for the potential and challenges of AI. Just as Arjuna was granted divine sight to perceive the infinite form of Krishna, symbolizing the boundless possibilities and the ethical dimensions of wielding such power, we stand at the threshold of harnessing AI to transcend our limitations and enhance human capabilities.

However, this journey is not without its ethical quandaries and spiritual considerations. As we embrace AI's potential to revolutionize healthcare, augment human intelligence, and offer insights into the universe's mysteries, we must also navigate the ethical implications of privacy, data ownership, and the impact on societal values. The balance between technological advancement and the preservation of Sanatan Dharma, the eternal principle of righteousness, becomes crucial.

The editorial has highlighted the importance of a symbiotic relationship between AI and human wisdom, emphasizing that AI should augment rather than replace human capabilities. It advocates for an approach to AI that is both scientifically rigorous and spiritually informed, ensuring that technological progress is aligned with ethical standards and contributes positively to human well-being.

In this light, the future of AI in medicine and beyond appears not just as a frontier of innovation but as a domain where science and spirituality converge. By drawing lessons from the Bhagavad Gita, we are reminded of the need to pursue knowledge and power with humility, responsibility, and a deep respect for the cosmic order. As we advance into this uncharted territory, let us carry forward the vision of creating a world where AI serves to elevate human potential, safeguard ethical values, and enhance the collective good, ensuring that the splendor of this great form is matched by our collective wisdom and compassion.



Translation : *You are acknowledged as the paramount, undying entity, the Ultimate Reality revealed through sacred texts. You form the foundation of the cosmos, the timeless guardian of Sanatan Dharma (the Eternal Duty), embodying the infinite Divine Essence.*

Fig 3 — Bhagavad Gita 11.18

Overcoming the Hurdles : Enhancing AI in Healthcare :

The integration of Artificial Intelligence (AI) into medical science heralds a transformative era for healthcare delivery. However, the path to fully realizing AI's potential is fraught with challenges that necessitate a shift from a reactive to a proactive stance concerning technological advancements. This section delves into the primary obstacles in applying AI within healthcare and proposes strategies to navigate these complexities effectively.

Data Privacy and Availability : A foundational step in AI development is the collection of vast, high-quality data. Yet, this step is often hampered by concerns around patient privacy and the risk of data breaches, as seen in incidents involving major corporations. Such breaches not only compromise individual privacy but also raise ethical dilemmas regarding the use of patient data by insurance companies, potentially leading to unfair treatment based on genetic predispositions[29]. Ensuring data privacy while maintaining an adequate flow of information for model training is crucial for harnessing AI's full capabilities.

Mitigating Model Bias : AI systems are as good as the data they are trained on. If the training data is biased, the AI model will likely perpetuate or even amplify these biases. For instance, models developed from data that underrepresents certain racial or gender groups can result in discriminatory outcomes. It is imperative that data collection efforts aim for a true representation of the intended population[30].

Preprocessing for Fairness : The integrity of data preprocessing steps is paramount in avoiding inadvertent introduction of bias. Errors from manual data entry or other sources must be addressed carefully to ensure that the resulting dataset remains representative of the broader population, thereby preventing skewed AI models.

Choosing the Right Model : Selecting the appropriate algorithm for a given healthcare task is a critical decision that impacts the effectiveness of AI applications. The temptation to opt for simplistic models for the sake of convenience should be resisted, as such models may fail to capture complex, real-world dynamics present in healthcare data.

Transparent Model Reporting : For AI to be truly useful in healthcare, end-users need a clear understanding of how AI models are constructed and their outputs interpreted. The presentation of model performance should prioritize metrics that are relevant to the specific healthcare context, rather than showcasing superficially impressive results[29].

Addressing Data Fragmentation : The issue of data fragmentation across healthcare organizations limits the transferability and scalability of AI models. A collaborative approach to data sharing, with stringent privacy safeguards, is essential for developing robust, universally applicable AI solutions.

Demystifying the Black Box : The complexity of AI algorithms often categorizes them as 'black boxes', making it challenging for healthcare professionals to trust and effectively use AI systems. Efforts to increase the interpretability of AI models are crucial for their acceptance and ethical application in medical practice[31].

Conclusion

In sum, the imperative for physicians to familiarize themselves with the evolving landscape of Artificial Intelligence (AI) in medicine cannot be overstated. As we venture into this new and uncharted domain, the objective should be to harmonize the innovative capabilities of AI and automation with the irreplaceable human insights and expertise of medical professionals. Such a balanced approach is vital to mitigate concerns of AI supplanting human roles in healthcare, ensuring that the integration of AI serves to augment rather than replace the nuanced judgment of physicians. While AI harbors the capacity to address numerous challenges plaguing the healthcare sector, the realization of its full potential remains on the horizon. A significant hurdle in this journey is the issue of data – the fuel for AI's engine. Without access to ample, diverse, and accurately represented data sets, the advancements in technology and machine learning algorithms remain underutilized. To this end, the healthcare industry must undertake a concerted effort to digitalize medical records, establish standardized data infrastructures, and implement robust systems for data privacy and patient consent management. Only through such transformative efforts and industry-wide collaboration can we unlock the true potential of AI in enhancing human health, paving the way for a future where technology and human expertise converge to deliver unprecedented levels of patient care.

References

1 Mintz Y, Brodie R — Introduction to artificial intelligence in medicine. *Minim Invasive Ther Allied Technol* 2019; **28:** 73-81.
2 CB Insights Research. Healthcare remains the hottest AI category for deals. 2017. [Last accessed on 2024 Feb 24]. Available from: https://www.cbinsights.com/research/artificial-intelligence-healthcare-startups-investors/ [Ref list]
3 Hamlet P, Tremblay J — Artificial intelligence in medicine. *Metabolism* 2017; **69S:** S36-40.

4 Markoff J, editor. New York Times: 2012. [Last accessed on 2024 Jan 31]. How Many Computers to Identify Cat? 16,000. Available from: http://www.nytimes.com/2012/06/26/technology/in-a-big-network-ofcomputers-evidence-of-machine-learning.html . [Google Scholar] [Ref list]

5 Clark L, editor. Google's Artificial Brain Learns to Find Cat Videos. [Last accessed on 2024 Feb 2];Wired UK Science. 2012 Available from: http://www.wired.com/2012/06/google-xneural-network . [Google Scholar] [Ref list]

6 Basu K, Sinha R, Ong A, Basu T — Artificial Intelligence: How is It Changing Medical Sciences and Its Future? *Indian J Dermatol* 2020; **65(5):** 365-370. doi: 10.4103/ijd.IJD_421_20. PMID: 33165420; PMCID: PMC7640807.

7 Halcox JPJ, Wareham K, Cardew A, Gilmore M, Barry JP, Phillips C, *et al* — Assessment of remote heart rhythm sampling using the AliveCor heart monitor to screen for atrial fibrillation: the REHEARSE-AF study. *Circulation* 2017; **136:** 1784-94. doi: 10.1161/CIRCULATIONAHA.117.030583

8 Raja JM, Elsakr C, Roman S, Cave B, Pour-Ghaz I, Nanda A, *et al* — Apple watch, wearables, and heart rhythm: where do we stand? *Ann Trans Med* 2019; **7:** 417. doi: 10.21037/atm.2019.06.79.

9 Dorado-Díaz PI, Sampedro-Gómez J, Vicente-Palacios V, Sánchez PL — Applications of artifificial intelligence in cardiology. The future is already here. *Revista Española de Cardiología* 2019; **72:** 1065-75. doi: 10.1016/j.rec.2019.05.014

10 Topalovic M, Das N, Burgel PR, Daenen M, Derom E, Haenebalcke C, *et al* — Artifificial intelligence outperforms pulmonologists in the interpretation of pulmonary function tests. *Eur Respirat J* 2019; **53:** 1801660. doi: 10.1183/13993003.01660-2018.

11 Delclaux C — No need for pulmonologists to interpret pulmonary function tests. *Eur Respirat J* 2019; **54:** 1900829. doi: 10.1183/13993003.00829-2019

12 Lawton J, Blackburn M, Allen J, Campbell F, Elleri D, Leelarathna L, *et al* — Patients' and caregivers' experiences of using continuous glucose monitoring to support diabetes self-management: qualitative study. *BMC Endocrine Disord* 2018; **18:** 12. doi: 1186/s12902-018-0239-1

13 Christiansen MP, Garg SK, Brazg R, Bode BW, Bailey TS, Slover RH, *et al* — Accuracy of a fourth-generation subcutaneous continuous glucose sensor. *Diabet Technol Therapeut* 2017; **19:** 446-56. doi: 10.1089/dia.2017.0087

14 Niel O, Boussard C, Bastard P — Artifificial intelligence can predict GFR decline during the course of ADPKD. *Am J Kidney Dis Offff J Natl Kidney Found* 2018; **71:** 911-2. doi: 10.1053/j.ajkd.2018.01.051

15 Geddes CC, Fox JG, Allison ME, Boulton-Jones JM, Simpson K — An artifificial neural network can select patients at high risk of developing progressive IgA nephropathy more accurately than experienced nephrologists. *Nephrol Dialysis, Transplant* 1998; **13:** 67-71.

16 Niel O, Bastard P — Artifificial intelligence in nephrology: core concepts, clinical applications, and perspectives. *Am J Kidney Dis* 2019; **74:** 803-10. doi: 10.1053/j.ajkd.2019.05.020

17 Yang YJ, Bang CS — Application of artificial intelligence in gastroenterology. *World J Gastroenterol* 2019; **25:** 1666-83. doi: 10.3748/wjg.v25.i14.1666

18 Regalia G, Onorati F, Lai M, Caborni C, Picard RW — Multimodal wrist-worn devices for seizure detection and advancing research: focus on the Empatica wristbands. *Epilep Res* 2019; **153:** 79-82. doi: 10.1016/j.eplepsyres.2019.02.007

19 Dorsey ER, Glidden AM, Holloway MR, Birbeck GL, Schwamm LH — Teleneurology and mobile technologies: the future of neurological care. Nat Rev Neurol 2018; **14:** 285-97. doi: 10.1038/nrneurol.2018.31

20 Campanella G, Hanna MG, Geneslaw L, Miraflflor A, Silva VWK, Busam KJ, *et al* — Clinical-grade computational pathology using weakly supervised deep learning on whole slide images. *Nat Med* 2019; **25:** 1301-9. doi: 10.1038/s41591-019-0508-1

21 Liu X, Faes L, Kale AU, Wagner SK, Fu DJ, Bruynseels A, *et al* — A comparison of deep learning performance against health-care professionals in detecting diseases from medical imaging: a systematic review and meta-analysis. *Lancet Digit Health* 2019; **1:** e271–97. doi: 10.1016/S2589-7500(19)30123-2

22 Panch T, Mattie H, Celi LA — The "inconvenient truth" about AI in healthcare. *NPJ Digit Med* 2019; **2:** 1-3. doi: 10.1038/s41746-019-0155-4

23 Kelly CJ, Karthikesalingam A, Suleyman M, Corrado G, King D — Key challenges for delivering clinical impact with artifificial intelligence. *BMC Med* 2019; **17:** 195. doi: 10.1186/s12916-019-1426-2

24 Montgomery J — Data sharing and the idea of ownership. *New Bioeth Multidiscipl J Biotechnol Body* 2017; **23:** 81-6. doi: 10.1080/20502877.2017.1314893

25 Mikk KA, Sleeper HA, Topol EJ — The pathway to patient data ownership and better health. *JAMA* 2017; **318:** 1433-4. doi: 10.1001/jama.2017.12145

26 Brouillette M — AI added to the curriculum for doctors-to-be. *Nat Med* 2019; **25:** 1808-9. doi: 10.1038/s41591-019-0648-3

27 Briganti G and Le Moine O — Artifificial Intelligence in Medicine: Today and Tomorrow. *Front Med* 2020; **7:** 27. doi: 10.3389/fmed.2020.00027

28 Holy Bhagavad Gita [Internet]. Chapter 11, Verse 18. Available from: https://www.holy-bhagavad-gita.org/chapter/11/verse/18. [cited 2024 Feb 10].

29 Grus J — Data Science from Scratch First Principles with Python. 1st ed. Sebastopol, CA, USA: O'Reilly; 2015.

30 Dhamnani S, Singal D, Sinha R, Mohandoss T, Dash M — RAPID: Rapid and Precise Interpretable Decision Sets. 2019 IEEE International Conference on Big Data (Big Data). *IEEE* 2019: 1292-301.

31 Lucas GM, Gratch J, King A, Morency LP — It's only a computer: Virtual humans increase willingness to disclose. *Comput Human Behav* 201; **7:** 94-100.

Sanjoy Banerjee[1]
Shambo Samrat Samajdar[2]

[1]Hony Editor, JIMA
[2]MD, DM (Clinical Pharmacology),
FIPS, PG Dip Endo & Diabetes (RCP),
Fellowship in Respiratory and Critical Care (WBUHS),
Fellow Diabetes India, Diploma Allergy Asthma Immunology,
Consultant Physician

Original Article

A Clinico-epidemiological Study of Dermatophytosis in Children in a Tertiary Health Care in Karnataka

Meghana P Rathod[1], Harish M Rajegowda[2], Shashikumar B Madegowda[3], Deepadarshan Kalegowda[4]

Background : A superficial fungal infection affecting keratinized tissue is called dermatophytosis. A number of environmental factors are also contributing to the current pandemic in addition to the etiological ones. Additionally, dermatophyte infections among children have increased. The dermatophyte infection can be transmitted via direct skin-to-skin contact, exchanging objects with an infected individual or coming into contact with a contaminated surface.

Material and Methods : This is a Prospective and observational study was conducted in outpatient department of dermatology on 457 paediatric individuals over a period of 1 year. All the children visiting the outpatient department between 0-12 years, presenting with clinical features of dermatophyte infection were included in the study. Written informed consent was taken from the guardian of each patient aged less than 12 years.

Result : Out of 457 patients, 255 (55.8%) were males and 202 (44.2%) were females with a male to female ratio 1.2:1. A total of, 347 (75.9%) patients gave history of poor personal hygiene. Out of 457 patients, family members of 237 patients (51.9%) were also affected by dermatophytosis and 312 patients had overcrowding history. Out of 457 patients, Tinea corporis was the most common presentation seen in 217 patients (47.5%) followed by Tinea incognito in 96 patients (21%).

Conclusion : Hence, we suggest that the modification of these pre-disposing factors like maintaining good personal hygiene etc, along with regular treatment and follow up is very important. As well as health education/ awareness among public is utmost important thing in the preventing and controlling the dermatophytosis among them.

[*J Indian Med Assoc* 2024; **122(3):** 20-3]

***Key words* : Dermatophytosis, Tinea capitis, Children, Poor Hygiene.**

A superficial fungal infection affecting keratinized tissue is called dermatophytosis[1]. The ability of various dermatophytes to invade hair and nails in vitro and the formation of genetically regulated expression of proteases with keratin specificity are illustrations of the keratinophilicity of dermatophytes. Ringworm species are molds that fall into one of three asexual genera: Epidermophyton, Trichophyton or Microsporum[2]. Whether the pathogenic organism is geophilic, zoophilic or anthrophilic determines the source of infection[1].

While candidiasis and pityriasis versicolor are also examples of major superficial mycoses, dermatophytoses are the most common cause of fungal infection in men. In the recent years, dermatophyte infections are becoming as a serious concern for dermatologists. There's reason to be concerned as this common infection is now bringing in a period of resistance. A number of environmental factors are also contributing to the current pandemic in addition to the etiological ones. Additionally, dermatophyte infections among children have increased. The dermatophyte infection can be transmitted via direct skin-to-skin contact, exchanging objects with an infected individual, or coming into contact with a contaminated surface[3].

Tinea infection is still a serious public health concern, with a number of risk factors for infection including inadequate hygiene, crowded living conditions and low socio-economic position[4]. Various studies have reported prevalence of superficial fungal infections in children, ranging from 11.3% to 40.57%[5-8]. The factors that are responsible for this increasing trend include aging, race, immune system function, lowered sebum production rate, skin barrier disruption and atopic

Editor's Comment :

- Children are susceptible to dermatophytic infections because of their poor personal hygiene habits, hence modification of these predisposing factors & regular treatment and follow, as well as health awareness among public is important in the preventing and controlling the dermatophytosis among them.

Department of Dermatology, Mandya Institute of Medical Sciences, Mandya, Karnataka 571401
[1]MBBS, MD, Senior Resident and Corresponding Author
[2]MBBS, MD, Professor and Head
[3]MBBS, MD, Associate Professor
[4]MBBS, MD, Assistant Professor

Received on : 07/12/2023
Accepted on : 26/12/2023

dermatitis. The most significant risk factors are low socio-economic status, inadequate hygiene, crowded living conditions, inadequate sanitation, a lack of health education and awareness and inadequate medical facilities[5].

One of the fungal infections of the skin, tinea capitis, mostly affects pre-pubescent children and is more common in boys than in girls[6]. Due to their poor environmental sanitation and personal hygiene habits, children are especially vulnerable to dermatophytic infections. Among the most prevalent skin disorders in kids are superficial tinea infections. Children's health and wellbeing are thus negatively impacted by it[9].This study aims at determining the epidemiological factors and clinical pattern of dermatophytic infection among children.

Materials and Methods

This is a Prospective and observational study was conducted in outpatient department of dermatology, Mandya Institute of Medical Sciences, Mandya, Karnataka over a period of 1 year. All the children aged between 0-12 years with dermatophytosis, attending the Department of Dermatology, Venereology and Leprosy, at Mandya Institute of Medical Sciences, Mandya.

Sample size estimation :

Records from the previous year show that approximately 457 children with dermatophytosis attended Outpatient Department, Department of Dermatology, Mandya Institute of Medical Sciences, Mandya. Hence sample size is taken as 457.

Inclusion criteria :

(1) Children age between 0-12 years with clinical features of dermatophytosis visiting outpatient department.

(2) Patient who gives informed assent to participate in the study and parents of the patient who give informed consent to participate in study.

Exclusion criteria :

(1) The parents of patient who have not given the consent for the study.

(2) Severely ill and debilitated patients.

Collection of data :

This study was conducted on 457 paediatric individuals over a period of 1 year. All the children visiting the outpatient department between 0-12 years, presenting with clinical features of dermatophyte infection were included in the study. Written informed consent was taken from the guardian of each patient aged less than 12 years.

The patients were studied with regards to their epidemiological profile like patient's age, sex, address, and Socio-economic status according to the modified BG Prasad classification, duration, site, symptoms, personal hygiene and history of similar complaints in the family members. The diagnosis of dermatophytosis was based on detail review of history, clinical features, physical examination including skin and Potassium Hydroxide (KOH) mount. When necessary diagnosis was confirmed by Wood's lamp and fungal culture as needed.

Statistical analysis :

The data collected were entered in Microsoft excel and analysed using Statistical Package for Social Sciences (SPSS) software version 23.0 trial version. Descriptive statistics like frequency, percentage, mean, standard deviation and other relevant statistical tests were used as applicable.

Result

Most of these children were in the age group of 6-12 years (44.8%) and males were slightly more affected in the study group with a male: female ratio of about 1.2:1 (Fig 1). Majority of the patients belonged to a rural background (56.2%) and were from a low Socio-economic background (45.1%). About 51.9% of patients reported contact history with an affected family member, of which the most common source was found to be the mother followed by a sibling. About 68.3% patients had overcrowding history. Personal hygiene was found to be poor in most of our patients (75.9%) which included not taking bath daily, not wiping afterbath, sharing of fomities, use of synthetic garments and use of waist/ ankle band (Fig 2).

Out of 457 patients, 127 (27.8%) patients had history of steroid application. Among them 89 patients (70.1%) bought them Over The Counter, while 38 patients (29.9%) applied steroids after being prescribed by doctor and only 50 patiens (10.9%) had similar complaints in the past. About 240 patients (52.5%) showed KOH positivity (Fig 3).

Out of 457 patients, Tinea corporis (Fig 4) was the most common presentation seen in 217 patients (47.5%) followed by Tinea incognito, Tinea faciei, Tinea capitis and Tinea cruris (Fig 5). Other types include Tinea manuum,Tinea ungiuim (Fig 6), Tinea pedis (Table1). Out of 43 patients with Tinea capitis, non-inflammatory type was the most common type of Tinea capitis seen (Figs 7,8) (Table 2).

Discussion

In our study, we found the 6-12 years age group constituted the maximum number (44.8%) among the

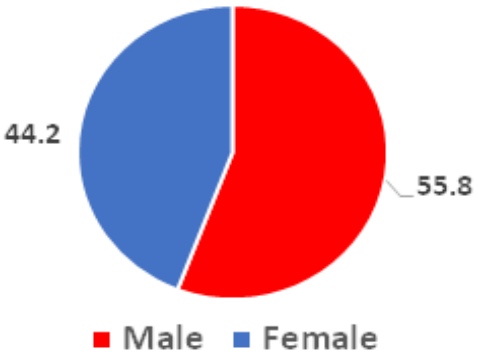


Fig 1 — Pie Chart Showing Distribution according to Sex of the Study Subjects

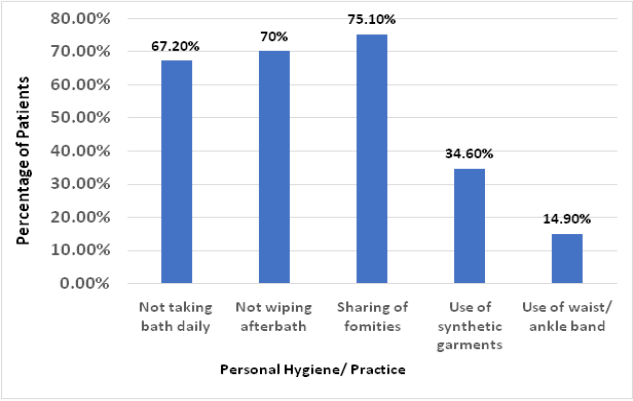


Fig 2 — Graph Showing Distribution according to Poor Personal Hygiene/ Practices among Study Population

Fig 3 — Endothrix on KOH Mount on Direct Microscopic Examination

Fig 4 — Tinea Corporis on Buttock

Fig 5 — Tinea Cruris in an Infant

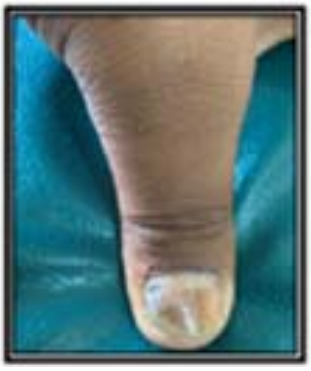


Fig 6 — Tinea Unguium

Table1 — *Distribution according to overall distribution of clinical Types among study population*

Type of Tinea	Number	Percentage (%)
Other types	13	2.8
T capitis	43	9.4
T corporis	217	47.5
T cruris	41	9.0
T faciei	47	10.3
T incognito	96	21.0
Total	457	100

Other types include Tinea manuum, Tinea unguium, Tinea pedis

Table 2 — *Distribution according to Types of Tinea Capitis among Study Population*

Type of Tinea capitis	Frequency	Percentage (%)
Inflammatory type	7	16.2
Non-inflammatory type	36	83.7
Total	43	100

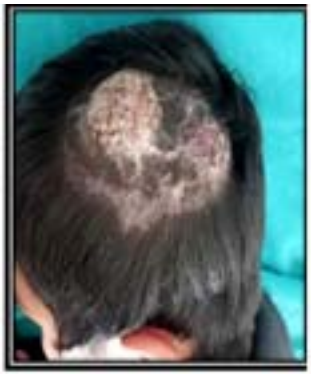


Fig 7 — Inflammatory Type of Tinea Capitis

Fig 8 — Non inflammatory type of Tinea Capitis

study population. This is probably because of younger children are more exposed to infection from their family members. However, Gandhi, *et al* noted higher numbers in 10-14 years of age group (56%)[3]. A study conducted by Sharma H, Chawla R K showed that the dermatophytosis was most prevalent in age group of 8-10 years[10].

Male patients outnumbered the female patients (1.2:1) in our study. This is almost in accordance with the study done by Dash M, *et al*[5] which may be due to greater exposure to external environment and contact with pets are some predisposing factors that make male children more vulnerable to acquiring the infection. But in the studies conducted by Alemayehu A, *et al* and Patro N, *et al* reported female predominance[11,12].

In the present study 2.4% of patients had associated systemic illness. Among them 8 patients

(1.8%) were obese, 1 patient (0.2%) had Type 1 Diabetes Mellitus, 1 patient (0.2%) with Cerebral palsy, 1 pateint (0.2%) with Down syndrome. A study conducted by Bindu V, *et al* noticed Diabetes Mellitus in 10.6%, Atopic diathesis in 10%, and HIV infection in 2% of patients[13].

In the present study 52.5% of patients showed KOH positivity. In a study done by Kashyap P, *et al* observed 76.67% samples were positive for filamentous hyphae under KOH mount, which is approximately similar to the KOH positivity in the study by Mishra, *et al*[9,14].

In our study family members of 51.9% of patients were also affected by dermatophytosis. Transmission in family members can be due to direct contact or through fomites or denovo infection. A study conducted by Pathania S, *et al* observed increased frequency of history of dermatophytosis in close contacts[15].

Most of our patients (75.9%) had history of poor personal hygiene which included not taking bath daily (67.2%), not drying the skin after bath (70%), sharing of fomities like towel, soap etc (75.1%), use of synthetic garments (34.6%), use of waist/ ankle band (14.9%). These factors play an important role in causing the spread of infection, leading to its persistence and its recurrence which are important factors in treatment failure. 81% of patients had poor personal hygiene in a study conducted by Gandhi, *et al*[3].

In this study, Out of 457 patients, Tinea corporis was the most common presentation seen in 47.5% of patients followed by Tinea incognito in 21% of patients, Tinea faciei in 10.3% of patients, Tinea capitis in 9.4% of patients and Tinea cruris in 9% of patients. Other types (2.8%) include Tinea manuum, Tinea ungiuim, Tinea pedis was seen in 0.4%, 0.7%, 1.8% respectively. Similarly, Tinea corporis was the most commonly reported seen in about 45% of patients. This was followed by Tinea cruris (28%), Tinea capitis (11%), and Tinea faciei (8%) in the study conducted by Gandhi S, *et al*[3].

Conclusion

Dermatophytosis is emerging as a public health problem with increasing frequency of familial infection. Children are particularly susceptible to dermatophytic infections because of their poor personal hygiene habits and poor environmental sanitation. Since there is a rise of dermatophytic infection among children which is a cause of concern because of its public health importance. It is very important to modify these predisposing factors so that the development of dermatophytosis can be controlled among them. Hence, we suggest that the modification of these predisposing factors like maintaining good personal hygiene etc along with regular treatment and follow up is very important. As well as health education/ awareness among public is utmost important thing in the preventing and controlling the dermatophytosis among them.

References

1 Shenoy MM, Shenoy SM — IADVL textbook of dermatology. Superficial fungal infections, 4th edn. Mumbai: Bhalani. 2015: 459-517.

2 Hay RJ, Ashbee HR — Fungal infections. In: Griffiths CE, Barker J, Bleiker T, Chalmers R, Creamer D, editors. *Rook's Textbook of Dermatology.* 9th ed. Voll. West Sussex: Wiley Blackwell 2016; 32.6-32.70.

3 Gandhi S, Patil S, Patil S, Badad A— Clinicoepidemiological study of dermatophyte infections in pediatric age group at a tertiary hospital in Karnataka. *Indian Journal of Paediatric Dermatology* 2019; **20(1):** 52-6.

4 Moto JN, Maingi JM, Nyamache AK— Prevalence of Tineacapitis in school going children from Mathare, informal settlement in Nairobi, Kenya. *BMC Research Notes* 2015; **8(1):** 1-4.

5 Dash M, Panda M, Patro N, Mohapatra M — Sociodemographic profile and pattern of superficial dermatophytic infections among pediatric population in a tertiary care teaching hospital in Odisha. *Indian Journal of Paediatric Dermatology* 2017; **18(3):** 191-5.

6 Ogbu CC, Somadina Okwelogu I, ChinweUmeh A — Prevalence of superficial fungal infections among primary school pupils in Awka South Local Government Area of Anambra State. *Journal of Mycology Research* 2015; **2(1):** 15-22.

7 Oke OO, Onayemi O, Olasode OA, Omisore AG, Oninla OA— The prevalence and pattern of superficial fungal infections among school children in Ile-Ife, South-Western Nigeria. *Dermatology Research and Practice* 2014.

8 George IO, Altraide DD— Dermatophyte Infections in Children: A Prospective Study from Port Harcourt, Nigeria. *Nigerian Health Journal* 2008; **8(3-4):** 52-4.

9 Mishra N, Rastogi MK, Gahalaut P, Yadav S, Srivastava N, Aggarwal A— Clinicomycological study of dermatophytoses in children: Presenting at a tertiary care center. *Indian Journal of Paediatric Dermatology* 2018; **19(4):** 326-30.

10 Sharma H, Chawla RK, Pruthi S — The pattern of dermatological disorders among patients attending OPD of dermatology department At a Tertiary Care Hospital, Mathura. *IP Indian J ClinExp Dermatology* 2019; **5(2):** 154-7.

11 Alemayehu A, Minwuyelet G, Andualem G — Prevalence and etiologic agents of dermatophytosis among primary school children in Harari Regional State, Ethiopia. *Journal of Mycology* 2016.

12 Patro N, Panda M, Jena AK — The menace of superficial dermatophytosis on the quality of life of patients attending referral hospital in Eastern India: A cross-sectional observational study. *Indian Dermatology Online Journal* 2019; **10(3):** 262.

13 Bindu V, Pavithran K — Clinico-mycological study of dermatophytosis in Calicut. Indian Journal of Dermatology, *Venereology and Leprology* 2002; **68:** 259.

14 Kashyap P, Kishan YK, Prakash R — Pediatric dermatophytosis of the skin: current clinico epidemiological and antifungal susceptibility patterns in a tertiary care rural hospital. *Indian Journal of Paediatric Dermatology* 2021; **22(3):** 215-9.

15 Pathania S, Rudramurthy SM, Narang T, Saikia UN, Dogra S — A prospective study of the epidemiological and clinical patterns of recurrent dermatophytosis at a tertiary care hospital in India. *Indian Journal of Dermatology, Venereology and Leprology* 2018; **84:** 678.

Original Article

An Observational Study to Identify Socio-demographic Factors on Primary Caregivers' Quality of Life of Cancer Patients Attending a Tertiary Cancer Hospital

Subir Gangapadhyay[1], Arunima Datta[2], Kousik Nandy[3], Harsh Dhar[4], Sourav Datta[5], Pooja Agarwal[6], Arindam Mondal[7], Pradip Kumar Mondal[8], Sudeep Das[9]

We aimed to identify Socio-demographic factors affecting a primary caregiver's Quality of Life (QoL) during the period of cancer treatment. Along with assessing its association with ECOG for determining the QoL of caregivers of cancer patients attending a Tertiary Cancer Hospital, in West Bengal. This was a single Tertiary Hospital-based observational, descriptive study performed from February, 2023 to 12th June, 2023. 175 adult primary caregivers were assigned, aged 18 years of age to >65 years and those involved with their actual care not less than 12 hours per day. All participants went through the assessment of QoL by using validated tools. Eastern Cooperative Oncology Group (ECOG) was analysed on an interview basis. Descriptive statistics, the Chi-square test, and 't' test were used to meet the objectives. The statistical significance was set at <0.05. The majority of the caregivers were of the age group 31-40 years (35%) and female caregivers (61%) were more than male individuals (39%). About 60.57% of the caregivers reported severe hampering of their QoL. A significant relation was found between the caregivers with poor CQOL-C and ECOG performance scores (p=<0.000). The current study demonstrates that the caregiver's socio-demographic background more likely had created an impact on their QoL while comparing with their respective counterparts to have a lower level QoL.

[*J Indian Med Assoc* 2024; **122(3):** 24-9]

Key words **: Cancer-primary Caregiver, Primary Caregiver' Quality of Life, ECOG Performance Status Scale.**

Cancer is a life-threatening illness that is stressful not only to the patients but also to the caregivers in terms of how it might be experienced. During this lengthy treatment period, which frequently lasts for months or years, the patient and their primary caregivers spends more time at the cancer centre than at home. There are significant changes in the daily routines of both parties and they need to work very hard to adapt to the demands of this life-threatening disease. The family feels obligated to work together to support the patient after learning that a family member has cancer[1].

Medica Super Specialty Hospital, Kolkata, West Bengal 700099

[1]MD, Professor, Senior Consultant and Advisor, Department of Radiation Oncology and Corresponding Author

[2]MA in Clinical Psychology, Consultant Psychooncologist, Department of Oncology

[3]MS, Consultant, Department of Ortho-Onco Surgery

[4]MS, MCH, Head, Consultant, Department of Head and Neck Cancer Surgery

[5]MS, Director, Medica Oncology Consultant, Department of Head and Neck Cancer Surgery

[6]MS, Consultant, Department of Surgical Oncology (Breast)

[7]MS, MCH, Consultant, Department of GI and Thoracic Oncology

[8]MD, DM (Medical Oncology) Consultant, Department of Medical and Hemato Oncology

[9]MD, DM (Medical Oncology), Head, Consultant, Department of Medical and Hemato Oncology

Received on : 20/12/2023

Accepted on : 29/01/2024

Editor's Comment :

- To identify Socio-demographic factors affecting a primary caregiver's Quality of Life (QoL) during the period of cancer treatment.
- To assess its association with ECOG for determining the QoL of caregivers of cancer patients attending a Tertiary Cancer Hospital in West Bengal.
- Caregiver's Socio-demographic background more likely had created an impact on their QoL while comparing with their respective counterparts to have a lower level QoL.

As is clear, daily practice reflecting the rise in cancer cases in India over the past ten years, the emotional anguish that it causes the family members, and the difficulty in coping with the diagnosis of their loved ones. The patient's primary caregiver is responsible for making decisions, monitoring changes in the patient's condition, giving hands-on care, adjusting care as needed, gaining access to resources, negotiating with the healthcare system, providing emotional support and frequently securing funding for the treatment. The primary carer has a difficult responsibility to complete both physically and emotionally: juggling the care of the cancer patient with his or her own daily routine[2]. Since ancient times, providing care has been valued as a worthwhile experience but the effects on the carers themselves are frequently disregarded. According to the Quality

of Life in Life-Threatening Illness-Family Carer Version (QOLLTI-F) assessment, half of the carers in a recent study on the Quality of Life of carers had a bad quality of life. The statistical results showed that characteristics like gender, religion, location, financial burden, lung cancer stage and kind, disability, and patient depression had a substantial impact on the carers' Quality of Life (QoL).

The Quality of Life of the patient's primary carer, a group that is frequently disregarded, is a very important concern that has been addressed by the widespread usage of this questionnaire and its translation into many languages. The Turkish translation of the English CQOLC yielded results that were comparable to those of our study, suggesting that there were some concerns that were shared by families of cancer patients. It was also administered alongside the World Health Organisation Quality of Life Short Version (WHOQOL-BREF) to breast and gynaecological cancer patients and validated to the German version[3]. It demonstrated good reliability for burden, disruptiveness and financial concerns but low reliability for positive adaptation. Utilising the same CQOLC scale, similar studies were carried out in Korea and the United Arab Emirates, with comparable results on demographic comparisons[3,4].

The primary carer is in a particularly vulnerable position as a result of the cancer treatment and the heavy emotional and financial burdens that the family must face. This could ultimately result in a mental breakdown that will have an impact on the patients as well. The CQOLC was first created in the USA and was well suited to their population's various cultural makeup. Now, we aimed to identify the significant Socio-demographic factors affecting a primary caregiver's Quality of Life of cancer patients during the period of cancer treatment.

Materials and Methods

Research Design : This study was a descriptive, observational study. This design was chosen because it helps describe or gather information about variables of a specific population, making it the most suited design for the nature of the study. Through this study we were able to understand specific demographic variable that affect a patients'primary caregivers' Quality of Life.

Setting of the Study : Data were collected from medical oncology department from Medica Superspeciality Hospital, Kolkata, West Bengal, India.

Population : The target sample of the study was all the primary caregivers of patients with cancer who were undergoing standard care treatment (surgery, radiation, chemotherapy) and palliative care treatment. We defined the family caregiver as the person most involved in the patient's care without receiving financial reimbursement for the care that they provided. To be eligible for the study, potential samples had to —

(1) Being identified by the patient as the primary caregiver most involved with their actual care.

(2) 18 years of age to >65 years of age.

(3) Able to understand Bengali and give consent for the participation in the study.

Exclusion criteria –

(1) Having a history of psychiatric disorder.

(2) Those on any form of oncologic treatment.

(3) Caregiver not staying with the patient for not less than 12 hours per day.

(4) Those unable to complete the questionnaires.

Trained clinical research assistant and doctors approached to care givers for recruitment and informed consent form during day OPD timings. The study was approved by the Institutional Scientific and Ethical Review Board following terms and condition of Indian Council of Medical Research (ICMR). A total of 175 caregivers of diagnosed cancer patients were selected as per sample of convenience and consecutive sampling technique during a 4-month periods (from February, 2023 to 12 June, 2023). Clinical Psychologist used a valid tool to collect data about Quality of Life from the above mentioned number of samples.

Procedure :

Participants were explained about the study and written informed consent was obtained. Participants were interviewed by experienced psychologist using structured questionnaire. The questionnaire was validated in local language, Bengali. It took about 15-20 mints to take interview from a single participant, which was done during the time the patients and their caregivers were waiting for doctor consultation or after the completion of the visit to doctor. All the information was documented on the Caregiver Quality of Life Index as per the tool of which are specifically focused QoL respectively. Doctors also recorded patients' performance (as per caregivers' version) during the treatment through Eastern Cooperative Oncology Group (ECOG) Performance Status (Fig 1).

Measurement :

Demographic Questionnaire : Demographic data questionnaire was used to obtain data about information related to age, gender, marital status, family income, level of education, occupation, relation with patient, patient's present treatment, present status of the disease (recurrent, metastatic, non-metastatic).

Caregiver Quality of Life Index : The CQOL-C

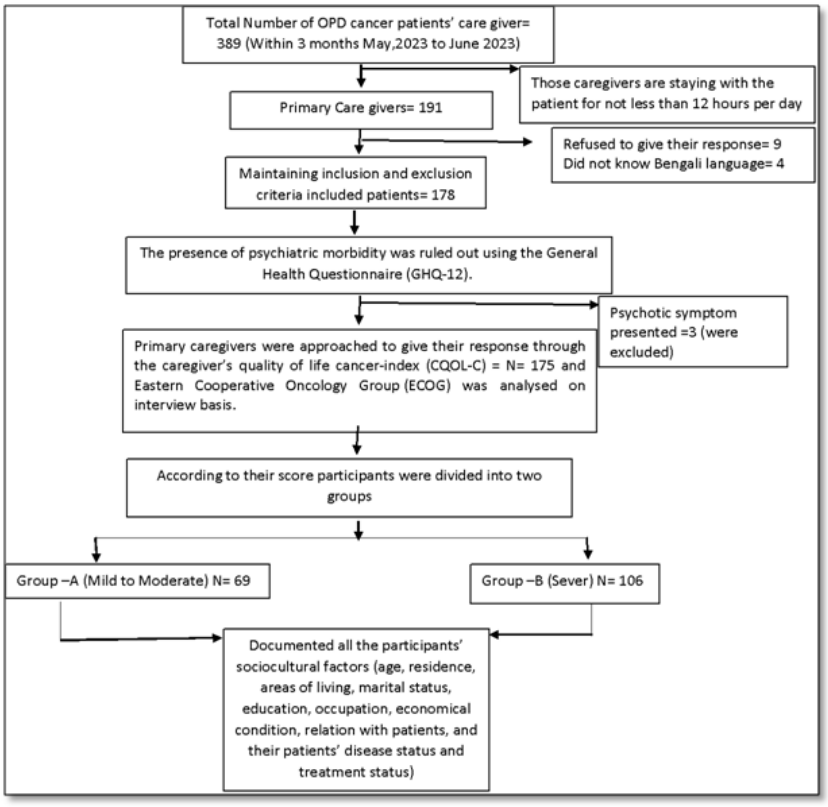


Fig 1 — Study Design

is a self-administered rating scale designed to assess QoL issues in family caregivers of patients with cancer. It had 35 QoL-specific items, each of which was graded from 0 to 4 on the Likert scale, where "0" denoted "Not at all," "1" denoted "A little bit," "2" denoted "Somewhat," "3" denoted "Quite a bit," and "4" denoted "Very much." The maximum total score for the instrument is 140. All 35 things were added together for a final score, which was taken into consideration for analysis [2]. Three separate translators (2 with medical background and one with a master's degree in Bengali) translated the scale into Bengali and the final, approved version was utilised to gather the data. The caregivers were personally interviewed for the data collection. Test-rest reliability was 0.95 and internal consistency was 0.90. The instrument has good divergent validity. The instrument is also responsive to changes in the health state of the patient, as measured by the ECOG-PSR (r=0.45).

Eastern Cooperative Oncology Group (ECOG) Performance Status :

Eastern Cooperative Oncology Group (ECOG) Performance Status Scale is one such measurement. It describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability (walking, working, etc).

Statistical Analysis :

Statistics were analysed using version 22.0 of SPSS software. Descriptive statistics were calculated as the Mean ± Standard Deviation of age and frequency of demographic factors was tabulated according to age, gender, marital status, family income, level of education, occupation, relation with patient, patient's present treatment, present status of the disease (recurrent, metastatic, non-metastatic), treatment history, CQOL-Cresponse in Mean±SD form and ECOG score. To define Socio-demographic impact on Caregivers' Quality of Life, we had dived two groups according to level of CQOL-C (following scale's norm)- Group-A (those whose score lies under mild and moderate) and Group-B (those whose score were lied under severlevel).We had used "t" test to compare the Mean±SD between mentioned two groups to determine the impact of Socio-demographic factors. We had used "t" test to compare the Mean±SD between mentioned two groups according to their patients' ECOG response.

Results

Demographic Information :

Table 1 depicts the baseline demographic and clinical characteristics of their patients of the study participants. In the present study percentage of female caregiver was more than male individuals (61% *versus* 39%). In part of age group, caregivers with age within 31-40 years were higher (35%) than other age groups, living with spouse (88%), 67% of participants were coming from urban areas and 48.5% of participants belongs under middle class family. Majority (33.5%) of the primary caregivers were related to their children (son or daughter).

In case of patients' Clinico-pathological and treatment history, most of the patients were diagnosed with solid tumour (79%) and 41% patients were under chemotherapy. 73.1% of patients were under treatment within <6 months.

In area of CQOLC response, 60.57% of caregivers having sever hampering their QoL.

Table 2 depicts the baseline demographic and

Table 1 — *Prevalence of Demographic details among all Participants*

Socio-demographic Factors	N=175
Gender :	
Male	39%
Female	61%
Age :	
<30 years	9%
31 to 40 years	35%
41 to 50 years	23%
51 to 60 years	14.5%
>60 years	18.5%
Relationship Status :	
Living with spouse	88%
Living without spouse	12%
Community areas :	
Urban	67%
Rural	33%
Education :	
Primary	10%
Secondary	44.2%
Graduate	45.8%
Socio-economic status (Kuppus- wamy scale) :	
Lower middle class	29.1%
Middle class	48.5%
Upper middle class	22.4%
Relation with patients :	
Children	33.5%
Spouse	28.4%
Sibling	27.1%
Parent	11%
Diagnosis :	
Solid tumour	79%
Haematological Malignancy	21%
Treatment : Standard care treatment	
Surgery	36%
Chemotherapy	41%
Radiation	5%
Chemotherapy and Radiation	10%
Palliative care	8%
Duration *of* treatment :	
<6 months	73.1%
>6 months	26.9%
CQOLC - score :	
Mild (0-30)	12% (N=12)
Moderate (30-60)	27.43% (N=48)
Sever (60-136)	60.57 (N=106)

clinical characteristics of the study participants. The majority of them belonged to lower middle-class Socio-economic status (according to Kuppus- wamy scale). Both the study groups were comparable at baseline except gender (p= <0.00) age (p= <0.00), Socio-economic status (p= <0.00), areas of living (rural and urban) (p= <0.00), relation with spouse (p= <0.00) and their patients' treatment at that time (p= <0.00).

Table 3 was presented the statistical variation between two groups according to the domain of the scale. The score of disruptiveness (p= <0.00), financial condition (p= <0.00) and positive adaptation (p= <0.00) was made statistical significant difference between two groups.

Table 2 — *Prevalence of Demographic details among Participants according to CQOLC's Response*

Socio-demographic Factors	Group-A (N=69)	Group-B (N=106)	P-value
Gender :			
Male	67%	49%	0.002*
Female	33%	51%	
Age :			
<30 years	21%	11.3%	0.000*
31 to 40 years	25%	9.1%	
41 to 50 years	18%	10%	
51 to 60 years	18.2%	31.1%	
>60 years	17.8%	38.5%	
Relationship Status :			
Living with spouse	69%	66.4%	1.21
Living without spouse	31%	33.6%	
Residential areas :			
Rural	43.2%	34.5%	0.002*
Urban	56.8%	65.5%	
Education :			
Primary	33.6%	34%	0.075
Secondary	34.2%	29.2%	
Graduate	32.2%	36.8%	
Socio-economic status :			
Lower middle class	21.3%	51%	0.000*
Middle class	18.5%	30.4%	
Upper middle class	60.2%	18.6%	
Relation with patients :			
Children	31.5%	11.5%	0.000*
Spouse	28.4%	39.2%	
Sibling	29.1%	13.4%	
Parent	11%	35.9%	
Diagnosis :			
Solid tumour	13.9%	71.2%	0.003*
Haematological Malignancy	86.1%	28.8%	
Treatment : Standard care treatment			
Surgery	36.9%	12.3%	0.000*
Chemotherapy	9.4%	45.1%	
Radiation	25.7%	10.1%	
Chemotherapy and Radiation	16.7%	9.7%	
Palliative care	11.3%	22.8%	
Duration *of* treatment :			
<6 months	33.1%	49.5%	1.3
>6 months	66.9%	50.5%	

Table 3 — *Mean Scores and Standard Deviations for each Subdomain of the CQOLC Index among all Participants*

Subdomain	Group A	Group B	p-Value
Burden	21.08±11.7	22.13±13.1	1.12
Disruptiveness	39.34±12.65	55.2±16.3	0.000*
Positive adaptation	55.09±18.7	31.06±2.1	0.003*
Financial Concerns	65.12±22.1	89.21±19.7	0.000*
Undefined Subdomain	12.09±12.5	13.11±1.9	1.14

Table 4 was elaborated in statistical form, variation in patients' performance (according to ECOG) and their caregivers' response about QoL.

Discussion

The findings from the present single institution, observational and descriptive study shows us that the number of female caregivers was higher than male

Table 4 — *Distribution of CQOLC Scores according to the Performance Status of their Patients*

ECOG-Performance Status	Group A	Group B	(Mean±SD) p-Value
Fully active, able to carry on all pre-disease performance without restriction	55.6%	5.2%	(51.23±12.4) *versus* (88.21±21.9) = 0.000*
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work	14.2%	15.7%	(50.23±11.6) *versus* (76.34±20.1) = 0.000*
Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	9.3%	21%	(48.12±17.4) *versus* (74.09±19.2) = 0.000*
Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	11%	27%	(49.3±19.1) *versus* (79.12±20.12) = 0.000*
Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	9.9%	31.1%	(42.09±13.2) *versus* (71.23±18.7) = 0.000*

individuals (61% *versus* 39%). QoL deterioration is evident among female primary caregivers compare with male (83.12±20.98 *versus* 51.16±12.07) of cancer patients in India. The overall goal of this study was to identify the significant clinico-demographic factors affecting a primary caregiver's Quality of Life of cancer patients during the period of oncological care.

Most of the primary caregivers fall in the age range of 40.43±12.33 years. According to the statistical analysis, age difference of the caregivers significantly correlated with their QoL scores (Table 2). It has been observed that young caregivers can handle the process of caregiving better and more smoothly than older caregivers. Moreover, young caregivers, often neglect their education; putting their education on hold or dropping out entirely which can impact their future career. That's why trends toward worse CQOL-C index scores were observed among caregivers under 30 years of age. In our study, the majority of caregivers were females than males. The women are commonly the ones that take care of the routine of the house. Simultaneously, the current study confirms symptoms of physical condition in older caregivers (>65 years) seems to be a risk factors for their reduced QoL[5]. This gender differences had created positive impact of the CQOL-C scores (Table 2)[6]. This is consistent with our tradition and culture where male provide financial support to the family as mostly they are the sole bread concerns. The loss in the caregiver's income and reduction in savings is regularly excluded in estimates quantifying the cost of cancer care. Specifically, lower income caregivers' who are responsible for other dependence are at high risk for losing a significant portion of their financial reserves because cancer treatment is relatively costly and this economic factors can affect caregiver's Quality of Life. It has been also observed that caregivers with low levels of education affected their QoL. In part of education, caregivers with primary level education or a lack of education find difficulty in understanding the symptoms of the disease and tends to have miscommunication with the doctors. The caregivers who are daughter or son, who are married were seen to have problems in their marital lives as their entire focus goes to the care of the patient and thus they tend to ignore their spouses and babies. The duration of caregiving also affects the QoL of the caregivers because during the long period of caregiving, the caregivers' experience stress and burden resulting from the rigorous activity of caregiving which can have a negative impact on their physical, psychological and social lives, thereby decreasing their QoL[7]. Since, West Bengal is culturally and economically diverse, it is very important to take into account the Socio-demographic aspects of the caregivers as it can impact the psychological distress of an individual.

The difficult experience of dealing with cancer is unique to each patient. When we compare the QoL scores according to the type of cancer, it has been observed that in patients with Head and Neck cancer, their primary caregivers' QoL is mostly affected than other types because late side-effects of the surgery, eg. it is difficult for the patients to communicate post-surgery and the facial changes in the patients also lead to distress in patients and their caregivers. Activities deteriorates which in turn becomes difficult for the caregivers to manage. In part of treatment perspective, those patients were under pain and palliative care, their caregivers' Quality of Life was more affected when comparing other treatment. It is difficult for them to accept the fact that cancer is no more curable or day to day their patients' physical deterioration after giving their best level of dedication to give a better Quality of Life or economical condition[8]. During the period of chemotherapy, patients who are highly symptomatic either due to cancer or due to side effects of chemotherapy need more constant and increased duration of caregiving time that prone to psychological, physical, financial and social reactions and leads to worse QoL to a caregiver[9].

Caregivers of patients with ECOG 2-3 experienced a worse QoL than better ECOG patients, which is understandable as patients with worse ECOG are more dependent on caregivers for their Activities of Daily Living (ADL). The knowledge of the caregiver's Quality of Life and burden during the treatment of cancer patients at any stage or ECOG are very important support for caregivers by the multidisciplinary team (social worker, nursing and psychology) could contribute to a better Quality of Life for patients and caregivers[10].

Limitations :

Our study was a single centred study with smaller sample size. The follow up of caregivers' QoL in case of good QoL as well as moderate towards sever QoL in the different phase of treatment modality was addressed but the study did not follow up caregiver population who had good QoL and mild, moderate psychological distress. Those populations need to be reassessed for early identification of QoL.

Conclusion

Majority of the caregivers in our study have presented worse score of QoL. QoL is affected by the Socio-demographic aspect that is a caregivers' marital status, economical condition, education as well as a patient's health performance. We are going to propose screening for differences in perception of patient QoL as a way of identifying distressed caregivers as well as provider-facilitated communication between patients and caregivers as possible interventions that should be examined in future research.

Relevance for Clinical Practice :

Cancer can impact the psychological well-being of both patients and their primary caregivers. Caregivers provide both practical and emotional support and often play an important role in the coordination of the best care for breast cancer patients. However, but, so far, there have been but few studies discussing the relationship between Socio-demographic factors and caregivers' Quality of Life. Present papers have documented the considerable impact that caregiving has on caregiver Quality of Life (QoL).

Financial support and sponsorship : Nil.

Conflicts of interest : There are no conflicts of interest.

References

1 Kulkarni SS — Quality of Life of Primary Caregivers Attending a Rural Cancer Centre in Western Maharashtra: A Cross-Sectional Study. *Indian J Med Paediatr Oncol* 2021; **42**: 268-72.
2 Weitzner MA, Jacobsen PB, Wagner ., Friedland J, Cox C — The Caregiver Quality of Life Index-Cancer (CQOLC) scale: Development and validation of an instrument to measure quality of life of the family caregiver of patients with cancer. *Qual Life Res* 1999; **8**: 55-63.
3 Ehmann AT, Mahler C, Klafke N — Validation of a German version of the Caregiver Quality of Life Index-Cancer (CQOLC) in a sample of significant others of breast and gynaecologic cancer patients. *Psicol Reflex e Crit* 2020; **33.**
4 Rhee YS — Korean version of the Caregiver Quality of Life Index - Cancer (CQOLC-K). *Qual Life Res* 2005; **14**: 899-904.
5 Jafari H, Ebrahimi A, Aghaei A, Khatony A — The relationship between care burden and quality of life in caregivers of hemodialysis patients. *BMC Nephrol* 2018; **19**: 1-8.
6 Manivannan M, Karunanithi G, Lakshminarayanan S — Correlation between Quality of Life and Burden in Caregivers of Advanced Stage Cancer Patients on Best Supportive Care. *Indian J Palliat Care* 2022; **29**: 89-93.
7 Vashistha V, Poulose R, Choudhari C, Mohan A — 283-Article Text -for regular issues-1713-1-10-20190716, 2019. **4**: 87-93.
8 Krug K, Miksch A, Peters-Klimm F, Engeser P, Szecsenyi J — Correlation between patient quality of life in palliative care and burden of their family caregivers: A prospective observational cohort study. *BMC Palliat Care* 2016; **15**: 1-8.
9 Kilic ST, Oz F — Family caregivers' involvement in caring with cancer and their quality of life. *Asian Pacific J Cancer Prev* 2019; **20**: 1735-41.
10 Singh K — Factors Impacting Quality of Life of Caregivers of Cancer Patients in the Sub-Himalayan Region: A Cross-Sectional Study. *Cureus* 2023; **15**: 2-9.

Original Article

A Retrospective Observational Study : To Study the Correlation of Endometrial Thickness *versus* Endometrial Pattern on Implantation in North Indian Females

Poonam Singh[1], Rajesh K Singh[2], Rajul Rastogi[3], Kshama Gandhi[4]

Background : To evaluate the relationship of endometrial thickness and endometrial pattern on implantation of transferred embryos inautologous and donor cycle.

Design : Retrospective study.

Materials and Methods : Patients (n=1081), age 21-40 years, autologous as well as donor embryo transfers performed between July, 2015 to February, 2022.

Intervention : Endometrial thickness and endometrial pattern measured on trigger day and embryotransfer day by Ultrasonography (TVS)

Results : A total of 530 gestational sacs, 441 pregnancies and 134 clinical pregnancies resulted from 1251 cycles. Endometrial thickness varied from 4mm-13mm in clinically positive pregnancies. No particular thickness seemed associated with positive pregnancy cases. Endometrial pattern II & III were seen to be associated with maximum positive cases. Endomertial pattern I was associated with lower pregnancy rates.

Conclusions : Endometrial thickness seems having less correlation with the pregnancy outcome. Endometrial patten is more important factor for conception. Endometrial pattern II & III seems having a correlation with implantation rate.

Support : Endometrial pattern, but not thickness, affects implantation rates in euploid embryo transfers (fertility and sterility Vol 104, No 3 September, 2015).

[*J Indian Med Assoc* 2024; **122(3):** 30-2]

Key words **: Endometrial thickness, Endometrial pattern, Implantation, Pregnency.**

Infertility is a major contributory factor that affects public health, distressing both men and women. As per WHO data, infertility is perceived to be a public health problem once its frequency surpasses 15%[1].

If even after detailed screening tests any causative aetiology of infertility has not been found, it is classified as "unexplained infertility".

After being treated 18.5% of these patients will remain unable to conceive. Thus, it is noteworthy that presently available diagnostic tests are insufficient to assess the causes behind unexplained infertility[2].

Once preliminary treatment modalities fail to bring intended results, couples may opt for Assisted Reproductive Technology (ART)

Although Ovarian stimulation practices have upgraded aggressively and enabled us to obtain plenty of mature oocytes as well as embryos for transfer, percentage of successful IVF has not improved proportionally[3]. Hence, successful implantation as well as endometrial receptivity is to be focused upon[4]. Implantation still is one of the foremost limiting parts in the field of ART & implantation is ultimately dependent upon endometrial receptivity[2,7].

Endometrial receptivity can be assessed by its patter and thickness to some extent, apart from color flow studies of endometrium by Trans Vaginal Sonography (TVS).

Editor's Comment :

- Endometrial receptivity plays a crucial role in the successful implantation of an embryo.
- The triple-layer pattern of the endometrium serves as an indicator of its receptivity.
- Even if the endometrium is sufficiently thick, its receptivity may still be compromised if the pattern is inadequate.

Material and Mehods

Total 1081 patients were included in the study. 1251 cycles of IVF/ICSI/ET/IUI were carried out during July, 2015 till February, 2022 at Teerthanker Mahaveer Medical College & Sparsh IVF centre.

Teerthanker Mahaveer Medical College & Research Centre, Uttar Pradesh 244001

[1]MBBS, MD, Professor, Department of IVF Obstetrics & Gynaecology and Corresponding Author

[2]MBBS, DMRD, DCH, Chief Consultant, Department of Radiology, Neuromed Diagnostic Centre, Uttar Pradesh 244411

[3]MBBS, MD, Professor, Department of Radiology

[4]MBBS, MD, Junior Resident, Department of Obstetrics & Gynaecology

Received on : 02/05/2023

Accepted on : 12/10/2023

Inclusion Criteria :

- Age <40 years with history of infertility, might be primary or secondary infertility, married for at least 2 years, sexually active.
- Normal size and shape of the uterus without any structural anomaly as evidenced by Trans Vaginal Ultrasound or Hysterography.
- Endometrial thickness <7 mm on day 14 of menstrual cycle.
- Able to attend follow up as per schedule.
- No known chronic medical illness.
- Gave Informed consent.

Exclusion Criteria:

- Patients having any endocrine disease.
- History of prior hysteroscopic surgeries.
- Congenital uterine anomaly, myoma, adenomyosis etc.
- Severe hepatic, renal or cardiovascular impairment
- Smokers.

Endometrial thickness and pattern of all the participating patients was noted by TVS on the day of embryo transfer or IUI - using by a Siemens S2000 scanner with a transvaginal multifrequency probe.

According to Endometrial thickness, patients were classified into type I, II,III TYPE of endometrium.

Type I : ≤7 mm

Type II : > 7 mm to ≤14 mm

Type III : > 14 mm.

According to endometrial pattern, patients were classified into GROUPS.

A : Triple-line pattern consisting of a central hyperechoic line surrounded by two hypoechoic layers.

B : An intermediate isoechogenic pattern with the same reflectivity as the surrounding myometrium and a poorly defined central echogenic line.

C : Homogenous, hyperechogenic endometrium.

Statistical Analysis :

Data was entered into predesigned proforma and was updated accordingly in Microsoft Excel sheet for analysis. Nominal data were expressed in numbers and percentage whereas for the normally distributed continuous variables, the data were given as Mean ± Standard Deviation. 't' test and ANNOVA tests were utilized as tests of significance. P value ≤0.05 was regarded as statistically significant.

Demographic Characteristics :

For this study, a total of 1085 patients with infertility were evaluated during designated study period.

Table 1 shows distribution of patients who were enrolled in the study according to age. The patients' age ranged from 20 to 40 years with majority of patients belonging to 26-30 years age group.

Table 1 — *Distribution of study population according to Age*

Age (years)	No of women	%
20-25	156	14.4
26-30	380	35.1
31-35	216	20.0
36-40	329	30.4

Table 2 displays the distribution of types of infertility. In my study, majority of patients had primary infertility. 65% patients had primary infertility whereas 35% patients came with secondary infertility

Table 2 — Distribution of type of Infertility among study population

Primary	65%
Secondary	35%

Observation and Results

The patients having type II & III endometrium, had maximum implantation rates. It is the pattern, which is more important rather then thickness, as pregnancies have occurred in up to 4.6 mm thick endometrium.

Discussion

Endometrial receptiveness is decisive for successful implantation. An endometrium that has thickness of <7 mm on the day of ovulation is regarded as thin[7]. Endometrial thickness and pattern are self-determining parameters that influences pregnancy consequences and a thin endometrium is a negative predictive factor for pregnancy in itself with or without ovarian stimulation[5-7].

Concerning endometrial thickness and pattern, Al Mohammady, *et al* 8 evaluated 100 women with infertility on ICSI cycles, he recorded the Ed Th as well as endometrial pattern on the day of HCG administration and afterwards Clinical Pregnancy Rate (CPR) was computed, after analysing the results, trilaminar pattern exhibited the maximum occurrence of pregnancy. Scrutiny of pregnancy rate with relation to different endometrial patterns and Ed Th set gave away the fact that trilaminar pattern with an Ed Th of 10-12.9 mm results in maximum CPR, so they concluded that Ed Th of 10-12.9 mm with trilaminar pattern is associated with higher clinical pregnancy during ICSI cycles. In our study although CPR was not a parameter, Chen, *et al*[β], after thoroughly analysing 2896 fresh IVF/ICSI cycles utilizing long protocol and calculating Ed Th and assessing endometrial pattern with TVS on the day of HCG administration deliberated that collective assay of Ed Th and pattern on the day of HCG injection, rather than separate evaluation of a parameter was a more reliable prognosticator of the IVF/ICSI-ET results.

Table 3 — *Percentage of Pregnancies of achieved in various patterns of Endometrium*

Group	Pattern A	B	C	P
I	11.1% (3/27)	6.9% (3/43)	22.2 % (4/18)	NS
II	40% (351/871)	33.1% (258/779)	25.1% (37/147)	<0.05
III	31.7% (70/221)	35.7% (35/98)	33.3 %(5/15)	NS
P	<0.05	<0.01	NS	

Conclusion

Our study shows, if the endometrium is type II or type III pattern, it is the favourable feature to conceive. Conception occurs in thin endometrium (up to 4.6 mm) if the pattern of endometrium is good.

Ehical Clearence :

The study was approved by Institutional Ethical Committee.

Refrences

1 Montgomery R — WHO considers new definition of infertility that includes being single [Internet].2016 [cited 24 october 2016]. Available from: bionews.org.uk/page_95744.

2 Brandes M, Hamilton CJ, van der Steen JO, de Bruin JP, Bots RS, Nelen WL, *et al* — Unexplained infertility: overall ongoing pregnancy rate and mode of conception. *Hum Reprod* 2011; **26(2):** 360-8. doi: 10.1093/humrep/deq349.

3 Diedrich K, Fauser BC, Devroey P, Griesinger G — Evian Annual Reproduction (EVAR) Workshop Group. The role of the endometrium and embryo in human implantation. *Hum Reprod Update* 2007; **13(4):** 365-77. doi: 10.1093/humupd/dmm011.

4 Karizbodagh MP, Rashidi B, Sahebkar A, Masoudifar A, Mirzaei H. Implantation Window and Angiogenesis. *J Cell Biochem* 2017; **118(12):** 4141-51. doi: 10.1002/jcb.26088.

5 Zhang S, Lin H, Kong S, Wang S, Wang H, Wang H, *et al* — Physiological and molecular determinants of embryo implantation. *Mol Aspects Med* 2013; **34(5):** 939-80. doi: 10.1016/j.mam.2012.12.011.

6 Dehghani Firouzabadi R, Davar R, Hojjat F, Mahdavi M — Effect of sildenafil citrate on endometrial preparation and outcome of frozen- thawed embryo transfer cycles: a randomized clinical trial. *Iran J Reprod Med* 2013; **11(2):** 151-8.

7 Kasius A, Smit JG, Torrance HL, Eijkemans MJ, Mol BW, Opmeer BC, *et al* — Endometrial thickness and pregnancy rates after IVF: a systematic review and meta-analysis. *Hum Reprod Update* 2014; **20(4):** 530-41.

8 Al Mohammady M, Fattah GA, Mahmoud M — The impact of combined endometrial thickness and pattern on the success of intracytoplasmic sperm injection (ICSI) cycles. *Middle East Fertility Society Journal* 2013; **18(3):** 165-70.

Original Article

Introduction of a 'Capsule-course' in Faculty Development Programme for the 'Tutors & Residents' in a Medical College of Kolkata

Munmun Das Sarkar[1], Smita Damke[2], Kuntala Ray[3], Hironmoy Roy[4]

Background : In RBCW & CISP programmes (total 6 days workshop) faculties above the tier Assistant Professor gets only eligiblility to participate. The tutors & residents of a department, who takes pivot role in practical/demonstration classes does not get scope to participate in NMC approved RBCW/CISP programmes. It makes a mandatory gap in faculties' knowledge-attitude-practice in successful implementation of CBME in department.

Objectives : (a) So this project was undertaken to implement a 'Capsule-course' in one-day orientation programme solely for the residents & tutors to sensitise them in relevant aspects of CBME, (b) to obtain immediate feedback for the workshop & (c) to assess the knowledge-attitude of their own perception after two months of the workshop

Materials and Methods : with proper approval, a one-day sensitization workshop on core aspects of CBME was arranged. Pre-test, post-test questionnaire were applied and feedback was taken from all participants. Forty (40) faculties participated in the workshop. After two months a self assessment questionnaire was introduced to assess their confidence/ ability level for CBME & its implementation.

Results : Total 40 fellows (18 demonstrators & 22 residents) joined the programme. During the workshop the pre-test & post test result showed statistically significant ($p<0.05$ at $df=19$) improvement in knowledge of the participants. On teachers' self assessment after two months of the workshop, it explored that fellows have initiated to frame learning objectives for their class (3.8 ±0.48), carry on DOAP sessions (3.9±0.87), providing effective feedback (4.2 ±0.483) to the students etc.

Conclusion : The one-day sensitisation program imparted positive impact on development of knowledge and changes in attitude among the residents & tutors in their teaching of practical/ demonstration classes. Such One-day sensitization workshop may be arranged for Demonstrators/Tutors/residents of all disciplines. Customized Faculty Development programs may also be arranged as continued education programme or refresher course for all faculties after assessing the actual need and gap analysis.

[*J Indian Med Assoc* 2024; **122(3):** 33-8]

***Key words* : Mini-RBCW, Mini-CISP, Faculty Development Programme, Refresher Module.**

The medical education system all over the world is witnessing a paradigm shift from current/ traditional type of medical education to competency-based medical education. The Competency-based Medical Education (CBME) is an outcome-based approach to design, implementation, assessment and evaluation of a medical education program with an organized framework of competencies[1-5].

The new Competency Based Medical Education (CBME) module for the undergraduate teaching has been mandated from the 2019 entrant batch in MBBS level. NMC has started the faculty developments programmes as- The RBCW/CISP programmes (Revised Basic Course Workshops/ Curriculum Implementation Support Programmes) to sensitise the faculties regarding the new aspects of the CBME. Unfortunately the basic teachers (tutors & residents), who plays pivot role in teaching the practical classes and bed side clinics, are not allowed to participate in the training programme. So with different topics extracted from the RBCW & CISP programme, the a 'Capsule-course' to the tutors & residents has been planned and conducted as one day sensitisation in a medical college of Kolkata as the pilot work.

Editor's Comment :

- NMC has introduced the BCME (erstwhile RBCW) as well as CISP course for the faculties of medical colleges 'from and above the rank of Assistant Professors'. Unfortunately the residents, tutors, who used to take huge load of practical demonstration classes remains out of those exposures. So in this article authors tried to implement a one day exposure course as "capsule course" with selected topics of both BCME and CISP curriculum which can be two ways used — in one hand this curriculum can give a mini-exposure to residents and tutors and in other hand can be used as refresher for the other facilities.

[1]MD, Professor, Department of Microbiology, Calcutta School of Tropical Medicine, Kolkata 700073

[2]MD, Professor, Department of Microbiology, Jawaharlal Nehru Medical College, Sawangi, Maharashtra 442005

[3]MD, Associate Professor, Department of Community Medicine, IPGME&R and SSKM Hospital, Kolkata 700020

[4]MD, Professor, Department of Anatomy, IPGME&R and SSKM Hospital, Kolkata 700020 and Corresponding Author

Received on : 28/02/2023

Accepted on : 01/04/2023

Aims and Objectives

(1) To conduct one-day faculty development programme for the residents & tutors, to sensitize them for CBME & its implementation.

(2) To explore the feedback of the participants of the one-day faculty development programme, after the workshop.

(3) To explore the knowledge & attitude of the participants of the one-day faculty development programme, after two months of the workshop.

Materials and Methods

- **Study design :** Longitudinal study.
- **Study setting :** Institution based, done in Calcutta National Medical College, West Bengal.
- **Study duration :** Six (06) months
- **Study participants & sampling :** tutors and residents of different disciplines were approached to be included in the work. For feasibility, tutors and residents of the pre & para-clinical disciplines were approached to be included in this work. Thus, total 40 participants were enrolled as first come-first serve basis.
- **Data collection method:**

As this was the project of Advanced Course in Medical Education under Jawaharlal Nehru Medical College NMC Nodal Centre, Sawangi, Maharashtra; so at first approval was obtained from them. Then, necessary permissions were obtained from the Principal, Calcutta National Medical College (CNMC), Kolkata and the Ethics Committee of the CNMC (Letter no. Microbiology CNMC 97 dt. 26/11/2020), Kolkata.

A team was built with the help of the members of Medical Education Unit of CNMC. The topics to be covered in the one day workshop were thoroughly discussed and finalised. Opinions were also taken from the experts in the field of medical education from other institutions to finalise the topics and their sequences.

Once the participants got finalised and logistics got approved from the college authority, the one day workshop on core aspects of CBME was arranged with the programme schedule as —

At the beginning of the programme and at the end of the programme, the participants were subjected to Pre-test and post-test with a predesigned pre-tested questionnaire to evaluate the changes in knowledge resulting from the workshop.

Feedback regarding the sensitization program was also taken from the attendees.

After two months time a cross sectional survey was carried on using a pretested predesigned semi-structured questionnaire amongst all the participant faculties and residents; ensuring the anonymity; upon their knowledge of CBME curriculum, attitude for implementation as well as planning to implement CBME curriculum and perceived constraints towards implementation. The responses received were recorded and analysed using Microsoft Excel sheet and suitable statistical tool.

- **Data analysis:** The responses received in pre-test and post-test survey during sensitization program, filled in Feedback form and preparedness perception assessment survey questionnaire have been analyzed using Microsoft Excel sheet and suitable statistical tool.

Result

Total 40 faculties participated in the one day sensitisation programme. Among them 22 were residents and 18 were demonstrators/ tutors of different disciplines.

Pre-test & Post test :

Paired t-test has been conducted with the mean value of pre-test and post-test of the itemwise correct responses. It has been seen that the t-value is 9.4516 with $p<0.05$ at df=19. So the increment between the score of the pre-test *versus* post-test is statistically significant in this case. From the pre-test & post-test results detailed in Table 1, it is evident that there is considerable increase in correct response against all 20 questions answered by the participants.

The improvement of knowledge of the participants after the sensitisation programme was statistically significant ($p<0.05$ at df=19). From this it may be concluded that the one day sensitisation program successfully achieved its objectives (Table 1, Fig 1).

Time	Topic	Duration
9.15 am	Registration	15 minutes
9.30 am to 9.45 am	Pre test survey	15 minutes
9.45 am to 10.00 am	Ice breaking and Group Dynamics	15 minutes
10.00 am to 10.30 am	Brief introduction of CBME	30 minutes
10.30 am to 11.00 am	CBME module- how to read it?	30 minutes
11.00 am to 11.15 am	Tea Break	15 minutes
11.15 am to 11.45 am	Domains of learning & Millar's pyramid	30 minutes
11.45 am to 12.15 pm	SLO making from competency	30 minutes
12.15 pm to 01.15 pm	SLO making - *Workshop* in groups	01.00 hour
01.15 pm to 2.00 pm	DOAP & other interactive teaching methods in SGT & practical sessions *(TL methods implacable for practical/ demonstration classes)*	45 minutes
2.00 pm to 2.30 pm	Lunch	30 minutes
2.30 pm to 3.00 pm	Assessment methods aligning to CBME	30 minutes
3.00 pm to 3.30 pm	How to frame checklist & conduct OSPE? - *Workshop*	30 minutes
3.30 pm to 3.45 pm	Tea Break	15 minutes
3.45 pm to 4.15 pm	How to give an effective feedback to the student?	30 minutes
4.15 pm to 4.30 pm	Exit ticket- the way to improvise ourselves	15 minutes
4.30 pm to 5 pm	Closure & valedictory	

Table 1 — *Comparison of the item wise correct responses by the participants in Pre & Post Test, on the day of the workshop held [Multiple Choice question] (N=40)*

Question	Correct responses in Pre-test	%	Correct responses in Post test	%
The full form of **CBME** is	34	85.0%	39	97.5%
Which of the **5 roles** of Indian Medical Graduate are defined by Medical Council of India	17	42.5%	37	92.5%
The **goal** of undergraduate medical education in India is to produce the professionals, who can	30	75.0%	39	97.5%
For traditional system of examination which statement lies **false**?	11	27.5%	33	82.5%
Competency is the measurable sets of knowledge, skill and	9	22.5%	37	92.5%
Acronym for **OSCE** stands for	17	42.5%	36	90.0%
Cognitive Domain involves all **except**	11	27.5%	38	95.0%
All are the examples of self-directed learning **except**	29	72.5%	39	97.5%
The most suitable statement regarding Modified Essay Question	12	30.0%	38	95.0%
All are the examples of Teaching Learning Methods, except	13	32.5%	39	97.5%
As per the present assessment system which statement is **false**?	3	7.5%	35	87.5%
Advantages of 'Traditional Lecture' are all **except**	22	55.0%	36	90.0%
For preparation of a good power point presentation, one must look into all **except**	21	52.5%	38	95.0%
True for 'small group discussion' are all **except**	17	42.5%	38	95.0%
Which of the following is **NOT** a component of SLO (Specific Learning Objective)	2	5.0%	37	92.5%
In a University Examination MCQ type question should be	17	42.5%	31	77.5%
Feedback should not be	28	70.0%	37	92.5%
For Practical Class DOAP session is often suggested, it includes all **except**	34	85.0%	40	100.0%
The CBME module directly tells us all **except**	2	5.0%	32	80.0%
If, for a competency the action verbs are "identify & describe", domain mentioned "skill", then which of the following is not appropriate?	25	62.5%	37	92.5%

Group	**Pre-test**	**Post-test**	**Value of Paired T-Test**
Mean	17.70	36.80	t = 9.4516, with df
SD	10.08	2.42	(degree of freedom)= 19
	p<0.05		

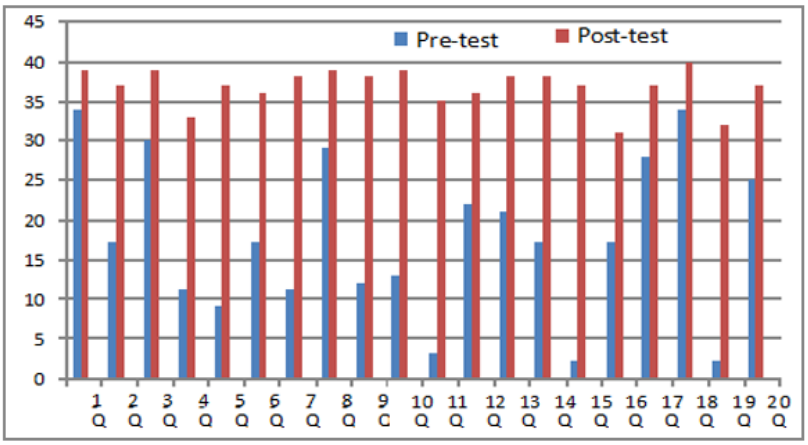


Fig 1 — Scores of Pre & Post-test of the participants

Feedback for the Workshop :

At the end of the one day sensitisation programme the participants were asked to submit feedback on the following two aspects for each session:- "How far do you feel knowledgeable for the session?"

Table 2 represents acquisition of knowledge on various aspects of the CBME curriculum during the sensitisation programme. The result shows that the participants felt that they had remarkable improvement of knowledge on this new curriculum. As per our assessment, the improvement of participants in every session has been reflected by an increase of score, with an average percentage increment of 189.03.

Knowledge - Attitude Assessment after Two Months of the Workshop :

A cross sectional survey was conducted using a pretested predesigned semi-structured questionnaire among the participants upon their knowledge of CBME curriculum, attitude for implementation as well as planning to implement CBME curriculum and perceived constraints towards implementation. The responses received are tabulated as under Table 3.

Discussion

This 'mini'- sensitisation workshop was conducted to sensitise the unsensitized faculties to run the CBME programme with highlights of the issues covered in revised basic Course workshop and the Curriculum Implementation Support Programme of NMC; with sole ambition to sensitise the tutors & residents.

There remains difference in perception regarding acquisition of knowledge (189.03%) of the lessons learnt in the different sessions. So, the feedback taken

Table 2 — *Perception of the participants for the knowledge gained in the workshop (responses taken in 5 point linear scale as 0 to 5)*

Name of the Session	How Far do you feel knowledgeable for the session?		
	Before the session (mean score)	After the session (mean score)	% increased rate
Ice breaking &Group Dynamics	1.7	4.27	151.17
Brief introduction of CBME	1.4	4.42	215.71
Alignment &Integration	1.3	4.2	223.07
Domain's of learning & Millar's pyramid	0.85	3.97	367.05
SLO Making from competency (workshop)	0.9	3.7	311.11
Newer teaching methods aligning to CBME	1.57	4.15	164.33
Assessment methods aligning to CBME	1.77	4.3	142.93
Importance of feedback in students assessment	2	4.2	110

In Table 2 the acquisition of knowledge on various aspects of the CBME curriculum during the sensitisation programme is detailed. The result shows that the participants felt that they had remarkable improvement of knowledge on this new curriculum. Overall percentage (%) of increment is 189.03%. As per our assessment, the improvement of participants in every session has been reflected by an increase of score, with an average percentage increment of 189.03.

is specific, directly linked to the purpose of learning and success criteria, could distinguish what learner has done well and could identify what has been misunderstood or not understood, focusing on the quality of the sensitization programme.

As regards the perception of participants regarding the multidisciplinary integrated teaching, though majority of them have never participated in such teaching activity before, but maximum participant felt positive regarding its benefit in students' education. Majority of them also believes that it is possible to adopt different modes of integrated teaching in their department. As per perception of the participants, such benefit can be best judged by data obtained from formative assessment ie, improved comprehension by students followed by Student's feedback and improved exam scores. It has also been observed that majority of participants believe that "giving and receiving Feedback" will definitely help to improve students' learning process.

The one-day sensitisation programme was organised just before the starting of the new curriculum-based Phase-2 MBBS programme to sensitise the faculties (mainly basic teachers/demonstrators) & residents of Phase-2, as per protocol who are not included in the NMC approved RBCW programme. Due to time constrain, some specific aspects of CBME could not be included in the one-day sensitisation programme and some aspects could not be stressed properly, hence the attendees are clearly lacking both in acquisition of knowledge in some areas of the new curriculum as well as perception and preparedness regarding implementation of CBME curriculum in their respective discipline.

But, considering the positive impact achieved, such faculty development programmes can be arranged in addition to RBCW programme and also for the basic teachers (demonstrators/tutors) & residents across the different phases, who are not included in the regular faculty development programmes as per protocol.

It the study of Howard Tandeter, *et al* (2014), importance of faculty development programme was stressed. Over 50% of respondents expressed interest in participating in most FD activities in most topics evaluated. The majority of teachers at medical schools in Israel lack formal training in areas considered essential to their academic performance. In spite of their high sense of competence they are interested in participating in FD activities[2].

Shaifaly M Rustagi, *et al* reported in their study that the proper implementation of CBME would require

Table 3 — *Participants' self assessment on ability to implement CBME & its components; after two months of the workshop (responses collected in 0 to 5 linear scales according to their perception)*

	Mean	SD
I can correctly appraise the learning need of the students	3.1	0.567646
I practice regularly to go through the CBME module in my discipline to get accustomed with the competencies given	3.3	0.674949
I can frame Specific learning objectives from a given competency maintaining its all ABCD component	3.8	0.483046
I always narrate the learning objective to the students in my class	3.5	0.707107
I practice regularly the lesson planning on the day before my class	3.2	0.421637
I practice regularly to address all four steps of DOAP to individual students in the demonstration class	3.9	0.875595
I practice regularly to arrange interactivity during the small group tutorial sessions allotted to me	3.1	0.567646
I practice regularly to collect anonymous 'exit ticket' from students after the class	4.1	0.674949
I can refine my teaching content & methods based on students' feedback	3.2	0.632456
I can frame the checklist for OSPE (aligning the SLOs) for assessment	3.1	0.737865
I practice to address comprehension-analysis-synthesis-application levels while assessing reasoning skill of the students	4.1	0.567646
I practice regularly to give effective feedback to every student whom I assess	4.2	0.483046
	3.508333	0.437884

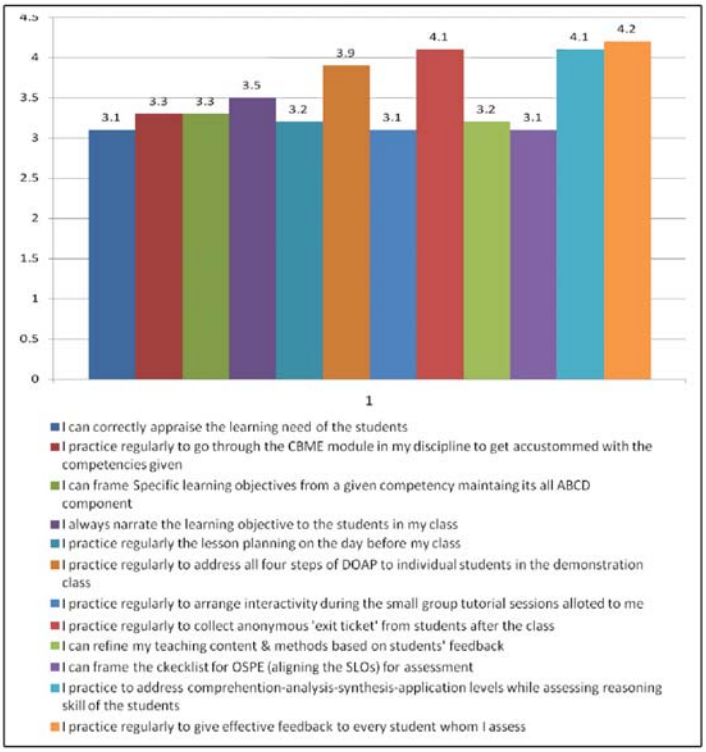


Fig 2 — Self-declaration of the practice of the participants

more clarity and continuous efforts by Medical Education Units (MEU) under guidance of the MCI to update their faculty in the form of Curriculum Implementation Support Programs (CISPs), Revised Basic Course Workshops (RBCWs) and advanced courses in medical education[3].

Shrivastava SR, *et al* conducted a descriptive qualitative study among the faculty members of the community medicine department. A total of 20 responses were obtained pertaining to the key aspects of CBME, of which 12 were identified as the salient variables depending on the cut-off value of 0.125 (Smith's Salience Score) and subjected to pile sorting. Eight challenges were identified in the implementation of the programme during the free listing and all were included in the second stage of pile sorting[4].

In the year 2020, Ghosh A, *et al* reported that the faculties who lacked any form of training, may miss to implement many vital aspects of teaching learning and knowledge of new curriculum which is completely new with respect to the didactic and traditional curriculum in the background of which the last generation of faculties have been trained. They have also suggested a new combined (3 days) program combining the content of both RBCW and CISP programs for training of new medical faculties[5].

Steve Mann, *et al* reported that Sixteen residents volunteered to participate in individual semi-structured interviews, with questions focussing on participants' knowledge of CBME and its implementation. The Residents anticipated improved assessment and feedback, earlier identification of residents experiencing difficulties in training and greater flexibility to pursue self-identified educational needs[6].

Shivani Upadhyaya, *et al* in their work explored that the Residents perceived aspects of this transformation as helpful but overall had mixed perceptions and variable understanding of the intended underlying framework. Understanding and disseminating successes and challenges from the resident lens may assist programs at different stages of CBME implementation[7].

Rashmi Ramanathan, *et al* in their study conducted among 1st year MBBS students (2019-2020 batch) reported that total of 987 students from 74 medical colleges in India were included and nearly three fourths of the participants opined that Foundation Course (FC), attitude ethics communication module and early clinical exposure were necessary. Horizontal integration was more appreciated to vertical integration. Maintaining log books was perceived as time consuming and cumbersome. Few reforms such as curtailing the duration of FC, diffuse sessions on stress and time management, better synchronized vertical integration, and an exemplary implementation of adult learning techniques can be undertaken[8].

Tameem, *et al* conducted a Questionnaire based study among the faculty members of department of Physiology and revealed lack of sensitisation of stakeholders and inadequate planning were identified as the predominant challenges in the implementation of CBME[9].

Dr. Sandeep Narwane, *et al* has reported that the responders perceived the new curriculum to have many advantages owing to introduction of competencies, horizontal and vertical integration as well as the AETCOM module. At the same time implementation of these curricula was opined to be a challenging task. The new curriculum also creates confusion and sense of inadequate arrangement[10].

Faculty members at medical teaching institutions have diverse responsibilities, such as teaching, research, patient care related matters and administration. Unlike other teachers, medical graduates and post-graduates become faculty members at different medical teaching institutions and they are asked to take on academic duties for which they have received no formal training[11]. The task of teaching in general is complex and difficult. Clinical teaching is especially difficult. Medical teachers

are expected to address a wide range of educational goals (knowledge, attitude and skills); to work with learners who vary greatly in their experience and abilities; to use variety of teaching methods (Lecture, small group, one to one etc) and to teach in different settings (Lecture hall, practical class, skill lab, inpatient, outpatient and community settings). Faculty development helps ensure that the educational reforms and initiatives are worthy and implemented properly. Professional organizations and experts advocate greater awareness and acquisition of knowledge in teaching and learning through comprehensive faculty development[12,13].

Therefore, in our study during the one-day sensitisation programme, pre-test and post-test was introduced to support the accomplishment of learning objectives with an improved understanding and to help the participants to focus on the key topics that were discussed and also to assess the knowledge gain during the programme. Feedback is a key element of the incremental process of ongoing learning. Providing feedback is a significant means of improving achievement in learning. It involves the provision of information about aspects of understanding and performance. Effective feedback is designed to determine a learner's level of understanding and skill development in order to plan the next steps towards achieving the learning intentions or goals.

Conclusion and Recommendation

This study provides the current picture of perception and preparedness of residents & tutors toward the new CBME curriculum alongwith requirement for more need based and specific faculty development programmes. Although the basic teachers, the residents and tutors are playing the pivot role and primary-contact teachers to the students, but the laid rule of NMC is debarring them to get sensitised from the RBCW/CISP programmes. So in the institutional level such one day 'Capsule-course' model may be implemented, which also may be used as the refresher course to the already sensitised fellows in long run.

Acknowledgement

The authors sincerely thanks to the faculties of Jawaharlal Nehru Medical College, Sawangi, Wardha, Maharashtra for their constant guidance in this project as the part of ACME (Advanced Course in Medical Education) programme. The authors convey their best regards to the Principal, Calcutta National Medical College; Dr Anindya Dasgupta, the the-then, MEU Co-ordinator, CNMC; Dr Satyajit Saha, Associate Professor, Department of Anatomy of Murshidabad Medical College (the the-then, member, CNMC); Prof Dr Parthapratim Pradhan, Principal, College of Medicine and Sagore Datta Medical College & Hospital, Kamarhati;. Dr. Swati Bhattacharyya, Professor, Department of Biochemistry; Dr Debjani Sengupta, Assistant Professor, Department of Community Medicine; Dr Sanjib Bandyopadhyay, Associate Professor, Department of Community Medicine of Burdwan Medical College; Prof Sanhita Mukherjee, Department of Physiology, Rampurhat Govt Medical College; Dr Arup Chakraborty, Assistant Professor, Department of Community Medicine, Medical College, Kolkata, Mr. Chironjib Datta, MT(Lab); and last but not least Mr. Sudip Kumar Sarkar ; for their constant support and motivation to carry on the work. The authors also do acknowledge to the faculties who have participated in the project.

References

1 Supe A — Graduate Medical Education Regulations 2019: Competency-driven contextual curriculum. *Natl Med J India* 2019; **32:** 257-61
2 Tandeter H, Castel OC, Nave R, Jotkowitz A — Needs Assessment for Faculty Development Activities in Medical Schools in Israel. J Fam Med 2014; **1(2):** 1-3.
3 Rustagi SM, Mohan C, Verma N, Nair BR — Competency-based Medical Education: The Perceptions of Faculty. *Journal of Medical Academics* 2019; **2(1):** 1-5.
4 Shrivastava SR, Shrivastava PS — Qualitative study to identify the perception and challenges faced by the faculty of community medicine in the implementation of competency-based medical education for postgraduate students. *Fam Med Com Health* 2019; **7:** 1-6.
5 Ghosh A, Bir A — Need of Evolution in MCI Teacher's Training Programs: Faculty Perceptions of a Tertiary Care Medical College in India. J Evid Based Med Healthc 2020; pISSN- 2349-2562, eISSN- 2349-2570/ Vol. 7/Issue 23/June 08, 2020, P 1113-8.
6 Mann S, Truelove AH, Beesle T, Howden S, Egan R — Resident perceptions of Competency-Based Medical Education. *Canadian Medical Education Journal* 2020; **11(5):** e31-e43;
7 Upadhyaya S, Rashid M, Andrea Davila-Cervantes, Anna Oswald — Exploring resident perceptions of initial competency based medical education implementation. *Canadian Medical Education Journal* 2021; **12(2):** e42-e56.
8 Ramanathan R, Shanmugam J, Gopalakrishna SM, Palanisami K, Narayanan S — Exploring the learners' perspectives on competency based medical education. *Journal of Education and Health Promotion* 2021; **10:** 1-6.
9 Tameem SN — Challenges in Implementation of the Competency Based Medical Education. *National Journal of Research in Community Medicine* 2021; **10(1):** 12-5.
10 Narwane S, Anikhindi A, Mahavarakar V — Study of perceptions of Competency Based Medical Education reforms in India. *Pravara Med Rev* 2021; **13(02):** 4 -13. DOI: 10.36848/PMR/2020/25100.51000;
11 Wilkerson L, Irby DM — Strategies for improving teaching practices: a comprehensive approach to faculty development. *Acad Med* 1998; **73:** 387-96.
12 Dimitrov DM, Rumrill Jr PD — Pre-test-post-test designs and measurement of change. Work 20 (2003) 159-165 IOS Press;
13 Shivaraju PT, Manu G, Vinaya M, Savkar MK — Evaluating the effectiveness of pre- and post-test model of learning in a medical school. *Natl J Physiol Pharm Pharmacol* 2017; **7(9):** 947-51.

Original Article

Effectiveness of Evening Primrose Oil (EPO) *versus* Tamoxifen in the Treatment of Mastalgia

Inakshi Chrungoo[1], Rajni Bhardwaj[2]

Mastalgia, also called Mastodynia, is the most common breast symptom in patients attending a breast clinic. Up to 70% of women are believed to develop pain in their breasts in their life time[1]. Despite its commonness, however, it is believed to be under reported due to social factors, partly due to reluctance of both, the patients to disclose it and of the Health Care Workers to ask about it[2]. Breast pain in childbearing age with or without a lump, is a common complaint and a cause of anxiety and fear of breast cancer[3]. Various modalities of management and treatment are suggested and employed. Herein, we present the results of a prospective study conducted on patients of breast pain, using two drugs ie, Evening Primrose Oil (EPO) and Tamoxifen, from among a spectrum of them.

[*J Indian Med Assoc* 2024; **122(3):** 39-42]

Key words **: Mastalgia, Cyclical Mastalgia, Non-cyclical Mastalgia, Evening Primrose Oil (EPO), Tamoxifen.**

The two most common causes of patients presenting with mastalgia are the fear of breast cancer and the presence of severe pain affecting the Quality of Life. The most important responsibility of the breast specialist is to consciously rule out cancer and reassure the patients. Mastalgia may be cyclical (worse before a period) or non-cyclical (with no relation with periods). Cyclical breast pain resolves spontaneously in 20-30% of women but tends to recur in 60% of them. Non-cyclical pain responds poorly to treatment but tends to resolve spontaneously in half of women. Non-breast pain can mimic mastalgia; chest wall pain mimicking mastalgia includes costochondritis (Tietze's disease), referred nerve root pain as in cervical spondylitis and herpes zoster before eruption of vesicles. Non-chest wall pain can arise from diverse causes such as ischemic heart disease, biliary pain, and peptic ulcer disease[4].

Mastalgia has been linked to a variety of conditions such as high levels of stress, anxiety, depression, chronic myalgia, irritable bowel syndrome, chronic pelvic pain and some psychiatric disorders suggesting multifactorial pathogenesis[5], yet it is emphasized that majority of these patients may have either physiological or pathological cause which needs to be addressed. Some factors such as caffeine, cigarettes smoking, high plasma fatty acids, prolactin and acute stress have been demonstrated as other possibilities[6].

Department of Surgery, Government Medical College and Hospital, Jammu, Jammu and Kashmir 180001
[1]MS, FMAS, Registrar and Corresponding Author
[2]MS, DGO, Assistant Professor

Received on : 09/09/2023
Accepted on : 28/11/2023

Editor's Comment :

- Mastalgia is the most common breast symptom in women.
- Various treatment modalities have been tried with varied response.
- Clinically evaluated the effectiveness of EPO and tamoxifen and found both to be effective, the latter being a better choice in the long run.

Management is multipronged. However, the first line of management remain life style changes[7] . The most important first step is reassurance after exclusion of cancer. A low-fat diet, high carbohydrates, regular exercise, well-fitting bra, a breast support and explanation with cancer reassurance, is suggested. This is the first line (conservative) treatment and may also include the "over the counter" analgesics as well. If not responding, the treatment will be upgraded to the second line therapy ie, medicines like Tamoxifen, GLA etc[8].

Evening Primrose Oil (EPO), a plant derivative, is obtained from the seed of *Oenotherablennis*. EPO is an Essential Fatty Acid (EFA) used empirically by many to reduce cyclical mastalgia. EPO is a rich source of EFA's and contains 7-14% Gamma Linolenic Acid (GLA). Its mechanism of action is thought to involve inhibition of prostaglandins, which potentially contribute to breast pain. Usual dose of EPO is 1000mg per day.

Tamoxifen is a synthetic anti-estrogen that, since its introduction for the treatment of patients with breast cancer in the early 1970's, has come to have a major role in the management of all stages of the disease. It is used in the treatment of mastalgia as it reduces estrogen levels. It acts as a Selective Estrogen Receptor Modulator (SERM). In the breast tissue, it

antagonistically competes with oestrogen for binding sites and causes antioestrogenic, as well as anti-tumour effect[9]. The dose of the tamoxifen used for management of breast pain ranges from 10 to 20mg per day.

Materials and Methods

The study was conducted in the Postgraduate Department of Surgery, Government Medical College, Jammu, J&K, over a period of one year, from 1st November, 2020 to 31st October, 2021. The study aimed at comparing the efficacy of Evening Primrose Oil (EPO) *versus* Tamoxifen in the treatment of Mastalgia.

In this study, sixty patients who fit the inclusion criteria were placed into two groups, comprising of 30 each, (Group A and Group B), on basis of Random sampling method after taking proper consent.

Group A : Patients receiving Evening Primrose Oil (EPO) 1000mg per day, single dose, orally.

Group B : Patients receiving Tamoxifen 20mg per day, single dose, orally.

Initial assessment of pain, at the time of presentation, was recorded, according to Visual Analogue Score (VAS). A detailed physical examination of the patient was done followed by relevant investigations. All patients were subjected to ultrasound examination of both breasts, abdomen and pelvic organs. Bilateral mammography was performed, wherever indicated.

The patients in both the groups were followed up for re-assessment later for improvement in symptoms at the end of four and eight weeks. They were again followed up at 16 weeks for assessment of recurrence of pain. A relief of pain was considered when the VAS score was equal to or less than 3 on subsequent follow ups.

All the findings were noted down for statistical evaluation. Statistical analysis was performed using IBM SPSS 21. The data was tested for normality and then analysis was done using student-t test and Mann Whitney –U test for continuous data. Categorical variables were compared,using Chi-Square test and Fisher's Exact test.

Observations and Results

The following observations were made: The maximum number of patients (45%) belonged to 28-37 age group. The youngest patient was 18 years old and the oldest was 45 years old. This was in contrast to some authors reporting age group of 41-50 years to be affected most by mastalgia[10]. Bilateral pain was seen to occur in 27 patients (45%) followed by left sided pain in 21 patients (35%) and right sided pain in 12 patients (20%).

The association with menstrual cycle (Cyclical Mastalgia) was seen in 34 patients (56.66%). The associated history included co-morbidities (like hypertension, diabetes mellitus, hypothyroidism) in 12 patients (20%), dysmenorrhea in 19 patients (31.66%), OCP's use in 5 patients (8.33%), and alcohol history in 2 patients (3.33%). There was no history of smoking in any patient. Majority of the patient were married (71.76%). Examination was normal in 51 patients (85%) at the first visit to hospital followed by breast tenderness in 4 (6.67%) patients, lumpiness in 3 patients, and nipple discharge in 1 patient. On USG examination of right breast, 50% were categorized by BIRADS 1, 46.67% as BIRADS 2 and 3.33% as BIRADS 3. On the other hand, left breast USG examination showed BIRADS 1 in 55%, BIRADS 2 in 41.67% and BIRADS 3 in 3.33%.

Ultrasound examination of the breasts at the time of presentations was normal grossly, with most (96%) having BIRADS 1 and 2 changes in both breasts. By and large it is suggested that without abnormal findings on physical examination, pre-menopausal women presenting with cyclical breast pain, do not require radiographic imaging routinely[11].

In general, in the present study, better relief in Mastalgia was seen to be obtained with EPO than with Tamoxifen (p=0.035) at the end of 4 weeks' treatment (Fig 1). However, at 8 weeks' treatment both drugs were observed to be equally effective with no statistical difference in their effectivity (p=0.11) (Fig 2). Impliedly continuation of treatment for longer period than 4 weeks' increased effectiveness. Individually also, both EPO and Tamoxifen were more effective at 8 weeks' treatment than at 4 weeks' treatment (p=0.0001) (Table 1). The pattern of relief of pain persisted with

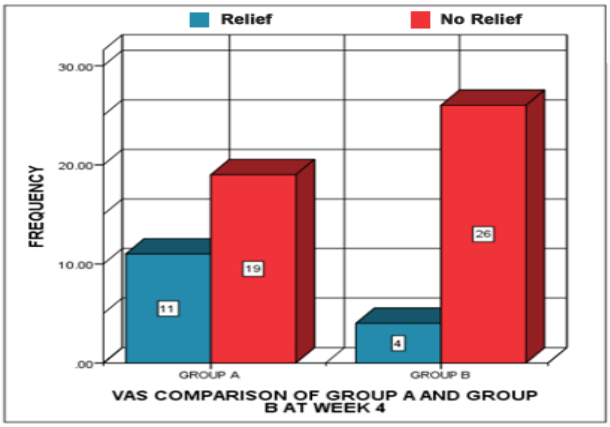


Fig 1 — Pain Relief at 4 weeks Group A (EPO) *versus* Group B (Tamoxifen)

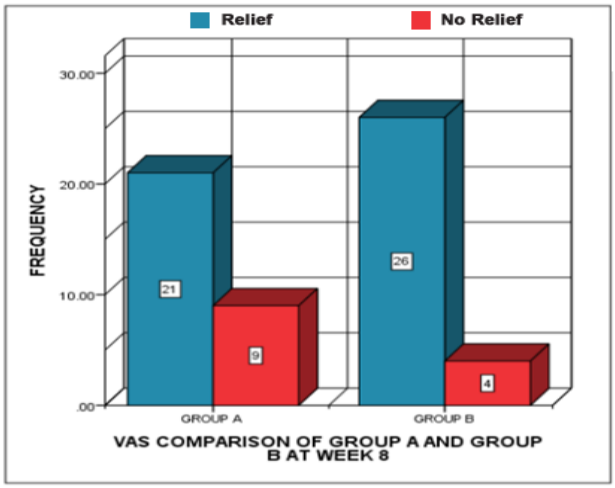


Fig 2 — Pain Relief at 8 weeks Group A (EPO) *versus* Group B (Tamoxifen)

both drugs after usage for 16 weeks. The pain recurrence at this stage was statistically insignificant in both the drug groups (p=0.60) (Table 2).

In Cyclical Mastalgia, while there was no difference between two drugs affecting a pain relief at 4 weeks' treatment (p=0.07) (Table 3), Tamoxifen was seen to be comparatively more effective than EPO, at the end of 8 weeks' treatment (p=0.046) (Table 4).

Table 1 — *Mean VAS at 4 weeks versus 8 weeks : Group A (EPO) versus Group B (Tamoxifen)*

VAS Score	Group A		Group B		P-value
	Mean	SD	Mean	SD	
0wks	7.53	1.33	7.53	1.27	0.98
4wks	4.26	1.50	4.97	1.88	0.93
8wks	2.73	1.53	2.73	0.98	0.99
P-value (4 weeks *versus* 8 weeks)	0.0001		0.0001		

Table 2 — *Recurrence of Pain at 16 weeks in Group A (EPO) and Group B (Tamoxifen)*

Recurrance Pain at 16 Weeks	Group A	Group B	P-value
Present	3	1	0.60
Absent	27	29	
Total	30	30	

Table 3 — *VAS comparison for Cyclical Mastalgia at 4 weeks for Drug A (EPO) and Drug B (Tamoxifen)*

	Relief	No Relief	Total	P-value
Group A	6	10	16	0.07
Group B	2	16	18	
Total	8	26	34	

Table 4 — *VAS Comparsion for Cyclical Mastalgia at 8 weeks, Group A (EPO) versus Group B (Tamoxifen)*

	Relief	No Relief	Total	P-value
Group A	12	4	16	0.046
Group B	14	4	18	
Total	26	8	34	

Discussion

The cause of mastalgia is not clear but there are several theories. Hormonal theory, especially in cyclical pain, is suggested by the onset at the age of menarche, its relationship with the menstrual cycle and its resolution with the menopause. There is some evidence that suggests that women with mastalgia have increased levels of saturated fatty acids and reduced levels of essential fatty acids, especially Gamma Linoleic Acid (GLA). This makes the cell membrane more sensitive to nociceptive depolarization and allows the estrogen receptor to be more available.

The initial management of Mastalgia includes non-medicinal therapy, reassurance and a good external breast support. The condition is usually benign but has a major impact on the work activities. Ozturk, *et al*[12] described mastalgia as a debilitating disorder, which has effects on one's daily life and causes significant medical costs. While the chances of mastalgia being a symptom of breast cancer is quite low, Dave, *et al*[13] emphasized that most breast cancers do not cause pain. Yet, at the same time it is important to screen women who are at risk. Upto 85% of women will show alleviation of pain episodes after getting reassurance of not having breast cancer[14].

Cyclical mastalgia, which occurs in two third of patients with mastalgia occurs one to two weeks before menstruation and is relieved by the onset of menstrual flow. Pain in the breast in the reproductive age is usually experienced either in the center, spreading to other parts of the breasts or to the other breast. It may be caused by normal cyclical changes in the hormones, and therefore responds very well to hormonal therapies.

Non-cyclical mastalgia is characterized by constant or intermittent breast pain and is not associated with menstrual cycle. Its etiology is unclear, occurs in older age and responds less to hormonal modulation and therefore more challenging to treat. Extramammary pain is linked to skeletal disorders like costochondritis etc.

In general, 92% of patients with cyclical mastalgia and 64% of non-cyclical mastalgia can obtain pain relief with conservative treatment[15]. Yet in approximately 8% of patients pain will be severe and will require medication after initial detailed assessment[16].

Conclusion

This study suggested that EPO and Tamoxifen both were effective in providing pain relief in mastalgia. EPO showed quick relief at 4 weeks. At the end of 8 weeks of treatment both drugs were equally effective.

For cyclical mastagia both EPO and Tamoxifen were effective drugs, yet the results seemed to be better with Tamoxifen. However, considering the small sample size of the study, this finding may not be held absolutely.The Pattern of pain relief in Mastalgia persisted till the end of 16 weeks after the start of treatment with no significant recurrence with either of the drugs.

References

1 Goyal A — Breast pain. *BMJ Clinical Evidence* 2011; **17:** 0812.
2 Iwata K, Nishimoto T — Persistent bilateral breast pain treated with traditional Kampo medicine. Journal of General and Family Medicine 2021; **22(6):** 347-9.
3 Thakur N, Hassan N Ul, Hassan Y — Mastalgia. *Int J Res Med Sci* 2021; **9(2):** 1-5.
4 Muhammad T, Shaamsudin S — Mastalgia Stat Pearls[Internet]. Treasure Island (FL): Stat Pearls Publishing; 2021 Jan. https://www.ncbi.nlm.gov/books/NBK562195/ Last update November 1, 2022.
5 Mohammed AA — Evaluation of mastalgia in patients presented to the breast clinic in Duhok city, Iraq: Cross sectional study. *Annals of Medicine and Surgery* 2020; **52:** 31-5. https://doi.org/10.1016/j.amsu.2020.02.012
6 Eren T, Aslan A, Ozemir IA, Baysal H, Sagiroglu J, Ekinci O, *et al* — Factors effecting mastalgia. *Breast Care* 2016; **11(3):** 188-93.
7 Malherbe K, Khan M, Fatima S — Fibrocystic Breast Disease [updated Aug 8 2023]. In Stat Pearls [Internet] Treasure Island (FL) : Stat Pearls Publishing; 2022 Jan. https://www.ncbi.nih.gov/books/NBK551609/
8 Ahmad Adni LL, Norhayati MN, Mohd Rosli RR, Muhammad J — A systematic review and meta-analysis of the efficacy of evening primrose oil for mastalgia treatment. *International Journal of Environmental Research and Public Health* 2021; **18(12):** 6295. https://doi.org/10.3390/ijerph 18126295
9 Farrar MC and Jacobs TF, Tamoxifen. Stat Pearls [Internet]. Treasure Island (FL). Stat Pearls Publishing PMID 30422500. 2023 Jan (updated Latest 2023, April 10).
10 Sarla GS — Mastalgia: etiopathogenesis and management: a 2 year experience. *J Compliment Med Alt Healthcare J* 2019; 10(3): 1-6. https://www.ncbi.nlm.gov/books/NBK/ 532905/
11 Cornell LF, Sandhu NP, Pruthi S, Mussallem DM — Current management and treatment options for breast pain. *In Mayo Clinic Proceedings* 2020; **95(3):** 574-80. Elsevier. PMID:32138883. DOI: 10.1016/J.Mayocp.2019-12.014
12 Öztürk AB, Özenlý Y, Öztürk SB, Önel S, Söker G, Seydaoglu G — The effect of psychoeducation on anxiety and pain in patients with mastalgia. *Nordic Journal of Psychiatry* 2015; **69(5):** 380-5. doi:10.3109/08039488.2014.989260. Epub 2014 Dec 27.
13 Dave R, Bromley HL, Taxiarchi V — No association between breast pain and breast cancer: A prospective study of 10830 symptomatic women presenting to a breast cancer diagnostic centre. *Brit J Gen Pract* 2022; **72 (717):** e234-e243. DOI : https://doi.org/10.3399/BJGP.2021.0475
14 Grullon S, Bechmann S — Mastodynia. [Updated 2023 June 5]. In: Stat Pearls [Internet] Treasure Island; Stat Pearls Publishing; 2023 Jan. https://www.ncbi.nlm.gov/books/NBK559249.
15 Sepulveda OAB, Santa DCG — MAstalgia In: Mastodynia 2019. *Ces Med* 2019; **33(2):** 111-8.
16 Rosolowich V, Saettler E, Szuck B — Mastalgia. *J Obstet Gynaecol Can* 2006; **28(1):** 49-57.

Original Article

Adolescent Health and Screen Time during a Period of Compulsory Online Education : A Cross Sectional Study from Eastern India

Shilpi Siddhanta[1], Debasish Bandyopadhyay[2], Subhrojyoti Bhowmick[3]

COVID pandemic had an impact on both physical and mental health of the adolescents. To slow down spread of pandemic, measures like social distancing, online education, lockdowns, etc were taken. Adolescents and young adults had decreased communication with peers and extended families. Their screen time including videogaming also increased due to virtual learning. This study was undertaken to assess and compare the screen-time, mental health, physical activities, sleep etc of adolescents when physical schools are closed for long durations among different age groups of adolescents and between males and females. This study was conducted on 78 adolescents aged 10-17 years who were attending the Paediatric Outpatient Department of a Government Hospital. It was conducted over 3 months during a period of compulsory online classes. However, there was no lockdown during this period. It was found that boys had increased physical activity duration in comparison to pre pandemic times (P-value 0.03509). The duration of playing videogames had significantly increased too for boys. Adolescents more than 13 years ie, in mid adolescence had higher screen time and more incidence of mood disturbances, depression or anxiety than the younger ones. However, there was no significant increase of stress factors due to their stay at home, or online education. Screen time and stress were significant factors for developing psychological changes among students. Most adolescents knew that watching screen excessively is bad though few tried to decrease screen-time. Duration of physical activity among students was not a significant factor for obesity or being overweight among students although, increase in sleeping time was significant factor. Most students' academic performance remained same or became better as reported by themselves. Most Adolescents have knowledge but need guidance and constant support for inculcating health promoting activities and habits like pursuing hobbies, exercise during periods of deviation from routine life.

[*J Indian Med Assoc* 2024; **122(3):** 43-9]

Key words **: Adolescent, Screen-time, Stress, Exercise, Anxiety, Depression, Mid Adolescence, Online Education.**

Adolescence is the period of rapid physical and psychological development starting from the onset of puberty to complete growth and development. All Adolescents pass through this transition phase of various physical, hormonal, psychological, behavioural and social developmental changes.

COVID-19 pandemic had an impact on both physical and mental health of the Adolescents[1]. In order to slow the spread of the pandemic, measures like social distancing, online education, restrictions during lockdowns, etc were taken. These had effect on the mental wellbeing of all[2]. Adolescents and young adults had decreased communication with peers and extended families and were at a higher risk of psychosocial and behavioral problems. This was especially because adolescents, often rely on their social connections to understand themselves well. Hence, they experience more intense reactions to these stressors[3]. In order to cope with stress, they resorted to video gaming and browsing internet, that in turn adversely affected their mental wellbeing. The screen time and internet browsing also increased due to virtual learning. Excess gaming was associated with depression and anxiety[4]. Gaming and internet browsing decreased the use of adaptive coping strategies like

Editor's Comment :

- Prolonged stay at home and studying online can have psychological impact on adolescents as well as increase their screentime.
- This impact is more as the age progresses to mid adolescence may manifest as anxiety, depression and mood disorders.
- Proper guidance and supervision especially by parents and teachers is essential.

Department of Paediatrics, Eastern Railway Hospital, Liluah, West Bengal 711204

[1]MBBS, DNB (Paediatrics), MRCPCH (UK), DCH (UK), Divisional Medical Officer and Corresponding Author

[2]MBBS, MD, Additional Chief Health Director, B R Singh Hospital, Kolkata, West Bengal 700014

[3]MBBS, MD, Clinical Director, Department of Clinical Research, Peerless Hospital and B K Roy Research Centre, Kolkata, West Bengal 700094

Received on : 16/03/2023

Accepted on : 24/05/2023

appropriate sleep, exercise, interacting with friends and relatives. Although many Adolescents used sleeping as a strategy to tide over this stressful period, most of them had inadequate sleep due to various reasons[5,6]. Poor sleep in turn had multiple adverse effects like depression, excessive daytime sleepiness and metabolic dysfunctions[7].

It has been studied that mental health illness like depression can also lead to serious physical health outcomes, such as the development of cardiovascular diseases[8]. Taking care of adolescent's health is essential to secure health,not only during later adulthood but of the future generation as well[9].

The responses of adolescents to a crisis situation like a pandemic depends upon whether they have been previously exposed to emergency situations, the Socio-economic circumstances of the family, physical and mental health issues and their cultural background[10,11]. Different studies have shown that crisis events negatively impact the psychological well-being of children and adolescents[12-14]. A recent study by Jiao, *et al* found that anxiety, depression, irritability, distraction and the fear that family members would contract the deadly disease were some of the most common problems of the pandemic[15].

This study has been conducted to assess the adolescents' knowledge, attitude and practice of watching screen especially almost after one and half years of pandemic. When adolescents had to attend compulsory online classes yet had freedom to play outside, their physical activity, duration of sleep and mental health status was evaluated. Very few studies have been conducted in this topic on Adolescents and online education. That is because this study as conducted in the unique period where students were undergoing compulsory online education. On the other hand they had the liberty to go outside their houses though in a restricted manner,as there was no lockdown in this period. This study shall bring out the unique characteristics of early adolescents and the mid Adolescence age especially in response to online education in a post pandemic situation. The response of girls and boys can also be evaluated during this situation. This study shall highlight the prospect of online education for adolescents in future.

Aims and Objectives

(1) To assess screen-time and physical activities of Adolescents when physical schools are closed for long durations.

(2) To assess the knowledge and attitude of adolescents towards screen-time.

(3) To compare the variation of screentime and physical activity among early and mid adolescents and between males and females.

(4) To screen the adolescent's mental health status and to evaluate factors contributing to adverse mental health outcomes during this study period.

(5) Relation between being obese/overweight and screen-time, sleep, exercise, other factors.

Materials and Methods

This study was conducted over 3 months ie, January, 2022 to March, 2022, covering 78 adolescents. In this study, adolescence is divided into early adolescence, between 10-13 years, mid adolescence between 14-17 years, late adolescents between 18-24 years. Only early and mid adolescents were included in this study.

This study was done during a period when the adolescents had to attend compulsory online classes. However, there was no lockdown for COVID during this period. Adolescents aged 10-17 years who were attending a Government Hospital in Howrah district, for consultation were interviewed with the help of a pre-designed, pre-tested, structured questionnaire. The adolescents were given consultation separately after Pediatric OPD maintaining appropriate privacy and confidentiality. This questionnaire covered demographic data, such as age, gender, address etc. Socio-economic status was assessed by taking into account the guardian's income, level of education and occupation of primary breadwinner. Weight and height was measured. Body Mass Index (BMI) was calculated. TV, videogame played online and time spent on internet were considered as screen time. Internet time mostly included online education other than internet browsing for entertainment purpose. Whether the adolescent was having stress due to friends, family, COVID and other diseases and other reasons was evaluated. Knowledge, attitude and practice of watching screen was assessed with various questions. Psychological problems were screened with the pre-tested questionnaire. Those who had symptoms of anxiety, sadness or gaming disorder were further evaluated for confirmation. For evaluating anxiety, GAD 7 anxiety questionnaire was used. A score more than 4 was noted as having anxiety. For evaluating depression, Becks depression Inventory was used. Scoring of 11-16 was classified as mild mood disturbances. More than 16 was categorised as depression. Internet gaming disorder as diagnosed with DSM V criteria. It is expected that adolescents should sleep 8-10 hours/day on a regular basis to promote optimal health. Sleeping hours more than 10 hours was excess and less than 8 was considered deficient

in this study. Physical activity in this study included mild and moderate physical activities. It included cycling, playing football, cricket, walking, running etc. Permission for study was taken from the institution. Verbal consent was taken from parents and adolescents. Both parents and children were explained regarding the questionnaire and the purpose of this study. Later both the parents and adolescents were given anticipatory guidance on healthy lifestyle. Those who were unwilling to participate, those adolescents who were ill, having pre existing neurobehavioral problems were excluded from the study. Data was analysed with the help of appropriate statistical methods.

Results

The study conducted with 78 Adolescents. There were 39 Boys and 39 Girls. 46(58.9%) were in early Adolescence and rest were in mid adolescence. 12.8% were overweight and 3.85% were obese in this study. 12.82% were involved in moderate physical activity out of 44 who were exercising regularly in this period. Rest were involved in physical activity with less than 1 hour duration or mild physical activity. In 42 students were not regularly involved in physical activity during pre-COVID times. Out of total 78 students increase in duration of physical activity from pre-pandemic period was 0.17±0.59 hours ie, 10.2 ± 35.4 minutes, which is significant with P value 0.0161 <0.05. For boys increase in duration of physical activity 0.19 ± 0.68 hours and for girls 0.14 ± 0.51 hours. Internet screen time was 3.03 ± 2.30 hours. Total screen time was 4.60 ± 2.98 hours in this study. 6.71% Adolescents had duration of sleep less than 7 hours and 14.10% had more than 10 hours. 15.38% had inadequate sleep duration of less than 8 hours in this study. However, mean duration of sleep was 8.32 ± 1.22 hours. 11.5% Adolescents complained of stress caused due to inability to communicate with friends. 11.5% had stress due to family conflicts. 42.3% complained that online education as very stressful. Although in 88.46% the academic performance remained same or better. 88.5% knew watching excess screen is bad but only 19.2% tried to decrease screen-time.

In Table 1, no significant difference was found with respect to stress, psychological changes and total screen time between boys and girls (P Value > 0.05). However duration of playing video games was significantly higher among boys.

In Table 2, no significant difference was found with respect to stress between early and mid adolescents (P value >0.05)

Psychological changes among mid Adolescents during the study period [17 (53.13%)] is significantly higher than of early adolescents [8 (17.39%)] with P value 0.0021 <0.05; Internet Screen time among students of ≥14 Years [4 (2.62)] is significantly higher than of ≤13 years [2 (3.1)] age.

In Table 3, it is shown that 46.15% students were on regular physical activity during pre-pandemic periodand during online schooling periods were 56.41%, which do not differ significantly (P value >0.05). Significant increase in duration of physical activity was noted during online schooling periods with no lockdown restrictions as compared to pre covidera(P value 0.0161<0.05). Significant increase in duration of physical activity is seen among boys during online schooling (P value 0.0351 <0.05), while for girls no significant increase is observed (P Value >0.05).

In this study it is found that, duration of physical activity among students is not a significant factor for obesity or over weight among students [P Value > 0.05)] . However, increase in sleeping time is significant factor for obesity or overweight (OR 1.75, 95% CI 1.07 - 2.98) with P value 0.0306.

There was no significant correlation between hours of sleep and exercise duration (P value 0.0473 approx value 0.05) and hours adolescents sleep and screen time (P value 0.1573) in this study.

Table 1 — *Showing Comparison of Knowledge Attitude Practice of screen time, stress, psychological changes and academic performance among adolescent Boys versus Girls*

	Boys (n=39)	Girls (n=39)	P Value
Screen Time (hours)			
TV Screen time	1.15±1.43, 1 (2)	0.83±1.07, 0.5 (1)	0.2957
Videogame Screen time	0.93±1.38, 0 (1)	0.22±0.54, 0 (0)	0.003*
Internet Screen time	2.86±2.23, 3.5 (3.3)	3.20±2.43, 3 (2.75)	0.622
Stress & Psychological Changes			
Stress level	22 (56.41%)	26 (66.67%)	0.485
Psychological changes	12 (30.77%)	13 (33.33%)	1
Changes in Academic Performance			
Academic performance score not-affected	33 (84.62%)	36 (92.31%)	0.481
Awareness on excess Screen time			
Knows excess screen time is bad	34 (87.18%)	35 (89.74%)	1
Tried to decrease screen time	9 (23.08%)	6 (15.38%)	0.566
Increase in Screen time			
TV and videogame Screen time increased	24 (61.54%)	18 (46.15%)	0.2561
TV, videogame and internet Screen time increased	35 (89.74%)	35 (89.74%)	1

Table 2 — *Showing comparison of Knowledge, Attitude and Practice of screen time, stress and psychological changes, academics of early and mid adolescents (Age 10-13 Years versus ≥14 years)*

	Age 10-13 Years (n=46)	Age ≥14 Years (n=32)	P Value
Screen Time (hours)			
TV Screen time	0.86±1.06, 0.5 (1)	1.19±1.51, 1 (2)	0.2902
Videogame Screen time	0.48±0.92, 0.5 (1)	0.70±1.33, 1 (2)	0.9806
Internet Screen time	2.30±1.79, 2 (3.1)	4.08±2.59, 4 (2.62)	0.0011*
Stress & Psychological Changes			
Stress level High	24 (52.17%)	24 (75.00%)	0.0716
Psychological changes	8 (17.39%)	17 (53.13%)	0.0021*
Changes in Academic Performance during COVID			
Academic Performance Score not-affected	43 (93.48%)	26 (81.25%)	0.1492
Knowledge and attitude on excess Screen time			
Knows excess screen time is bad	39 (84.78%)	30 (93.75%)	0.2947
Tried to decrease Screen time	9 (19.57%)	6 (18.75%)	1

*P Value <0.05

Table 3 — *Showing Adolescents's Physical activity during Pre-pandemic period and after more than a year of pandemic and among Boys versus Girls*

	Pre-pandemic	>1 year of pandemic	P Value
Adolescents doing regular physical activity (n = 78)	36 (46.15%)	44 (56.41%)	0.0614
Physical activity, Outdoor games Duration (hours) (n=78)	0.48 ± 0.72	0.65 ± 0.93	0.0161*
Physical activity, Outdoor games duration (hours)			
Boys (n = 39)	0.55±0.87, 0 (1)	0.74±1.05, 0.5 (1)	0.0351*
Girls (n = 39)	0.41±0.56, 0 (0.75)	0.55±0.82, 0.5 (1)	0.0597

* P Value <0.05

Stress and Psychological Changes :

Psychological changes are observed among 32.05% students with mild mood disturbances (8.97%), anxiety (16.67%), depression (11.5%) and internet gaming disorder (3.85%). TV, internet gaming and internet Screen-time is significant factor for developing psychological changes among students (OR 1.19, 95% C.I. 1.01 - 1.43) with P value 0.0353 < 0.05;. Stress is also a significant factor for developing psychological changes (OR 29, 95% C.I. 5.49-537.33) with P value 0.00145<0.05. However, no significant relation has been found between screen time and stress among students (P value > 0.05) in this study . It is also observed that, development of psychological changes among students under stress [24 (50.00%)] is significantly higher than students with no stress [1 (3.33%)] (P value 5.182e-05 < 0.05).

Statistical Tools Used :

Categorical variables are expressed as No (%), while continuous variables are expressed as Mean ± SD, Median (Inter Quartile Range). Statistical tools used were Wilcoxon signed test (test for paired observation), Wilcoxon rank sum test, McNemar's test, Pearson's Chi-square test and logistic regression. P Value <0.05 considered significant; Statistical package used R version 3.5.3.

Discussion

Mental Health :

The prevalence of anxiety and depression among adolescents in this study was 16.67% and 11.5% respectively, of mild mood disturbances was 8.97% and internet gaming disorder was detected in 3.85%. Slightly lower rates were found in a study by Meherali S, *et al*[15]. This correlates with a review by Shanbehzadeh S, *et al*, where common mental health problems were anxiety (range 6.5% to 63%), depression (4% to 31%) and post-traumatic stress disorder (12.1% to 46.9%). However, depression among adolescents in this study was lesser than general population[17]. In another study byJiaqiXiong, *et al*, symptoms of anxiety (6.33% to 50.9%), depression (14.6% to 48.3%), post-traumatic stress disorder (7% to 53.8%), psychological distress (34.43% to 38%) and stress (8.1% to 81.9%) have been reported in the general population during the COVID-19 pandemic in different countries[18]. In this study there was no significant difference of stress level or psychological changes between boys and girls,where as in general population female gender is a risk factor[18]. Psychological changes like anxiety, depression, etc in students with stress is significantly higher than students without stress ,as also found in another study[19].

Sleep :

Sleep affects physical, mental and emotional development of the adolescents and it has a potential impact on their academic performance[20]. Adolescents should sleep 8-10 hours/day on a regular basis to promote optimal health. Consistent sleep habits such as regular bedtime, wake-up time, and similar sleep schedules on weekends and weekdays help in better sleep outcomes. 15.38% adolescents had inadequate sleep duration in this study whereas in a study by Mathew G, *et al* sleep duration was found to be

inadequate in more 60% of the children[21]. The pooled prevalence of any sleep disturbance in children during the pandemic was 54% in another study by Sharma M, *et al*[22], which is more than this study (20.81%). In a study by Moitra P, *et al* more than half (52.5%) of the adolescent participants had poor sleep quality during COVID pandemic[23].

Physical Activity :

In a study by Moitra P, *et al*,only 12% engaged in moderate to vigorous physical activity[23]. This is similar to this study where exercise or physical activity more than 1 hour is 12%. Satija A, *et al* in a study found that Adolescents who are unfit are more likely to be deprived, female even in non-deprived families, have obesity in the family and have academic non achievement[24]. In this study significant increase in duration of physical activity observed for all, especially for boys but, for girls no significant increase in duration of physical activity was noted.

Screen Time :

In this study, internet gaming disorder was found in 3.85% adolescents. Problematic gaming behaviour is associated with adverse effect on mental health like depression, anxiety, obsessive-compulsive disorder and somatisation[25]. The prevalence of internet addiction was found to be 24.4% in a study by Warburton WA, *et al*, which was higher than this study[26]. It has been found that adolescents having problems with impulse control and unmet needs in everyday life may be more vulnerable to internet gaming disorder. While treating and counselling the adolescents, focussing on risk factor had proven to be beneficial[23]. In a study by Moitra P, *et al* 65.4% adolescents used social networking sites for at least 2-3 hours/day, and for 70.7% adolescents screen time had taken up the majority of their leisure time. A higher screen-time was associated with lower physical activity and increased sleep[23]. Screen time spent was a significant factor for developing psychological problems in this study. Although hours spent on watching screen was not significant factor for developing stress problems. No significance has been found between screen time and sleep duration in this study. Post pandemic internet and total screen-time is significantly higher among students in mid adolescence than early adolescence in this study. This could be partly due to the increased duration of online classes in higher standards.

In a systematic review by Oosterhoff B, *et al* potential negative effect of the pandemic on adolescent mental health was highlighted. The practice of social distancing due to the COVID-19 pandemic seem to be difficult for adolescents to process, which results in poor mental health outcomes[27]. The Adolescents lack the ability to process difficult circumstances, like the pandemic . This may be due to their negative coping skills. This puts them at risk for depression, stress and trauma[28]. The adolescents need to be taught proper life education by health care professionals, teachers and parents. The lack of positive coping skills among adolescents is not uncommon. They must be provided with the skills to cope in order to make them resilient and mentally well during periods of crises. The teaching and practice of positive coping skills can lead to mentally well adolescents, who can easily cope with rapid changes. Social support was another major factor for their wellbeing. Adolescents had experienced low to moderate social support during the pandemic, which contributed to increases in anxiety and depression[29]. Hence, it is essential that support should be provided to adolescents at home in these critical situations. Studies have shown that the strengthening of social support leads to positive mental health outcomes[29]. Another important requirement for adolescents is social connectedness, which they reported to be less during online education. For most of adolescents their smartphones were “necessary” and “connecting” although they reported high distractibility due to this[30]. Compulsory online education and exposure to excess screen has been a concern as there was both isolation from peers and relatives increased dependance on technology during the pandemic[31]. Proper guidance and supervision regarding use of social media and internet is essential for adolescents and young adults.

Limitations of this study were reporting was done by recall method by adolescents only. This was a small study having limited number of participants. Further studies can be done comparing physical schools and online schools, to explore the positive and negative aspects of online education. Online education can open prospects of distant education. Another limitation was that complete data of the other members of the family especially for calculating total per capita income per month was not recorded. Hence, this data couldnot be interpreted with Kuppusamy scale. Hence statistical analysis was not done with this data.

Conclusion

The present study brought forth the adolescents’ screen time viewing, physical activity levels, stress and mental health problems more than 1 year after a pandemic especially when there was no lockdown due to COVID and they were studying online. Boys had increased physical activity duration while pursuing

online education, though their duration of playing internet games had increased too. Adolescent more than 13 years ie, in mid adolescents showed more tendency for watching screen and reported more incidence of mood disturbances, depression or anxiety in the study period. However, there was no significant increase of stress factor due to their stay at home, or online education. Most adolescents knew that watching screen excessively is bad though few tried to decrease screen-time. Most students' academic performance remained same or became better as reported by themselves. Parents should support adolescents for ensuring a control on the screen usage, especially by being role models regarding physical activity and screen-time. Parents, teachers, Pediatricians and healthcare workers should work on early identification of anxiety and depression symptoms in adolescents[32]. Mobile applications and games to promote healthy lifestyle and tracker of early symptoms of mental health problems can be utilized for benefit of the adolescents and young adults.

Recommendation / Implications

Adolescents more than 13 years old are more vulnerable to increased screen-time and psychological effects of depression, mood disturbances or anxiety than the younger ones especially when physical schools are closed. Most adolescents have knowledge but need guidance and constant support for health promoting activities and habits like pursuing hobbies, physical activity during periods of deviation from routine life.

Acknowledgement

Special thanks to Dr Arindam Kundu, for his statistical analyses.

Conflict of Interest : None

References

1 Nicola M, Alsafi Z, Sohrabi C, Kerwan A, Al-Jabir A, Iosifidis C, *et al* — The socio-economic implications of the coronavirus and COVID-19 pandemic: a review. *Int J Surg* 2020; **78:** 185-93. doi: 10.1016/j.ijsu.2020.04.018

2 Pfefferbaum B, North CS — Mental health and the COVID-19 pandemic. *New Engl J Med* 2020; **383:** 510-2. doi: 10.1056/NEJMp2008017

3 Steinberg L, Morris AS — Adolescent development. *Annual Review of Psychology* 2001; **52(1):** 83-110. doi: 10.1146/annurev.psych.52.1.83.

4 Männikkö N, Ruotsalainen H, Miettunen J, Pontes HM, Kääriäinen M — Problematic gaming behaviour and health-related outcomes: a systematic review and meta-analysis. *J Health Psychol* 2017; **25:** 67-81. doi: 10.1177/1359105317740414

5 Owens J — Insufficient sleep in adolescents and young adults: an update on causes and consequences. *Pediatrics* 2014; **134:** e921–32. doi: 10.1542/peds. 2014-1696

6 Kaur H, Bhoday HS — Changing adolescent sleep patterns: Factors affecting them and the related problems. *J Assoc Physicians India* 2017; **65:** 73-7.

7 KaurG, Singh A — Sleep hygiene, sleep quality and excessive daytime sleepiness among Indian college students. *Sleep Med Disord* 2011; **4:** 1076-83.

8 Chaddha A, Robinson EA, Kline-Rogers E, Alexandris-Souphis T, Rubenfire M — Mental Health and Cardiovascular Disease. *Am J Med* 2016; **129**: 1145-8. doi: 10.1016/j.amjmed.2016.05.018.

9 World Health Organization Adolescent Health. [(accessed on 18 December 2020)];2019 Available online: https://www.who.int/southeastasia/health-topics/adolescent-health

10 Brooks SK, Smith LE, Webster RK, Weston D, Woodland L, Hall I, Rubin GJ — The impact of unplanned school closure on children's social contact: Rapid evidence review. *Eurosurveillance* 2020; **25**: 2000188. doi: 10.2807/1560-7917.ES.2020.25.13.2000188.

11 JG, Campione-Barr N, Metzger A — Adolescent development in interpersonal and societal contexts. *Annu Rev Psychol* 2006; **57**: 255-84. doi: 10.1146/annurev.psych.57.102904.190124.

12 CDC Helping Children Cope with Emergencies|CDC. [(accessed on 21 December 2022)];2020 Available online: https://www.cdc.gov/childrenindisasters/helping-children-cope.html

13 Dalton L, Rapa E, Stein A — Protecting the psychological health of children through effective communication about COVID-19. [(accessed on 14 March 2021)]. *Lancet Child Adolesc Health* 2020; **4**: 346-7. doi: 10.1016/S2352-4642(20)30097-3

14 Guessoum SB, Lachal J, Radjack R, Carretier E, Minassian S, Benoit L, Moro MR — Adolescent psychiatric disorders during the COVID-19 pandemic and lockdown. [(accessed on 14 March 2021)]; *Psychiatry Res* 2020; **291**:113264. doi: 10.1016/j.psychres.2020.113264. Available online: https://www.sciencedirect.com/science/article/pii/S0165178120318382

15 Jiao WY, Wang LN, Liu J, Fang SF, Jiao FY, Pettoello-Mantovani M, Somekh E — Behavioral and Emotional Disorders in Children during the COVID-19 Epidemic. [(accessed on 14 March 2021)]; *J Pediatr* 2020; **221:** 264-6.e1. doi: 10.1016/j.jpeds.2020.03.013. Available online: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7127630/

16 Meherali S, Punjani N, Louie-Poon S, Abdul Rahim K, Das JK, Salam RA, Lassi ZS — Mental Health of Children and Adolescents Amidst COVID-19 and Past Pandemics: A Rapid Systematic Review. *Int J Environ Res Public Health* 2021; **18(7):** 3432. doi: 10.3390/ijerph18073432. PMID: 33810225; PMCID: PMC8038056.

17 Shanbehzadeh S, Tavahomi M, Zanjari N, Ebrahimi-Takamjani I, Amiri-Arimi S — Physical and mental health complications post-COVID-19: Scoping review. *J Psychosom Res* 2021; **147:** 110525. doi: 10.1016/j.jpsychores.2021.110525. Epub

2021 May 20. PMID: 34051516; PMCID: PMC8133797.

18 Xiong J, Lipsitz O, Nasri F, Lui LMW, Gill H, Phan L, *et al* — Impact of COVID-19 pandemic on mental health in the general population: A systematic review. *J Affect Disord* 2020; **277:** 55-64. doi: 10.1016/j.jad.2020.08.001. Epub 2020 Aug 8. PMID: 32799105; PMCID: PMC7413844.

19 Hu J, Huang Y, Liu J, Zheng Z, Xu X, Zhou Y, *et al* — COVID-19 Related Stress and Mental Health Outcomes 1 Year After the Peak of the Pandemic Outbreak in China: the Mediating Effect of Resilience and Social Support. *Front Psychiatry* 2022; **13:** 828379. doi: 10.3389/fpsyt.2022.828379. PMID: 35264988; PMCID: PMC8898823..

20 Gupta R, Bhatia MS, Chhabra V, Sharma S, Dahiya D, Semalti K, *et al* — Sleep patterns of urban school-going adolescents. *Indian Pediatr* 2008; **45:** 183-9.

21 Mathew G, Varghese AD, Benjamin AI — A Comparative Study Assessing Sleep Duration and Associated Factors among Adolescents Studying in Different Types of Schools in an Urban Area of Kerala, India. *Indian J Community Med* 2019; **44(Suppl 1):** S10-S13. doi: 10.4103/ijcm.IJCM_19_19. PMID: 31728081; PMCID: PMC6824174.

22 Sharma M, Aggarwal S, Madaan P, Saini L, Bhutani M — Impact of COVID-19 pandemic on sleep in children and adolescents: a systematic review and meta-analysis. *Sleep Med* 2021; **84:** 259-67. doi: 10.1016/j.sleep.2021.06.002. Epub 2021 Jun 11. PMID: 34182354; PMCID: PMC8687656.

23 Moitra P, Madan J — Impact of screen time during COVID-19 on eating habits, physical activity, sleep, and depression symptoms: A cross-sectional study in Indian adolescents. *PLoS One* 2022; **17(3):** e0264951. doi: 10.1371/journal.pone.0264951. PMID: 35259203; PMCID: PMC8903250.

24 Satija A, Khandpur N, Satija S, MathurGaiha S, Prabhakaran D, Reddy KS, *et al* — Physical Activity Among Adolescents in India: A Qualitative Study of Barriers and Enablers. *Health Educ Behav* 2018; **45(6):** 926-34. doi: 10.1177/1090198118778332. Epub 2018 Jul 3. PMID: 29969921.

25 Männikkö N, Ruotsalainen H, Miettunen J, Pontes HM, Kääriäinen M — Problematic gaming behaviour and health-related outcomes: A systematic review and meta-analysis. *Journal of Health Psychology* 2020; **25(1):** 67-81. doi:10.1177/1359105317740414

26 Warburton WA, Parkes S, Sweller N — Internet Gaming Disorder: Evidence for a Risk and Resilience Approach. *Int J Environ Res Public Health* 2022; **19(9):** 5587. doi: 10.3390/ijerph19095587. PMID: 35564981; PMCID: PMC9103383

27 Oosterhoff B, Palmer CA, Wilson J, Shook N — Adolescents' Motivations to Engage in Social Distancing During the COVID-19 Pandemic: Associations with Mental and Social Health. *J Adolesc Heal* 2020; **67**: 179-85. doi: 10.1016/j.jadohealth.2020.05.004.

28 Zhang C, Ye M, Fu Y, Yang M, Luo F, Yuan J, Tao Q — The Psychological Impact of the COVID-19 Pandemic on Teenagers in China. *J Adolesc Health* 2020; **67**: 747-55. doi: 10.1016/j.jadohealth.2020.08.026.

29 Qi M, Zhou S-J, Guo Z-C, Zhang L-G, Min H-J, Li X-M, *et al* — The Effect of Social Support on Mental Health in Chinese Adolescents During the Outbreak of COVID-19. *J Adolesc Health* 2020; **67**: 514-8. doi: 10.1016/j.jadohealth.2020.07.001

30 Cockerham D, Lin L, Ndolo S, Schwartz M — Voices of the students: Adolescent well-being and social interactions during the emergent shift to online learning environments. *EducInf Technol (Dordr)* 2021; **26(6):** 7523-41. doi: 10.1007/s10639-021-10601-4. Epub 2021 Jun 14. PMID: 34149300; PMCID: PMC8202218

31 Williamson B, Eynon R, Potter J — Pandemic politics, pedagogies and practices: digital technologies and distance education during the coronavirus emergency. *Learning Media and Technology* 2020; **45(2):** 107-14. doi: 10.1080/17439884.2020.1761641

32 John TJ — IAP policy on age of children for pediatric care. *Indian Pediatr* 1999; **36:** 461-3.

Original Article

A Cross Sectional Clinical Study to Evaluate the Pattern of Acute Hair Loss in Patients after SARS-CoV-2 Infection

Meet Barbhaya[1], Afia Modasiya[2], Aanal Patel[2], Nirav Bapat[3], Krina Patel[4]

Background : Dermatologists have largely studied the cutaneous involvement of Coronavirus Disease 2019 (COVID-19), It is still debated whether the skin manifestations are a direct consequence of COVID-19 pathogenicity or a consequence of thrombogenic and immune deregulatory responses triggered by SARS-CoV-2 infection. Multiple studies are available focusing on the cutaneous manifestation of COVID-19 but only few reports are available regarding the Telogen Effluvium as a sequelae of COVID infection.

Materials and Method : The cross-sectional study included 130 patients who presented with the complaint of hairfall and had a history of getting infected with COVID during the second wave (confirmed cases of SARS-CoV-2). We divided the average per day shedding into mild (200-400 hairs/ day), moderate (400-600/day) and severe (>600 hairs/day).

Results : A Chi-square test of independence was performed to examine the relation between severity of COVID infection and severity of hairfall. The relation between these variables was not significant, X2 (4, N=130)=2.244, p=0.691. So we can conclude that the severity of covid infection is independent of the severity of hairfall.

Conclusion : Inflammatory process in mild COVID disease may not be causing severe acute condition during active infection but is affecting the immediate anagen release leading to increased hair loss after 2-3 months of infection. More research is needed to identify the inflammatory process underlying COVID infection which may even be affecting other systems of the body and may appear as a late sequelae.

[*J Indian Med Assoc* 2024; **122(3):** 50-3]

Key words **: SARS-CoV-2 Infection, Telogen Effluvium, Pandemic.**

The current pandemic of COVID-19 due to Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) which has rapidly spread across the globe infecting around 63 crore people and 64 lakh deaths Worldwide till date. Various studies have been published citing the various cutaneous manifestations of COVID infection including chilblain-like, maculopapular and vesicular lesions, urticaria, livedoid/ necrotic lesions, are few which are frequently reported. Multiple studies are available focusing on the cutaneous manifestation of COVID-19 but only few reports are available regarding the Telogen Effluvium as a sequelae of COVID infection. The skin manifestations are still being questioned as to whether they are a direct result of COVID-19 pathogenicity or a result of thrombogenic and immunological deregulatory responses triggered by SARS-CoV-2 infection[1]. Psychological stress and drug therapy associated with the COVID-19 can even be attributed as a causative etiology for post COVID Telogen Effluvium.

Editor's Comment :

- The article underscores a paradigm shift in understanding SARS-CoV-2 as primarily an auto-inflammatory rather than infectious condition, emphasizing the significant impact of the body's immune response compared to the virus itself. Addressing conditions like Acute Telogen Effluvium (ATE), characterized by non-scarring hair loss post-infection, requires a multifaceted approach including counseling, reassurance, and interventions like multivitamin supplements, topical peptides, antioxidants, and microneedling with PRP therapy. Vigilant follow-up is crucial for early detection of potential post-COVID sequelae, highlighting the necessity for comprehensive screening even in cases of mild disease.

Telogen Effluvium (TE), first described by Kligman in 1961, is a diffuse, non-scarring shedding of hairs, resulting from the early immediate release of hair from anagen phase and entry of the hair into the telogen phase. Acute Telogen Effluvium present as acute onset of hair loss (increased loss of hair on brushing/combing or during shampoo) post triggering event like high fever, surgical trauma, psychological stress, sudden loss of weight, hemorrhages or sometimes (around 1/3rd of cases) no trigger factor identified.

Telogen Effluvium is mainly a clinical diagnosis assisted by history, clinical routine test, trichoscopy

Department of Dermatology, GMERS Medical College and Hospital, Sola, Ahmedabad, Gujarat 380060
[1]MBBS, MD, DVL, Resident and Corresponding Author
[2]MBBS, Resident
[3]PhD (Biostatistics), Assistant Professor, Department of Community Medicine
[4]MD, DVL, Professor and Head

Received on : 08/06/2023
Accepted on : 09/01/2024

and sometimes a trichogram. A diffuse loss of hair volume with patients complaining of thinning of pony tail, positive hair pull test and nonspecific findings on trichoscopy like single hair projecting from follicular units with no loss of follicular units are generally adequate to make a diagnosis of Telogen Effluvium.

The primary objective of the study was to study the pattern of hair fall as a sequelae of COVID-19 infection.

Secondary objective was to check whether there was a association between the severity of COVID-19 symptoms with the severity of hairfall the patients suffered.

Materials and Method

An observational cross-sectional study was carried out in the Department of Dermatology at tertiary care hospital after taking approval from the Ethics committee. The study included 130 patients who presented with the complaint of hairfall and had a history of getting infected with COVID during the second wave (confirmed cases of SARS-CoV-2). Patients with a previous history of hair disorder or any debilitating conditions, chronic illness, crash diet causing acute weight loss were excluded to rule out any possible bias. A complete detailed history was elicited assisted by trichoscopy and a final clinical diagnosis was made. Patients were grouped into Mild, Moderate and Severe disease according to definition given by AIIMS/ICMR COVID-19 National task force/Joint monitoring group. Also the severity of hairfall was assessed using a visual analogue scoring tool which had hair of short, medium and long lengths by dividing a bundle of hair of each length into nine piles of increasing hair amount that were then photographed and arranged in order of size. The tool was developed and validated by Martínez-Velasco, María Abril, *et al*[2]. All Patients were asked to select the photographed hair bundle that best correlated with the amount of hair they shed on an average day. The tool didn't classify the amount of average shed as mild, moderate or severe but for the statistical analysis we divided the average per day shedding into mild (200-400 hairs/ day), moderate (400-600/day) and severe (>600hairs/day). Patients were treated with multivitamin supplements and microneedling with PRP therapy and mostly all patients responded within 1-2 months.

Statistical Analysis :

The Chi-square test of independence was used for statistical analysis. The p-value <0.05 was considered statistically significant.

Results

In this study, 130 patients were included, consisting of 124(95.40%) Female and 6(4.60%) Male. The mean age of the study population was 37.74 ± 11.84 years with the age range from 20-75 years. The average duration of onset of hair fall post COVID infection was 3.08 ± 1.05 months and median onset of hairfall was 3 months after infection with a range from 1-4 months. The median period of presenting to OPD for consultation since onset of hairfall was 30 days.

Table 1 shows Distribution of Patients according to Severity of COVID disease and Hairfall with Chi-square analysis.

A Chi-square test of independence was performed to examine the relation between severity of COVID infection and severity of hairfall. The relation between these variables was not significant, X^2 (4, N=130)=2.244, p=0.691. The analysis suggests that the severity of COVID infection is independent of the severity of hairfall.

Around 77(59.20%) patients gave positive history about pre COVID hairfall but with median hairfall of ≤100 average hair shed per day and all 77(100%) patients had aggravation of hair fall with median of 700 hair sheds /day (moderate hair fall) with mean onset of aggravation at 3.09 ± 1.10 months.

Discussion

The present study was conducted in the Department of Dermatology at GMERS Medical College and Hospital, Ahmedabad in the month of August, 2021.

In this cross sectional observational study 130 patients were enrolled fulfilling the inclusion and exclusion criteria.

A detailed history with thorough clinical examination assisted by trichoscopy, coupled with recent recovery from COVID infection and ruling out the other causes of hairloss a diagnosis of Acute Telogen Effluvium as a post COVID infection sequelae was made in all 130 patients.

Study consisted of 124(95.40%) Female and 6(4.60%) Male. This discrepancy may be because female patients are more aware and concerned regarding the hair fall than the male patients.

Table 1 — *Distribution of Patients according to Severity of COVID disease and Hairfall with Chi-square analysis*

COVID-19 disease severity according to ICMR Guidelines	Severity of Hairfall			
	Mild	Moderate	Severe	Grand Total
Mild	27(20.77%)	50(38.46%)	37(28.46%)	114(87.70%)
Moderate	1(0.77%)	6(4.61%)	6(4.61%)	13(10.00%)
Severe	1(0.77%)	1(0.77%)	1(0.77%)	3(2.30%)
Grand Total	29(22.30%)	57(43.85%)	44(33.85%)	130(100.00%)

Chi square : 2.244; Degree of freedom : 4 ; P-value : 0.691

The Mean (SD) duration of onset of hairfall was 3.08(1.05) with a range of 1-4 months. Majority of patients presented had onset of hairfall after 2-3 months from recovery of COVID infection but 10 patients (7.7%) presented with onset within 1 month. A case series of 14 patients[3] is available with median onset of hairfall 2 months post COVID while our study had median onset 3 months post COVID.

Most frequently noted trichoscopic findings were single hair emerging from the follicular unit, terminal regrowing hair and empty hair follicles.

114(87.7%) patients suffered from asymptomatic/ mild symptoms of COVID-19, 13 (10%) patients had moderate disease and 3 (2.3%) patients had severe disease. 29 (22.30%), 57 (43.85%) and 44 (33.85%) patients had mild, moderate and severe hairfall respectively. A Chi square test of independence gave a statistically non-significant p-value (0.691) stating severity of hair fall was independent of the severity of COVID disease which supported the hypothesis of study that Telogen Effluvium associated with SARS-CoV-2 infection was independent of the severity of the COVID infection.

In multiple studies, it has been reported that those with more severe COVID-19 infections are associated with higher levels of proinflammatory cytokines[4,5]. Overproduction of proinflammatory cytokines and oxidative stress-inducing cytokine storms lead to Acute Respiratory Distress Syndrome and multiorgan dysfunction associated with higher mortality.

Telogen effluvium is associated with infections like typhoid fever,malaria, chikungunya, tuberculosis with severe febrile conditions (which is a sign of a higher level of cytokine production), acute psychological stressors, or with significant surgeries (higher cortisol levels), or crash diets (leading to nutritional deficiency) and vaccines causing immune stimulation. During fever, the cytokines initiate apoptosis of hair follicle keratinocytes starting with catagen then followed by telogen[6]. Proinflammatory state and cytokine storms can explain the TE associated with moderate to severe COVID disease but in mild COVID disease, the majority of patients, though asymptomatic or having a low-grade fever for a day or two, loss of taste and smell sensations and having an average level of inflammatory marker panel, a large percentage of patients suffered from Telogen Effluvium as a sequela. This could be due to the production of some inflammatory cytokines, which may not be causing acute systemic abnormality but may be causing immediate anagen release. This is important as it may even have affected some other system in the body and may show a late post-infection sequelae.

The involvement of psychological stress associated with COVID infection cannot be ruled out as a cause of Telogen Effluvium. The production of various neurotransmitters, neuropeptides and hormones in response to psychological stressors, in particular, may produce significant alterations in the hair growth cycle by driving the transition of anagen hair to the telogen phase. However, fear, stress and anxiety is more prevalent among the hospitalized patients and with a severe disease rather than those suffering from mild infection.

Study by Sharquie KE[7] consisted thirty-nine patients; their ages ranged from 22 to 67 years with a mean and SD of 41.3±11.6 years with 36 (92.3%) females and 3 (7.69%) males which was consistent with our study. 15 (38.46%) patients reported mild COVID symptoms, 24 (61.53%) patients presented with moderate disease and no patient required hospitalization.

In a large-scale study[8] (538 cases) in Wuhan, China, investigating clinical sequelae of COVID-19, the prevalence of alopecia as a sequela was detected in 28.6% of patients.

In a multicentric study by Moreno-Arrones OM, *et al*[9] 214 patients with a diagnosis of ATE were enrolled and 89.7% (191 patients) had a confirmed diagnosis of prior SARS-CoV-2 infection.

To the best of knowledge, this is the first study in India that highlights the relation between severity of COVID-19 and acute Telogen Effluvium and investigated the etiopathogenesis of hair shedding during the pandemic of this virus infection.

Conclusion

SARS-CoV-2 is more of an auto-inflammatory condition rather than an infectious condition. Damage caused by your own immune system to the body is far more than the damage caused by COVID virus to the body. ATE is a non-scarring diffuse hair loss, usually occurs 3 months after the event that causes hair loss, and may last up to 6 months. Majority of cases require only proper counseling and reassurance. Multivitamin supplements, topical peptides mimicking hair growth factors, antioxidants, microneedling with PRP therapy may improve the hair quality and may shorten the period of hair shedding with quicker normalizing the hair to the baseline. Exact mechanism is still unknown related to the COVID associated Telogen Effluvium but is mainly attributed to the immune stimulation and cytokine storm in response to the virus. Stringent screening through regular follow up is required for early identification and diagnosis of other serious post

COVID sequelae still unknown to us even in mild disease.

Limitations : There are limitations to our study. The study had a smaller sample size and the population not representative of the general population. In addition, our data did not include all patients affected by COVID-19 but only those patients who visited the clinic with complaints of hairfall. Nevertheless the aim of the study was not to study the prevalence of the Telogen Effluvium among the patients of COVID-19 infected patients but to study the occurrence of TE against the severity of COVID-19.

Financial support and sponsorship : Nil.

Conflicts of interest : There are no conflicts of interest.

References

1 Starace M, Iorizzo M, Sechi A, Alessandrini AM, Carpanese M, Bruni F, *et al* — Trichodynia and telogen effluvium in COVID-19 patients: Results of an international expert opinion survey on diagnosis and management. *JAAD Int* 2021; **5:** 11-8.

2 Martínez-Velasco MA, Vázquez-Herrera NE, Maddy AJ, Asz-Sigall D, Tosti A — The Hair Shedding Visual Scale: A Quick Tool to Assess Hair Loss in Women. *Dermatol Ther (Heidelb)* 2017; **7(1):** 155-65.

3 Rossi A, Magri F, Sernicola A, Michelini S, Caro G, Muscianese M, *et al* — Telogen Effluvium after SARS-CoV-2 Infection: A Series of Cases and Possible Pathogenetic Mechanisms. *Skin Appendage Disord* 2021; **7:** 377-81.

4 Tufan A, Avanoğlu Güler A, Matucci Cerinic M — COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. *Turk J Med Sci* 2020; **50(SI 1):** 620-32. 10.3906/sag-2004-168.

5 Jose RJ, Manuel A — COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med* 2020; **8(6):** e46 e47. 10.1016/S2213-2600(20)30216-2.

6 Trueb RM — *Hair growth and disorders.* 1st edn. Berlin: Springer; 2008. Diffuse hair loss. In: Blume-Peytavi U, Tosti A, Whiting DA, Trueb R, editors; pp 259-72.

7 Sharquie KE, Jabbar RI — COVID-19 infection is a major cause of acute telogen effluvium. *Ir J Med Sci* 2021; **31:** 1-5.

8 Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. *Xiong Q, Xu M, Li J, Liu Y, Zhang J, Xu Y, Dong W Clin Microbiol Infect* 2021; **27(1):** 89-95.

9 Moreno-Arrones, OM — SARS-CoV-2-induced telogen effluvium: a multicentric study. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2021; **35,3:** e181-e183. doi:10.1111/jdv.17045.

Original Article

Clinico-epidemiological Profile of Snake Bite Envenomation at a Tertiary Care Centre in Eastern Rajasthan : A Longitudinal Prospective Study

Pankaj Kumar Jain[1], Himanshu Goswami[2], Pranav Kumar Bhat[2], Manoj Seval[3]

Background : To study the epidemiology and clinical profile of Snake Bite Envenomation in patients presenting to Tertiary Care Centre in Eastern Rajasthan.

Methodology : A cross sectional study was conducted on 30 patients presenting to emergency department with history of Snake Bite between the months of March, 2020 to November, 2020. The data about demography were collected using proformas, patients were admitted and followed up till discharge. Data was analysed.

Results : Out of 30 patients maximum were between age group 19 to 44 (70 %) and 60 % were male, much of them (93.3%) presented between July to November. Lower extremities were the most commonly involved body part (53.33%). Most common type of Snake Bite was due to Viper (46.67%) followed by unknown bite (36.67%), 73.3 % patients presented with local toxicity. Numbers of ASV vials required for treatment were 20, on average.

Conclusions : Snake Bite is a serious health concern in nations with thriving agriculture sector like India. And the successful specialised treatment is Anti Snake Venom (ASV). Death and complications in snake bite are due to treatment delays.

[*J Indian Med Assoc* 2024; **122(3):** 54-7]

Key words **: Snake Bite, Anti Snake Venom, Neurotoxic, Envenomation.**

More than 100,000 people die from Snake Bite envenomation each year, and in around 400,000 cases, it results in severe disability or disfigurement[1]. South Asia is the most affected region due to snake bite envenomation[2,3] and India contributes to 50 per cent of the estimated deaths due to venomous Snake Bite globally[1]. In India, the highest numbers of deaths due to Snake Bite have been reported in Uttar Pradesh, Andhra Pradesh, Bihar, Tamil Nadu, West Bengal and Maharashtra[4].

Varied countries and geographical regions within the same country, such as India, have different epidemiological and clinical presentations[5]. Although Pit vipers can cause hematoxicity, Russell's vipers have substantially higher fatality and morbidity rates[6]. Cobra and viper bites can cause a local reaction with soft tissue necrosis, whereas Krait bites seldom cause a local reaction[7]. Ptosis, external opthalmoplegia, dysphagia, dysphonia, paralysis of the facial muscles, and respiratory muscle weakness are the primary neurotoxic clinical symptoms. The primary cause of mortality and morbidity in south India[8] is Russell's viper causing hematoxicity and nephrotoxicity.

Editor's Comment :

- After suspecting any snake bite, the patient should be taken to the hospital immediately and Anti Snake Venom (ASV) should be administered as soon as possible, if indicated.

The frequency of contact between snakes and humans has a significant impact on the incidence of Snake Bites. Seasonal peaks in the frequency of snake bites are typically linked to increases in agricultural activities or seasonal rains, sometimes coinciding with exceptional snake migration and activity.

The length of time it takes for symptoms to appear after a venomous Snake Bite and how they manifest clinically can vary depending on the species involved, how much venom was injected, and where the bite occurred. Most bites that envenomate induce localised discomfort, swollen soft tissues, and ecchymosis. Bullae and hemorrhagic or serum-filled vesicles may form at the bite site over the course of many hours to days. Systemic symptoms can vary and can include haemorrhage from any anatomic site, nausea, tachycardia or bradycardia, hypotension, and renal failure. About 50% of Pit viper and Russell's viper bites, 30% of cobra bites, and 5-10% of saw scale viper bites don't cause any symptoms or tell-tale signs of envenoming[8].

Department of General Medicine, Government Medical College, Kota, Rajasthan 324010
[1]MD, Associate Professor
[2]MBBS, Junior Resident
[3]MBBS, Junior Resident and Corresponding Author

Received on : 22/06/2023
Accepted on : 28/11/2023

The only effective particular treatment for Snake Bite envenoming is anti snake venom (ASV)[9]. From a medical perspective, polyvalent antivenom neutralises the venoms of numerous distinct species in a specific geographic area[10]. For instance, it works well against the four common snake species found in India: saw-scaled viper, Russell's viper, Indian krait and common cobra.

The purpose of the current study was to understand the clinical, epidemiological and long-term effects of snake bite.

Material and Methods

Study Design & Setting : 30 patients with Snake Bites older than 14 years old who were admitted to the medical ward and Intensive Care Unit at the Government Medical College Hospital in Kota, Rajasthan, between March 2020 and November 2020 were included in this cross-sectional study.

Inclusion Criteria : Patients older than 14 years with a definite history of Snake Bite and developed features of envenomation.

Exclusion Criteria : Patients with no signs of envenomation after a period of observation were excluded.

Sample Size Calculation : Sample size calculation was based on the incidence of Snake Bite during that particular season of year.

Methodology : The history that patients provided was used to gather information about patients who had been bitten by snakes, which was then recorded into proformas that were created especially for evaluation. The location of the bite, travel time to the hospital, the patient's occupation, any treatments received before arriving, the total amount of ASV administered, as well as the treatment's success, were all noted. Only when the snake was brought along with the victim by the patient or the medical staff, was the species of snake identified. Local toxicity at the site of the bite, systemic toxicity or both were clinical characteristics of bites. Pain, oedema, bruising, blistering, cellulitis, bleeding and consequences such compartment syndrome, abscess development and gangrene were all parts of local toxicity. Hemostatic dysfunction or neurological characteristics were used to define systemic toxicity. Neurotoxicity symptoms included drowsiness, paraesthesia, ptosis, external ophthalmoplegia, facial muscle paralysis, regurgitation via the nose, trouble swallowing, respiratory and widespread flaccid paralysis. Fang marks, venepuncture sites, coagulopathy, hemolysis and prolonged bleeding from recent wounds are examples of hemotoxicity symptoms.

If they had clinical signs of envenomation, all patients with Snake Bites were given polyvalent Anti Snake Venom (ASV) when they arrived at the hospital. For all patients with Snake Bites, a starting dose of 10 vials of ASV was administered. Clinical response to ASV was maintained, as did the 20-minute Whole Blood Clotting Time (WBCT 20). A repeat dose of ASV was administered if the signs of envenomation persisted.

Statistical Analysis : Statistical Analysis was done with mean, range, numbers and percentage.

Results

Participants : A total of 54 patients were found potentially eligible candidates for the study, out of which 10 were not eligible due to various reasons and 44 were confirmed eligible candidates. Out of 44, 30 candidates completed the follow up and 14 lost to follow up & did not consent for the study (Fig 1 & Table 1).

There were 30 cases of Snake Bite during the study period of nine months. The overall distribution of Snake Bite was higher in male (n = 18, 60%) then females (n = 12, 40%). Majority of the Snake Bites were in the age group of 18- 45 years (n = 21, 70%). The mean age of snake bite was 34.5, median 33 and range 15-62 years.

Majority of the Snake Bite cases were admitted during the months of July to November (n = 28, 93.3%). Snake Bites occurred more on lower limbs. Maximum of 16 bites were on lower extremity (53.33%)(Table 2).

Majority of patients (n = 24, 80%) reached hospital within 6 hours of bite. The mean time duration between Snake Bite and access to hospital was 4.43 hours. Snake identified the most common was viper (n = 14, 46.6%). Maximum of 6 Patients(20 %) cases showed evidence of neurotoxic manifestation, apart from local toxicity which was present in most of the cases(n= 22, 73.3 %). Among local toxicity most common symptom was pain at bite site (n= 22, 73.3%) followed by local swelling (n=15, 50%).

Among neurotoxic manifestations most common symptom was ptosis (n=4, 13.3%) followed by double vision (n=3, 10%).General flaccid paralysis and respiratory muscle weakness was evidenced in 2 patients necessitating mechanical ventilation.In bleeding manifestations, haematuria was seen in both patients with bleeding gums and local bleeding at bite site.

Treatment : All Snake Bite patients received injection tetanus toxoid. The average dose of ASV administrated to all Snake Bite cases was 25.5 vials (range 5-60, median 27.5). Two snake bite cases

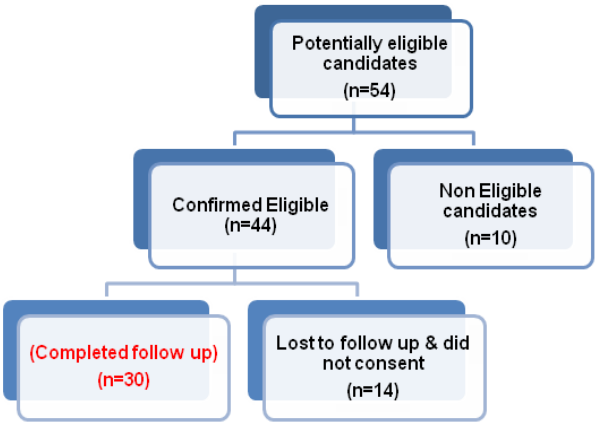


Fig 1 – The study flow diagram

Table 1 — *Demography and Basic Characteristics*

Items	N	Percentage
Age group (years)		
19 - 44	21	70 %
≤18	3	10 %
≥45	6	20 %
Gender		
Male	18	60 %
Female	12	40 %
Admission month		
March	1	3.33 %
April	2	6.66 %
May	0	0 %
June	1	3.33 %
July	3	10 %
August	7	23.33 %
September	8	26.66 %
October	5	16.66 %
November	3	10 %
Body part involved		
Upper extremities	13	43.33 %
Lower extremities	16	53.33 %
Trunk	1	3.33 %

received <10 ASV vials, 12 cases received 10-20 vials, 12 cases received 21- 40 ASV vials, more than 40 vials in 4 patients.

Majority of patients (n=28, 93.3%) were discharged. The average duration of hospital stay was 4.13 days, range 2-14 days.Two patients died due to delay in ASV administration after bites as both cases were brought 24 hours after the bite.

Discussion

According to study conducted by Mathew, *et al*[11]and Gajbhiye R, *et al*[12], the majority of the patients were males (70% & 52.4% respectively) which is similar to our study (60%). This is likely related to their outdoor activity. In our investigation, the majority of Snake Bites occurred in people between the ages of 18 and 45

Table 2 — *Type of Snake Bite, Manifestations & ASV given*

Characteristic	Number	Percentage
Snake Type		
Viper	14	46.67%
Cobra	3	10%
Krait	2	6.67%
Unknown Bites	11	36.67 %
Manifestation		
Neurotoxic	6	20 %
Hematotoxic	2	6.6 %
Local toxicity	22	73.3 %
Number of ASV Vials given		
10- 20	12	40%
21- 40	12	40%
>40	4	13.33%
< 10	2	6.67%
Total	30	100%

(n=21), which is comparable to the findings of Gajbhiye R, *et al*[12] (66 %) and other studies from India[13], Nepal[14], and India[15].

Similar to Gajbhiye R, *et al*[12], the majority of bites occurred from July to November (n=28, 93.3%) because it was monsoon season. Similar to Gajbhiye R, *et al*[12], bites to the extremities were more frequent in the current investigation (upper extremity n=13, lower extremity n=16, 63%).

Most of the patients (n=24,80%) reached hospital within first 6 hours comparable to Mathews M, *et al*[11] WHO reported 70% cases came to hospital within 6 hours. Timely arrival at hospital may be because of increased awareness of people for early medical help.

The majority of snakes found in our study were vipers (n=14, 46.6%) which is similar to study conducted by Mathews M, *et al*[11] (64.4%).While Gajbhiye R et al[12] reported neurotoxic manifestations in 19% and 27% of cases, respectively, our investigation found hematotoxic manifestations in 10% of cases and neurotoxic manifestations in 16.7% of cases.

Anti Snake Venom (ASV) was given in the current trial at an average dose of 25.5 vials (range 5-60, median 27.5).The exact dose of ASV to be administered in the cases of Snake Bite is still a matter of discussion, with some studies showing insignificant association between cure and ASV dose administered[17].

The study's low mortality rate (n=2,6.67%) may be attributable to increased public awareness of the need for prompt medical attention, improved transportation and access to hospitals, the availability of facilities such as ventilator support, better ICU care, and a dialysis facility, among other factors. Joshi M, *et al*[16] and Mathew M, *et al*[11] also showed similarly low mortality.

Limitations of the study : Limitations of our study are short sample size & single health facility based study. Thus the results cannot be generalized to the population.

Conclusion

In nations with a thriving agricultural sector, such as India, Snake Bites remain a serious health concern. The only successful specialised treatment for a Snake Bite is Anti Snake Venom (ASV). The study also demonstrates that a high prevalence of complications and a high fatality rate in individuals with Snake Bites are related to treatment delays.

Funding : No funding source.

Conflict of interest : None declared.

Ethical approval : The study was approved by the IEC.

Refrences

1 Gutierrez JM, Calvete JJ, Habib AG, Harrison RA, Williams DJ, Warrell DA — Snakebite envenoming. *Nat Rev Dis Primers* 2017; **3:** 17063

2 Chippaux JP — Snakebites: Appraisal of the global situation. *Bull World Health Organ* 1998; **76:** 515-24.

3 Kasturiratne A, Wickremasinghe AR, De Silva N, Gunawardena NK, Pathmeswaran A, Premaratna R, *et al* — The global burden of snake bite: A literature analysis and modeling based on regional estimates of envenoming and deaths. *PLoS Med* 2008; **5:** e218.

4 Mohapatra B, Warrell DA, Suraweera W, Bhatia P, Dhingra N, Jotkar RM, *et al* — Snake bite mortality in India: A nationally representative mortality survey. *PLoSNegl Trop Dis* 2011; **5:** e1018.

5 Kalantri S, Singh A, Joshi R, Malamba S, Ho C, Ezoua J, *et al* — Clinical predictors of in-hospital mortality in patients with snake bite: a retrospective study from a rural hospital in central India. *Tropical Med Internat Health* 2006; **11(1):** 22-30.

6 Joseph JK, Simpson ID, Menon NC, Jose MP, Kulkarni KJ, Raghavendra GB, *et al* — First authenticated cases of life threatening envenoming by the hump- nosed pit viper (Hypnalehypnale) in India. *Transact Royal Society Trop Med Hygiene* 2007; **101(1):** 85-90.

7 Kularatne SA — Common krait (Bungaruscaeruleus) bite in Anuradhapura, Sri Lanka: a prospective clinical study, 1996-98. *Postgraduate Med J* 2002; **78(919):** 276-80.

8 Mohapatra B, Warrell DA, Suraweera W, Bhatia P, Dhingra N, Jotkar RM, *et al* — Million Death Study Collaborators. Snakebite mortality in India: a nationally representative mortality survey. *PLoS Neglected Tropical Diseases* 2011; **5(4):** e1018.

9 World Health Organization. WHO guidelines for production, control and regulation of snake antivenomimmunoglobulins. WHO; 2018. Available from: *http://www.who.int/blood products/snake_antivenoms/snakeantivenomguide/en/*, accessed on January 31, 2019.

10 Warrell DA — Snake venoms in science and clinical medicine 1. Russell's viper: biology, venom and treatment of bites. *Transact Royal Society Trop Med Hygiene* 1989; **83(6):** 732-40.

11 Mathews M — *Int J Res Med Sci* 2019; **7(11):** 4059-63.

12 Gajbhiye R — Incidence and management practices of snakebite: A retrospective study at Sub- District Hospital, Dahanu, Maharashtra, India. *Indian J Med Res* 2019; **150:** 412-6.

13 Inamdar IF, Aswar NR, Ubaidulla M, Dalvi SD — Snakebite: Admissions at a tertiary health care in Maharashtra, India. *SAfr Med J* 2010; **100:** 456-8.

14 Pandey DP, Vohra R, Stalcup P, Shrestha BR — A season of snakebite envenomation: Presentation patterns, timing of care, anti venom use, and case fatality rates from a hospital of Southcentral Nepal. *J venom Res* 2016; **7:** 1-9.

15 Pandey DP — Epidemiology of snakebite based on hospital survey in Chitwan and Nawalparasi districts, Nepal. *J Nepal Health Res Counc* 2006; **4:** 51-7.

16 Joshi M — Clinical profile of patients with acute poisoning. *GCSMC J Med Sci* 2015; **4(2)**.

17 Chieh-Fan C, Tzeng-Jih L, Wen-Chi H, Hua-Wei Y — Appropriate antivenom doses for six types of envenomations caused by snakes in taiwan. *J Venom Anim Toxins incl Trop Dis [Internet]* 2009; **15(3):** 479-90.

Review Article

A 100 Years Journey of Insulin

Rakesh Chandra Chaurasia[1]

The discovery of insulin and the journey of evolution has revolutionized the saga over the last 100 years. Diabetis Millitus (DM) is a worldwide health issue that causes serious disability. The complications like renal failure, amputation, and loss of eyesight are huge social burdens and their economic cost are also enormous. Being a central etiological factor Insulin™ is a mode of therapy. There are ranges of conventional to newer insulin. The latest insulin has come through various stages after the advent of recombinant DNA technology. The native insulin molecule is modified via substitution, replacement or addition of some amino acids to form Insulin analogs™ (designer insulin) along with a change in biological activity and their pharmacological profile. The more recent inclusion is smart insulin. Other newer insulin is under various phases of a clinical trial. This article highlights a hundred years of anniversary pertinent to insulin along with significant milestones in medical history.

[*J Indian Med Assoc* 2024; **122(3):** 58-62]

Key words **: Amino Acids, Hyperglycemia, Hypoglycemia, Devices, Madhumeha.**

Diabetes Mellitus (DM) is mentioned as 'Madhumeha' (honey urine) in ancient Indian texts - Charaka & Sushruta Samhita. Madhu means sweetness like honey and meha means to flow. The term Diabetes Mellitus was introduced by Thomas Willis (a British physician-1621-75) to clinically differentiate this from diabetes insipidus.

Diabetes Mellitus (DM) is a global disease that results in significant morbidity and mortality. These days, developed nations have witnessed an explosive increase in the incidence of DM, predominately related to lifestyle changes. International Diabetes Federation estimated that more than 500 million people Worldwide are affected and its prevalence is expected to more than double by the end of the third decade of this century[1].

Diabetes Mellitus is caused by a decrease in the circulating concentration of insulin ie, insulin deficiency and a decrease in the response of peripheral tissue to insulin ie, Insulin resistance. These abnormalities lead to alterations in the metabolism of carbohydrates, amino acids, lipids and ketones. Clinically, most patients are classified as either Type -1 DM or Type - 2 DM. Other causes are gestational (GDM) and secondary. Maturity-onset Diabetes of Youth (MODY) is another alarming variety that incidence is growing so fast. The central feature of diabetes syndrome is hyperglycemia, responsible for the development of complications. Treatments directed to maintenance of normal blood glucose level. Regular exercise, adequate diet, and average body weight control blood parameters and counteract several co-morbid conditions[2].

Editor's Comment :

- Insulin was discovered 100 years ago and is still the mainstay of almost all Type 1 and non-responding Type 2 Diabetes Mellitus.
- Originated from animals as conventional bovine and porcine insulin, now the era is diverted toward biosynthetic human insulin, then designer insulin and most recently under trials innovative smarts insulin.
- Insulin is the only miracle medicinal molecule linked with the maximum number of prestigious Nobel Prizes.
- For community awareness 14th November, the birth anniversary of Banting is designated as - World Diabetes Day.

The evolution of insulin therapy over the past 100 years since the discovery of insulin is testimony to the biomedical bench-to-bedside process. Insulin is the mainstay of treatment of virtually all types of DM-1 and non-responding Type-2 DM. These days, numbers of insulin preparations are available viz conventional, purified, human and more recent insulin analogs. Such analogs offer an advantage over other insulin due to the convenience of dosing at mealtime and their more physiological pharmaco-kinetic profile, which may allow patients to achieve better glycemic control. These analogs are popularly known as 'designer insulin' due to changes in the design pattern of native insulin[3].

Historical Scenario :

The history of insulin discovery is a saga of trials, failure, hope, discovery and rediscovery. In 1886, Paul Langerhans, a German medical student, noted that the pancreas contained two distinct groups of cells- the acinar cells which secrets digestive enzymes, and cells that are clustered in the island (islets of

[1]MD, Professor, Department of Pharmacology, MLN Medical College, Prayagraj, Uttar Pradesh 211002 and Corresponding Author

Received on : 25/04/2023
Accepted on : 02/08/2023

Langerhans], which he suggested to serve as second function(?). This comes to light in 1889 when Minkowski and Von-Mering showed that pancreatectomized dogs exhibit a syndrome similar to DM in humans.

There were numerous attempts to extract the pancreatic substance (insulin) responsible for blood glucose regulation. In 1900, Gurg-Zuellzer in Berlin attempted to treat a dying DM patient with an extract of the pancreas. In 1911, EL Scott, a student at Chicago University attempted to isolate an active principle and treated several diabetic dogs with encouraging results. In between 1916-20, the Romanian physiologist Nicolas Paulesco found that injection of pancreatic extract reduces urinary sugar and ketones in diabetic dogs but their significance appreciated after several years.

Frederick Banting, a young Canadian surgeon together with Charles Best, a fourth-year medical student, successfully obtain a pancreatic extract after degeneration of acinar tissue by ligating the pancreatic duct, which decreased the blood glucose concentration in diabetic dogs. Leonard Thompon, 14 years was the first patient to receive the acinar extracts prepared by Banting and Best at Toronto Hospital with blood glucose 500 mg/dl and demonstrated marked clinical improvement. The remarkable work on insulin came with lots of hope for diabetics. That news spread in most parts of the world like wildfire[4].

Insulin & Nobel Prizes :

Banting and Best faced difficulty to obtain active extract reproducibly. This led to the greater involvement of Macleod, a professor of physiology at Toronto and JB Collip, (a chemist with expertise in the extraction and purification of epinephrine). The stable extract was eventually obtained from animal sources. The prestigious prize in Medicine and Physiology was awarded to Banting and McLeod in 1923. Banting announced that he would share his prize with Best. MacLeod did the same with Collip. Frederick Sanger determine the primary structure of insulin and was awarded Nobel Prize in 1969. Dorothy Hodgkin gets Nobel Prize to determine the tertiary structure by means of X-ray diffraction studies[5]. Insulin is the only miracle molecule concerned with a maximum number of Nobel Prizes. The 14th of November – the birth anniversary of Banting is celebrated as 'Diabetes Awareness Day'[6].

Insulin Structure :

Frederick Banting and Charles Best first extracted insulin in 1921. Sanger established the amino-acid sequence in 1960. Hodgkin and co-workers elucidated three- dimensional structure of insulin in 1972.

Insulin consists of two peptide chains A and B, interconnected with two intra-subunit and one inter-subunit disulfide bridges at the A7-B7 and A20-B19 position of amino acid in the chain. A-chain is composed of 21 amino acids while a B-chain has 30 amino-acid residues. Therefore, human insulin has a total of 51 amino acids with a molecular mass of approximately 5734 Daltons[7]. Insulin exists as a monomer, dimer and hexamer. The monomer is the biologically active form of insulin.

Conventional to Newer Insulin — A Long Journey :

The clinical introduction of Insulin, almost a century ago in 1921 has revolutionized the treatment of diabetes. Initially, insulin was manufactured from bovine and porcine sources. Bovine insulin differs from two amino acids while porcine insulin by one amino acid[4]. The conventional commercially available preparation contained some antigenic impurities that act as an allergen to some users. In 1983. Human insulin is produced by recombinant DNA technology using special strains of E coli or yeast. Insulin allergy, lipodystrophy, and resistance were almost eliminated with the development of biosynthetic human insulin almost. The present-day approach is to deliver insulin in a physiological manner, which will refer to a rapid release at mealtime and the low stable release of insulin in between meals. These initiate the making of new designs of insulin from existing ones.

Need of Advanced Insulin — Why ?

The value of glycemic control in the prevention of complications was emphasized in landmark clinical trials in 1990 (United Kingdom Prospective Diabetic Study UKPDS) and (Diabetic Control and Complication Trial DCCT). The scientific evidence of the trial provides a basic need for newer insulin formulation, which could mimic closely both mealtime and the basal component of endogenous insulin secretion. This urges the development of insulin analogs. Because of the change in the design of native insulin such newer preparations are popularly known as 'designer insulin'. With the advent of genetic engineering, human insulin is now produced by recombinant DNA technology using a special strain of E.coli and yeast. Modification of amino-acid sequences of human insulin has produced different designs with different pharmacological profiles[8]. Other insulins are under clinical trial to enhance patient compliance.

Basic Issue in Designing :

Any amino–acid moieties are not utilized due to adverse effects or carcinogenic potential. As general

amino acids, no 25-30 of the B-chain is most suitable to target for design. Thus, only a few molecules such as lysine, proline, etc are receptive to an effective change and are the sites where the current engineering trends for newer insulin analogs focused. The analog should mimic the physiological profile, pharmacologically better than the existing one along with a better safety profile. Insulin analogs provide the overall view of the structure-activity-relationship between insulin biochemistry and action.

Therefore, insulin structure thus provides many options for the modification of newer variables[9].

Newer Insulins in Clinical Practice :

Newer insulin analogs differ from native insulin in amino-acid sequence and are obtained by a novel technique of genetic engineering by induction and deletion in A and B chains of the native form ie, by modification in the design of insulin. Therefore, designer insulin is identical to human insulin except for the positions of some amino acids that are changed. The designer insulin is classified according to onset and duration of action into the following category.

1 - Rapid Acting Insulin —

- Insulin Lispro
- Insulin Aspart
- Insulin Glulisine

2 - Long Acting Insulin —

- Insulin Glargine
- Insulin Detemir
- Insulin Degludec

Lispro was the first short-acting insulin analog approved in 1996, followed by aspart in 2000 and glulisine in 2004. On the other hand, glargine was approved in 2000 and detemir in 2005. The most recent ultra-long-acting degludec was approved in 2015. After structural modification, the solubility, onset and duration of their biological action get changed[10].

Apart from rapid and long-acting designer forms, biphasic ones, better known as intermediate-acting insulin are also available. They provide both mealtime and basal coverage in a single preparation. Premix biphasic insulin analogs are combinations in various proportions, Insulin degludac & insulin aspart is the first analog combination that contains both long-acting and rapid-acting insulin. It is a unique combination that provides a stable insulin action over a 24-hour period[11]. Brief descriptions of currently available preparation are mentioned :

Insulin Lispro — The amino-acid lysine and proline near the carboxyl terminal of the B-chain has reversed. Proline at B28 has been moved to B29 and lysine from B20 has been moved to B28. Thus, normally occurring Pro-Lys sequence at B28 and B29 is reversed to Lys-Pro. To enhance shelf life, insulin lispro has stabilized into hexamer and dissociated into monomer almost instantaneously following injection. This property results in characteristic rapid absorption with an onset of action within 5-15 minutes and a shorter duration of action ie, 3-5 hours.

Insulin Aspart — This was created by the substitution of neutral proline at B28 with negatively charged aspartic acid. This modification reduces the normal proline B28 and glycine B23 monomer-monomer interaction, inhibiting insulin self-aggregation and rapidly breaking into monomer after injection, resulting in ultimate rapid onset and shorter duration of action.

Insulin Glulisine — Glutamic acid replace lysine at B29 and lysine replace asparaginase at B3. This will cause a reduction in self-association and rapid dissociation into active monomer. The net result is the short onset and duration of action.

Insulin Glargine — This is the first long active analog produced by alteration in both A and B chains. Two arginine residues are added to the carboxyl terminus of the B chain and asparagine in A21 is replaced with glycine. It is a clear solution at an acidic pH. This pH stabilizes the insulin hexamer and forms an amorphous micro-precipitate. From these crystalline depots, insulin is slowly released resulting in prolonged sustained and predictable absorption patterns. Insulin Glargine has a slow onset of action and achieved maximum effect after 4-5 hours with maximum activity maintained for 12-24 hours or longer. It has 6-7 fold greater binding than native insulin-to-insulin receptors. Glargine insulin is administered at any time during the day with equivalent efficacy, usually given once daily. Although some very insulin-sensitive individuals will benefit from split dosing like twice a day. There are two generations of Glargine insulin on the basis of the concentration of units of insulin per ml First G – 100U/ml (introduced in 2000), and Second G- 300U/ml (introduced in 2015).

Insulin Detemir — Detemir is obtained by the removal of threonine at position B10 of 14-carbon myristoyl fatty acid at the epsilon group of lysine at B 29. The addition of fatty acid stabilizes and increases the solubility of insulin. This modification has increased its association with insulin to albumin and imparted the molecule with reversible albumin binding capacity, thereby prolonging the duration of action through slow dissociation from albumin. Insulin detemir is soluble at a neutral pH of 7 which overcomes the problem of precipitation and crystallization. This insulin is more slowly absorbed and its effect last for more than 24

hours. Therefore insulin detemir should be given once daily at a fixed time[12].

Insulin Degludec — Most recent inclusion in the list of long-acting insulin is ultra-long-acting insulin named degludec. A single amino acid threonine is deleted at the B-30 position and is conjugated to hexadecanedioic acid via gamma L glutamyl spacer linker at amino acid lysine at position B-29. This structure allows the formation of multi-hexamer as a depot in subcutaneous tissues that result in the slow release of monomers into systemic circulation thus there is no peak activity. It has a duration of action that lasts up to 42 hours, the highest among other long-acting preparation, Degludac can be given thrice weekly and is commonly called as ultra long-acting insulin[13].

Pharmacological Profiles :

The designer insulin mimics the physiological pattern. These analogs bind with the insulin receptor and act like native insulin. They display longer non-peaking profiles with better glycemic control.

Rapid-acting insulin analogs offer more flexible treatment regimens. These bear a close resemblance to normal mealtime insulin and therefore improve post-prandial glycemic control and will reduce the risk of hypoglycemia. This has the additional benefit of allowing insulin to be taken immediately before a meal. These analogs retain their structure in the monomeric or dimeric configuration on subcutaneous injection and are thus absorbed three times more rapidly than usual insulin. As a result, there is a rapid increase in plasma insulin levels and early onset of hypoglycemic action. These analogs can be injected just before or just after mealtime ie, 'shoot and eat.' Some formulations are also suitable for intravenous administration, much better via an insulin pump[14].

Long-acting insulin analogs have a slow onset and prolonged action. They provide a low basal concentration of insulin continuously throughout the day. Increased stability, less variability and a more selective action do help treatment strategies to achieve far superior glycemic control, therefore, preventing complications. They have flat and prolonged hypoglycemic effects ie, no peak. These analogs exhibit a longer action of up to 24 hours and should be injected once daily. The ultra-long-acting insulin can be given thrice a week[13].

As biphasic insulin analog is a combination of both long-acting and rapid-acting insulin in various proportions, thus they provide mealtime and basal coverage in a single preparation[15].

Insulin Delivery Devices :

Being a peptide hormone, insulin gets destroyed by gastric acid if taken orally while absorption from the parenteral routes is not reliable but also inconvenient to the patient as for self-administration is concerned[16]. Considering all parameters and ease of self-administration, the subcutaneous route is the most widely accepted way of insulin administration[17]. There have been landmarks in the insulin delivery system starting from the syringe (1924) to the most current, precise and accurate means. Common insulin delivery system includes insulin syringes, insulin pen, jet injector, and insulin infusion port/ pump. Recent innovations are under trial, a few of them are continuous intraperitoneal insulin infusion, patch pumps, oral insulin, artificial pancreas and insulin inhaler[18].

Future of Insulins :

Once weekly Insulin – Design modification of insulin icodec include three amino acid substitutions (one at A chain, two at B chain) and a C20 fatty diacid side chain that is attached through a hydrophilic linker at B-29 K. These changes yield strong yet reversible binding to albumin, reduced enzymatic degradation, and slower receptor-mediated clearance, resulting in a half-life of approximately 196 hours.

Hepato preferential Insulin — Insulin peglispro is a pegylated basal insulin that has a rapid effect in suppressing hepatic glucose production and a lesser delayed effect on peripheral glucose uptake. The hepatic preferential effect has been attributed to its large molecular size.

Inhaled Insulin — A formulation inhaled as a dry powder with a shorter duration of action about 3 hours (afrezza) and 6 hours(exubera) .

Oral Insulin — Isosema, tregopil,oramed, and lyn are oral insulin, under clinical trial.

Glucose Responsive Insulin — Also called 'smart insulin' because of the dynamic regulation of insulin secretion. As exogenous insulin contains a glucose-responsive moiety. This sensor would release insulin when blood glucose concentration exceeds the normal range but not when they are within target[19].

Newer Adjunctive Modalities :

Incretin is a group of hormones that includes Glucagon-like Peptide (GLP-1) and Glucose-dependent Insulinotropic Polypeptide (GIP-1). In spite of a potent insulinotropic incretin, GLP-1 has a short life span and is quickly metabolized by Di Peptidyl Peptidase IV (DPP-IV) enzyme within 1 to 2 minutes. Incretin action can be enhanced by degradation resistant GLP-1 receptor agonists (incretin mimetics) and by inhibitors

of dipeptidyl peptidase iv. activity [incretin enhancers]. Currently, available incretin mimetic are injectable agents and includes exenatide, liraglutide, pramlintide, etc. Being a polypeptide, exenatide and another agent must be administered by the subcutaneous route. These agents are used as add-on drugs with metformin or sulfonylurea, with insulin. The usual side effects are nausea, vomiting, diarrhea, and really fatal narcotizing hemorrhagic pancreatitis[20].

Incretins are rapidly metabolized by the enzyme Di Peptidyl Peptidase –IV (DPP-IV) Inhibitors, Their action can be enhanced by inhibiting enzymes, ie, by the use of specific enzyme inhibitors (gliptins). The DPP-1V inhibitors include sitagliptin, saxagliptin, vildagliptin and linagliptin. The most common adverse effects are headaches and nasopharyngitis. Gliptins are used in combination with metformin and sulfonylurea[21].

Amylin is another polypeptide hormone co-secreted with insulin. It also inhibits glucagon release and suppresses appetite. Pramlintide is an available amylin mimetic representative used subcutaneously as an adjunct to insulin, by separate injection[22].

Sodium-glucose Transport Protein (SGLT2) is responsible for glucose absorption from the kidney. Its inhibitor reduces blood glucose by inhibiting renal glucose re-absorption. Numbers of agents are under clinical trial. Insulin-like Growth Factor (IGF-1) is tried in severe insulin resistance. Aldose reductase inhibitors inhibit the formation of polyol from sugar thereby reducing the thickening of the basement membrane. Glucosamino-glycane (CAG) has some preventive role in diabetic nephropathy. Cannabinoids receptor antagonists, lipase inhibitors, and T-cell inactivators are under trial as diabetic preventive agents[23].

Conclusion

2021 is marked as the centenary year of Insulin discovery. It was ground-breaking innovation in the history of diabetes care. Diabetes Mellitus is a global health problem of grave morbidity and mortality. Insulin was discovered 100 years back and is still the only documented scientific way of medical hope. During that period the number of preparations is introduced one by one with a definitive advantage over the previous one. Although insulin has been available for several years, major advances have been made over the past few decades after the advent in advance of biotechnology, especially genetic engineering. The most recent approach is to deliver insulin in a physiological manner. This is only possible after the advent of certain analogs, the most popular among them is designer insulin. These are well tolerated and closely mimic physiological patterns to achieve better metabolic control. 1921 to 2021 has witnessed the milestones of insulin innovation from conventional animal origin to genetically engineered human insulin, designer as well as smart insulin. Exactly 100 years before that in 1923, Nobel Prize was awarded to stalwarts for their breakthrough invention.

Conflict of Interest – not stated .

Ethical Consideration – Not required

Acknowledgment – to all references

References

1 Devis SN — Insulin; Goodman & Gilman's- The Pharmacologic Basis of Therapeutic; *Mc Graw Hill Publication* 2006; **11:** 1613-28.
2 Davidson MB, Nathan DM, Buse JB — Management of Hyperglycemia. *Diabetes Care* 2006; **29:** 1963-72.
3 Michael B — The discovery of insulin, Toronto University Press 25th anniversary edition, 1982, available at http;// www.jstor. org. assessed on Feb 2023.
4 Vecchio I, Zinman B — 100 years journey and research and clinical achievement. *Diabetologia* 2021; **64(5):** 947-53.
5 The history of the Nobel Prize for the discovery of insulin; available at https;pubmed.ncbi.nlm.nih.gov
6 World Diabetes Day. available at https;// www, who.int.campaigns. assessed on Feb 2021
7 Ganong WF — Structure of Insulin; Review of Medical Physiology. *McGraw Hill Publication* 2001; **21:** 337
8 Bennett PN, Brown MJ — Sources & Preparation of Insulin; Clinical Pharmacology. *Elsevier Publication* 200; **9:** 680.
9 Peterson JS — Insulin analogs –Design aspect; Novo Nordisk Diabetes Update 2006; 19-28.
10 Finkel R, Clark MA, Cubeddu LX — Insulin and its analog's; Pharmacology. *Wolter Kluwer* 2009; **4:** 287-96.
11 Katzung BG — Insulin preparation , Structure of rapid acting insulin; Basic & Clinical Pharmacology. *Mc Graw Hill Publication* 2006; **10:** 688-91.
12 Brenner GM, Stevens CW — Long acting Insulin; Pharmacology. *Saunders Elsevier* 2010; **3:** 392-3.
13 Rang HP, Dale MM, Ritter JM — Pharmacokinetics- Aspects of Insulin preparation. *Pharmacology: Elsevier Publication* 2003; **5:** 387-8.
14 Chaurasia RC — Diabetes Milletus – designer aspect of therapy. *The Indian Practitioners* 2014; **87(10):** 630-4.
15 Kalra S — Insulin Degludac Aspart; The first coformulation of Insulin analog. *Diabetes Ther* 2014; **5(1):** 65-72. doi: 10.1007/s13300-014-0067-x
16 Srivastava SK — Newer Agent for DM. *Medical Pharmacology* 2012; **1:** 1102-3.
17 Selam JLM — Evolution of diabetes insulin devices. *Journal of Diabetes Science-technology* 2010; **4:** 505-13.
18 Shah RB, Patel M, Maahs DM — Insulin delivery method, past, present and future. *International Journal of Pharmaceutical Investigation* 2016; **6:** 1-9.
19 Ratnakaran R, Zinman B — The ongoing evaluation of basal insulin therapy over 100 years. Diabetes Obes Metabolism, 2022; **24 Suppl 1:** 17-26. DOI: 10.1111/dom.14552
20 Sharma HL& KK — Incretin mimetics; DPP iv inhibitors. *Principle of Pharmacology* 2011; **2:** 640-1.
21 Brenner & Stevens. Incretin mimetic & Amylin analogue; Pharmacology; Saunders Elsevier 2010; **3:** 393.
22 Ghosh S, Elhad T, Malik I — Incretin based therapies for Type-2 DM; *JIMA* 2008; **106:** 373-4.
23 Nyati P — Miscellaneous agents; Future Potential. Pharmacology; *SEED* 2002; **2:** 523-24.

Case Series

Postpartum Hemorrhage in IVF Pregnancies — A Case Series

Santosh S Basarakod[1], Charishma Halemani[2], Rajashree S P[3], Chaitra N[4]

Postpartum Hemorrhage (PPH) is the leading cause of maternal mortality Worldwide especially in low income countries. PPH is associated with various risk factors, ART conception is one among them. IVF conception is an independent factor for third stage complications like PPH. With increasing use of ART Worldwide, the risk of PPH also increases. This article emphasizes on the association between the IVF pregnancies and postpartum hemorrhage. Five cases are discussed in this series which are conceived through IVF. Three cases had twin gestation and 2 cases had singleton pregnancy. Four cases were primary PPH and 1 was secondary PPH. Three cases were atonic PPH, 1 traumatic PPH and 1 case was retained product of conception. All these cases were managed conservatively without the need for hysterectomy. Focal atony of the lower uterine segment, a distinct entity for PPH was also noted in 2 cases which is described here.

[*J Indian Med Assoc* 2024; **122(3):** 63-5]

Key words **: Postpartum Hemorrhage, Invitro Fertilization, Focal Atony of the Lower Uterine Segment.**

Postpartum Hemorrhage (PPH) is a serious obstetric complication having severe maternal morbidity and mortality. PPH is the leading cause of maternal mortality Worldwide especially in low income countries which accounts nearly one-quarter of all maternal deaths globally[1]. Each year, about 14 million women experience PPH resulting in about 70,000 maternal deaths globally[2]. Traditionally, PPH is defined as blood loss of more than 500 ml following vaginal delivery or more than 1000 ml following cesarean section. The main cause of PPH is uterine atony[3], followed by retained placenta, placental abnormalities, genital tract laceration and coagulopathies.

There are numerous risk factors associated with PPH. The presence of these predisposing factors gives a clue to remain vigilant and one such risk factor is Assisted Reproductive Techniques (ART). Women conceived using ART are associated with higher prevalence of perinatal complications than pregnancies conceived spontaneously[4]. These includes higher risk of twin gestation, increased risk of preterm birth, hypertensive disorders, antepartum hemorrhage, placental disorders. Also, IVF conception is an independent factor for third stage complications like PPH, manual removal of placenta, blood transfusion in the third stage[4].

Department of Obstetrics & Gynaecology, Dr B R Ambedkar Medical College, Bengaluru, Karnataka 560045

[1]MBBS, MS, Senior Resident

[2]MBBS, MS, CMO, Imphal, Department of Obstetrics & Gynaecology, Assam Rifles, Imphal, Manipur 795001

[3]MBBS, MS, Assistant Professor, Department of ENT

[4]MBBS, MS, Senior Resident and Corresponding Author

Received on : 03/04/2023

Accepted on : 23/09/2023

Editor's Comment :

- IVF is an independent risk factor for 3rd stage of labour complications.
- In view of increasing use of ART worldwide one needs to be vigilant during labour of IVF pregnancies to prevent catastrophic complications.

In last few decades, there has been an upward trend in the use of Assisted Reproductive Techniques (ART) worldwide[5]. This is mainly attributed to late marriage, delayed child bearing, lifestyle changes affecting fertility and better knowledge and availability of these services. With increasing use of ART, the incidence of Postpartum Hemorrhage also rises, adding to maternal mortality and morbidity. This article emphasizes on the association between the IVF Pregnancies and Postpartum Hemorrhage (PPH).

Case 1

A woman of 25-year-old primigravida with post IVF conception at 35 weeks of gestation with DCDA twins with overt diabetes on treatment, with pre-eclampsia with severe features with hypothyroidism was admitted. She was planned for cesarean delivery in view of non-cephalic presentation of first twin. She delivered twin male babies of weight 3 kgs and 2.3 kgs respectively. Intraoperatively, uterus was atonic and was managed medically with estimated blood loss of 600ml. During the vaginal toileting, active bleeding was noted. Uterotonics were repeated and bimanual compression of uterus was done. Patient was reassessed and found to have persistent bleeding from the cavity. Uterine tamponade with Foley's catheter with vaginal packing was done and patient was observed. Bleeding was controlled and total blood loss was 1.5L. Patient was

shifted to ICU and maintained on uterotonics and blood transfusion. The vaginal pack and tamponade was removed next day. Patient was stable and discharged on day 8.

Case 2

A 27-year-old G3A2 at 38 weeks 5 days of gestation, conceived following invitro fertilization with gestational diabetes on treatment was taken up for cesarean delivery in view of failed induction. She delivered an alive female baby of weight 2.8kgs. Hemostasis was achieved and abdomen was closed. During the immediate postpartum period, vaginal bleeding was noted and around 350g of clots were removed on vaginal toileting. Medical management of PPH was initiated along with bimanual compression for 15 minutes. Despite these measures, the bleeding was not controlled and thus decision for re-exploration taken. On laparotomy, the Lower Uterine Segment (LUS) was flabby and bulged out. The uterus was reopened and around 400g clots removed. Placental bed bleeding was noted and multiple haemostatic sutures were taken. Bilateral uterine and ligation of Ovarian- Uterine anastomosis and B Lynch sutures were taken. Blood transfusion and medical management of PPH was continued. Abdomen was closed after ensuring the hemostasis. Estimated blood loss was 2.5L. Patient was shifted to ICU on mechanical ventilator and was monitored for 1 day. Patient recovered and was discharged on postoperative day 8.

Case 3

A 29-year-old G2A1 with post IVF conception of DCDA twins at 36 weeks of gestation with pre-eclampsia with severe features was taken for emergency cesarean delivery in view of unfavorable cervix. She delivered twin female babies of weight 2.3kgs and 1.85kgs. Intraoperatively, upper segment of uterus was contracted but LUS was flabby and bulging. On compression, the blood was oozing from the suture line. Bilateral uterine and ligation of Ovarian-Uterine anastomosis along with the use of uterotonics was carried out. Uterine sutures were reinforced with Lambert's suture and hemostasis achieved. Estimated blood loss was 2200ml. Uterotonics were continued and patient was shifted to ward. Patient was discharged on postoperative day 8.

Case 4

A 34-year-old G2P1L0 conceived following IVF with overt diabetes on insulin was planned for induction of labor at 38+1 weeks of gestation. Pre-induction cervical ripening was done with 2 doses of PGE2 followed by augmentation of labor with oxytocin. She delivered a live female baby of weight 3.85kgs vaginally and AMTSL done. Excessive bleeding was noted from the vagina and on examination vitals were stable and uterus was contracted. Vaginal exploration was done and a cervical tear of 3 cm long was noted at 9'o clock position. Tear was sutured and hemostasis achieved. Estimated blood loss was 600ml. Patient was discharged on post-natal day 4.

Case 5

A 30-year-old P1L2 woman presented with complaints of bleeding per vagina with passage of clots and giddiness on postoperative day 7. She had conceived following IVF and had twin pregnancy. Antenatally she was diagnosed with pre-eclampsia and underwent emergency cesarean section for pre-eclampsia with unfavorable cervix. Her intrapartum and immediate postpartum period was uneventful. However, she presented on POD 7 with above complaints. On examination, patient was pale looking with cold peripheries, found to have hypotension and tachycardia. Per abdominal examination revealed soft, flabby uterus and healthy abdominal wound. On per vaginal examination, around 100g of clots were evacuated. Immediate resuscitation was done to stabilize the patient with antibiotics, methylergo-metrine, tranexamic acid and blood transfusion. Transvaginal ultrasound showed RPOC of 8*6cm in cervical canal. She underwent dilatation and evacuation and 300ml of foul smelling clots were removed with ovum forceps. Antibiotics were continued and she was discharged on day 7 of admission.

Discussion

The Postpartum Hemorrhage is defined based on quantity of blood loss. Usually a blood loss of more than 500 ml following vaginal delivery or more than 1000 ml following cesarean section is considered significant. However, in developing countries where anaemia is prevalent, any bleeding that is enough to compromise the woman's hemodynamic stability is taken as PPH.

The common causes of PPH are grouped into 4 T's – Tone (uterine atony), Trauma, Tissue (placenta-related problems), Thrombin (failure of the blood coagulation system). In our case series, 3 cases were atonic PPH, 1 traumatic PPH and 1 case was retained product of conception. The first 4 cases were primary Postpartum Hemorrhage which presented in immediate postpartum period within 24 hours while case 5 was secondary PPH which presented after 24 hours on day 7 postoperatively.

Various risk factors for PPH are extremes of age, a previous cesarean section, history of PPH, anaemia, prolonged labor, placenta previa, placental abruption. The risk of atonic PPH in IVF pregnancy is 2.7 times higher than that of spontaneous pregnancy[6]. IVF conceptions considered as an independent factor for third stage complications like PPH are discussed in this case series. Of the 5 cases discussed, 3 had twin gestation and 2 had singleton pregnancy. Twin pregnancy is a known risk factor for PPH mainly attributed to overdistended uterus, but even the singleton pregnancies conceived through ART have a higher incidence of PPH. A recent pathology study analyzed the morphological characteristics of the placental basal plate in ART pregnancies and found a higher mean thickness of Rohr fibrinoid layer and a higher percentage of loss of decidua which correlated with bleeding at birth[7]. The loss of decidua is due to hormonal treatments in early pregnancy which results in changes structural and/or functional changes in the extracellular matrix of the decidual layer. Thus, may produce suboptimal angiogenesis and placentation, predisposing to PPH[7]. It is also suggested that muscle weakness/ hypofunction may be a reason for a global increase in atonic PPH[8]. This is mainly due to the fact that after IVF treatment, women tend to take a physical rest leading to decreased exercise levels.

A common factor that was noted in case 2 and case 3 was focal atony of the Lower Uterine Segment (LUS). LUS was flabby and bulging out which was noted during the operation. Primary atony of the Lower Uterine Segment is a distinct entity, causing PPH which is characterized by well contracted fundus and Upper Uterine Segment and ballooned out LUS[9]. The diagnosis is often difficult to make clinically as fundus of uterus is well contracted. Ultrasonography is helpful is such situation. LUS bleed is a challenge to manage, balloon tamponade of lower segment, compression sutures, stepwise devascularization of uterus may be needed.

For the management of PPH, a step wise approach is instituted. Medical therapy is first initiated, followed by mechanical methods and if it fails, organ-sparing surgical intervention is instituted with hysterectomy as the last resort. In this case series, atonic PPH was managed with mechanical method with uterine tamponade in one case while 2 cases required surgical intervention. While step wise devascularization of uterus was performed in 2 of the cases, uterine compression sutures were taken for one case. Case 4 with traumatic PPH was managed with vaginal exploration and suturing the cervical tear. The case of secondary PPH was managed with dilatation and evacuation of products of conception and antibiotics with uterotonics. All the cases were managed conservatively without the need for hysterectomy. The postoperation recovery was good in all cases.

Conclusion

One should be vigilant and anticipate the complication of Postpartum Hemorrhage when managing a woman conceived with IVF. Early recognition and prompt treatment should be the goal to improve the maternal outcome. Primary atony of the Lower Uterine Segment a distinct entity causing PPH poses a challenge in diagnosis and management, hence, awareness regarding this entity is needed. Further studies are needed to determine the etiology and develop appropriate therapy.

Funding : None

Conflict of Interest : None declared

References

1 Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, *et al* — Global causes of maternal death: A WHO systematic analysis. *Lancet Glob Health* 2014; **2:** e323-e333. [CrossRef]
2 WHO Postpartum hemorrhage (PPH) summit - 30 September 2022 http://www.who.int/reproductivehealth/en
3 GG Prevention and Management of Postpartum Haemorrhage: Green-top Guideline No. 52. *BJOG* 2017, **124:** e106-e149.
4 Wertheimer A, Melamed S, Ashwal E, Sapir O, Oron G, Ben-Haroush A, *et al* — Complications of the third stage of labor are more prevalent in IVF pregnancies. *J Matern Fetal Neonatal Med* 2022; **35(4):** 663-7. doi: 10.1080/14767058.2020.1730797. Epub 2020 Feb 23. PMID: 32089031.
5 Ishihara O, Adamson GD, Dyer S, de Mouzon J, Nygren KG, Sullivan EA, *et al* — International committee for monitoring assisted reproductive technologies: world report on assisted reproductive technologies, 2007. *Fertil Steril* 2015; **103:** 402-13.
6 Yanaihara A, Ohgi S, Motomura K, Hirano A, Takenaka S — In Vitro Fertilization pregnancy is one of the risk factor for atonic bleeding in problem – free pregnancy. *J Preg Child Health* 2017; **4:** 308. doi: 10.4172/2376-127X.1000308.
7 Nakamura Y, Yaguchi C, Itoh H, Sakamoto R, Kimura T, Furuta N, Uchida T, *et al* — Morphologic characteristics of the placental basal plate in in vitro fertilization pregnancies: a possible association with the amount of bleeding in delivery. *Hum Pathol* 2015; **46:** 1171-9.
8 Yanaihara A, Hatakeyama S, Ohgi S, Hirano A — Tendency Prediction for Atonic Bleeding Following a Problem-Free Pregnancy. *J Clin Gynecol Obstet* 2019; **8(2):** 39-43. doi: https://doi.org/10.14740/jcgo540
9 Panda B, Laifer S, Stiller R, Kleinman G — Primary atony of the lower uterine segment as a distinct cause of early postpartum haemorrhage: A case series and management recommendations, *Journal of Obstetrics and Gynaecology* 2009; **29:** 7, 628-632, DOI: 10.1080/01443610903114493.

Case Report

A Rare Case of Carcinoma Base of Penis : Evaluation on Ultrasound Color Doppler, Computed Tomography and Magnetic Resonance Imaging

Suchita Sureshkumar Bahurupe[1], Suresh Vasant Phatak[2], Avinash Dhok[3]

Carcinoma base of penis is an extremely uncommon condition. Usually glans penis is the most commonly affected site. A 55-year-old male presented with a mass at the base of penis. High frequency ultrasound and Doppler showed an ill-defined, heterogeneous, predominantly hyperechoic mass at the base of penis. No calcification was present within the mass, Moderate vascularity was present. Computed tomography showed a relatively well-defined, lobulated, soft tissue attenuation mass with heterogeneous enhancement on post-contrast study. On Magnetic Resonance Imaging, the mass was hypointense on T1WI, hyperintense on T2WI and STIR with restricted diffusion on DWI and heterogeneous post gadolinium enhancement. Histopathological examination findings were consistent with Squamous Cell Carcinoma of base of penis.

[*J Indian Med Assoc* 2024; **122(3):** 66-8]

Key words **: Carcinoma Penile Base, Penile Doppler, Circumcision, Penile Tumor Imaging.**

Penile Carcinoma can develop in at any age but is mostly seen in men at the age of 50-70 years. Patient classically presents with palpable penile mass with pain, foul smelling pus discharge and bleeding. The mass may be nodular, ulcerative or lobulated. Patients can develop physical and psychological consequences. The frequently involved site for penile carcinoma is the glans, prepuce and shaft in descending order of prevalence[1]. Involvement of base of penis is uncommon .Presence of foreskin is the significant predisposing factor for penile Carcinoma. Non-circumcised people have higher incidence of developing Carcinoma. Other predisposing factors include chronic inflammatory conditions, smoking, psoralen treatment, poor hygiene, ultraviolet photochemotherapy and human papillomavirus infection. Physical examination aids in determining the size and extent of mass. Ultrasound (US), Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are useful for staging penile Carcinoma. MRI is the most sensitive imaging modality for evaluation and staging. Squamous Cell Carcinoma is the most common histopathological type in penile malignancy[2]. In our case report, we have described US, CT and MRI features in a 55-year patient who presentedwith mass over the base of penis.

Case Report

Patient Information — A 55-year old patient presented with a mass at the base of penis for 2 months.

Editor's Comment :

- Carcinoma base of the penis is an extremely uncommon malignancy.
- Physical examination fails to determine the exact depth of invasion.
- MRI is the most sensitive & accurate modality for evaluation, staging & follow up.

Clinical Examination — Relatively well-defined, non-mobile, firm, non-tender mass at the base of penis. No local skin discoloration or raised local temperature.

Diagnostic Assessment — High Frequency Ultrasound demonstrated an ill-defined, heterogeneous but, predominantly hyperechoic mass of size 3.94 x 3.8 x 3.49 cm at the base of penis. The mass was thick-walled with multiple echogenic foci within it. There was no calcification within the mass (Fig 1). Moderate vascularity was seen on Color Doppler (Fig 1). Contrast Enhanced Computed Tomography (CECT) showed relatively well-defined, lobulated, soft tissue density mass lesion of size 3.9 x 3.87 x 3.4 cm at the base of penis and extending upto shaft. The mass was also involving the distal corpus spongiosum, both corpora cavernosa and overlying fascia. Mass showed heterogeneous enhancement on postcontrast study. Few sub centimetric lymph nodes with maintained fatty hilum. were also present in bilateral deep inguinal region. On MRI, the mass was well-defined, lobulated. It was hypointense on T1 weighted image and hyperintense on T2 weighted image and STIR along with restricted diffusion on DWI. The lesion had encased the distal corpus spongiosum, both corpora cavernosa and overlying fascia with proximal infiltration. It had also involved small length of penile urethra (Figs 2-4). Post gadolinium contrast study showed heterogeneous enhancement.

Department of Radiology, NKP Salve Institute of Medical Sciences and Research Centre, Nagpur, Maharashtra 440019
[1]MBBS, Junior Resident
[2]MD, Professor
[3]MD, Professor and Head and Corresponding Author

Received on : 19/09/2023
Accepted on : 28/11/2023

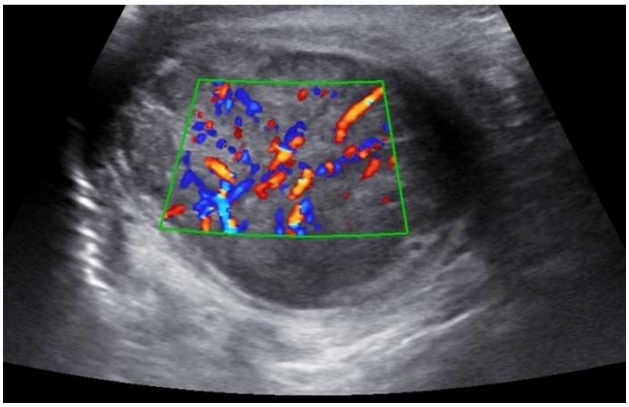


Fig 1 — Colour Doppler showing moderate-high vascularity within the mas

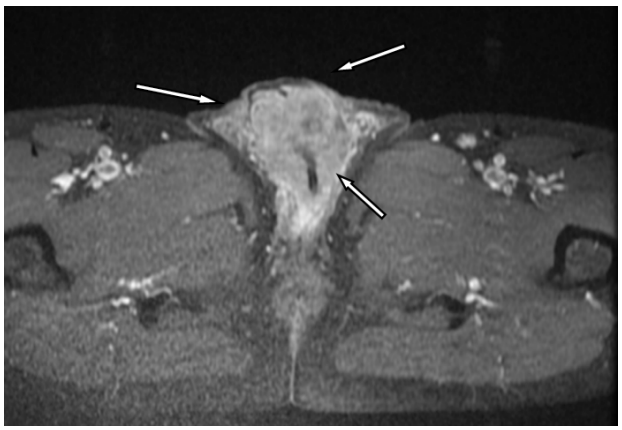


Fig 2 — Contrast enhanced MRI showing moderate heterogeneous enhancement of mass

Diagnosis — Histopathological examination findings were consistent with Squamous Cell Carcinoma of base of penis, stage T4N2M0.

Discussion

Penile Carcinoma is third most common male specific cancer, after testicular cancer and prostate cancer, affecting approximately 1/100,000 male population. Accurate demonstration of penile Anatomy is important for correct diagnosis and management of penile carcinoma. The penis is comprised of a base,present in the superficial perineal pouch, body consists of three tubular structures, ie, paired corpora cavernosa on the dorsolateral aspect and corpora spongiosum in the midline on ventral aspect, which also extends anteriorly as the glans penis. There are three connective tissue layers (tunica albuginea, buck fascia and dartos fascia) which cover the corpora of the penis[3]. When Penile Carcinoma is diagnosed in its localized form, the survival rate is quiet high at approximately 85%. In presence of regional lymphadenopathy, it drops down to 57%, and in distal metastases, the rate further drops to 11%[4]. Physical examination fails to determine depth or extent of tumor infiltration[5]. Lymph node involvement is

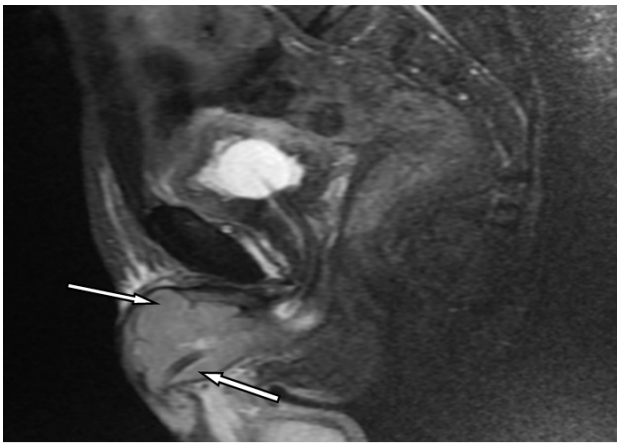


Fig 3 — Sagittal T2 weighted MRI showing iso-hyperintense mass at the base of penis with loss of fat plane

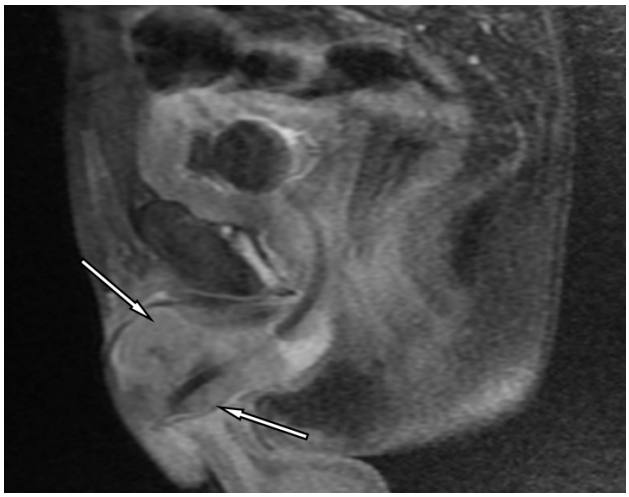


Fig 4 — Sagittal T1 weighted MRI showing hypointense mass at the base of penis with loss of fat plane

crucial in determining the prognosis of Penile Carcinoma. The spread via lymphatics is influenced by primary tumor location. Specifically, superficial inguinal nodes drain skin of penis and prepuce, while glans of penis drains into deep inguinal lymph node. Internal iliac lymph nodes drain erectile tissue, penile urethra[4]. Staging of Penile Carcinoma is done by TNM classification system as per AJCC 8th edition. The T indicates Tumor extent, TX- Tumor assessment not possible, T0- Primary tumor not demonstrable, Tis- Carcinoma in situ, T1a- Invasion of subepithelial connective tissue without lymph nodal involvement andT1b- Lymph nodal involvement. T2 - Corpus spongiosum invasion, T3- Corpus cavernosum invasion and T4- Invasion into other adjacent structures. The N stage gives idea about the spread to regional lymph nodes and ranges from NX- Assessment of regional lymph nodes not possible, N1- Less than 2 unilateral lymph nodes involvement,N2- More than 3 unilateral or bilateral lymph node involvement and N3- Extra nodal extension of any lymph nodal involvement like metastasis

in pelvic lymph nodes. The M indicates spread to distant organs or tissues, MX-Assessment of distant metastasis not possible, M1- distant metastasis[3]. High Frequency Ultrasound Doppler is the first line imaging modality for a Penile Carcinoma. It provides information about tumor extent and invasion into corpora. Superficial Inguinal lymphadenopathy can be detected, but Ultrasound is less sensitive in detecting deep inguinal and pelvic lymph nodes.Non contrast CT shows hypoattenuating mass. Post contrast CT provides contrast-enhanced images of soft tissue involvement, tumor characterization and also depth of lesion. CT is the imaging modality of choice for detecting metastasis. It also shows bony involvement. Lymph nodes in deep inguinal and pelvic region are also detected on CT[2]. On CT penile mass is usually iso-hypodense with moderate heterogeneous post contrast enhancement. On MRI, Penile Carcinoma is usually seen presenting as solitary, infiltrating mass and appear hypointense on T1WI and T2WI. MRI is a reliable method for accurately evaluating the local extension of the Penile Carcinoma, depth of tumor invasion,involvement of tunica albuginea, involvement of other surrounding structures. Moreover, MRI enables better visualization of adjacent soft tissues structures like urethra. Small and deep situated lymph nodes are also better demonstrated on MRI. Due to its superior ability to characterize soft tissues and multiplanar assessment of superficial structures, MRI is generally preferred over CT in evaluating and staging Penile Carconoma[3]. Diffusion-weighted imaging (DWI) is another MRI technique that does not rely on contrast administration. On DWI if the lesion shows restriction, it is indicative of malignant etiology[6].

Conclusion

Carcinoma of the base of penis is an extremely uncommon condition, affecting approximately 1/100,000 male population. Accurate demonstration Penile Anatomy and characterization of mass is important for correct diagnosis and management of Penile Carcinoma. High Frequency Ultrasound Doppler, CT and MRI are crucial modalities in diagnosis, staging, management and follow up.

References

1 Galgano SJ, Norton JC, Porter KK, West JT, Rais-Bahrami S — Imaging for the Initial Staging and Post-Treatment Surveillance of Penile Squamous Cell Carcinoma. *Diagnostics* 2022; **12(1):** 170.

2 Singh AK, Saokar A, Hahn PF, Harisinghani MG — Imaging of Penile Neoplasms. *Radio Graphics* 2005; **25(6):** 1629-38.

3 Gupta S, Rajesh A — Magnetic Resonance Imaging of Penile Cancer. *Magn Reson Imaging Clin* 2014; **22(2):** 191-9.

4 Krishna S, Shanbhogue K, Schieda N, Morbeck F, Hadas B, Kulkarni G, *et al* — Role of MRI in Staging of Penile Cancer. *J Magn Reson Imaging* 2020; **51(6):** 1612-29.

5 Multimodality imaging of penile cancer: what radiologists need to know | SpringerLink [Internet]. [cited 2023 Mar 14]. Available from: https://link.springer.com/article/10.1007/s00261-014-0218-6.

6 Chernyak V — Novel Imaging Modalities for Lymph Node Imaging in Urologic Oncology. *Urol Clin* 2011; **38(4):** 471-81.

Drug Corner

Hypertension Therapeutics Reimagined : Nebivolol and Telmisartan — A Contemporary Review

Dayanand K Kumbla[1]

Hypertension, a prevalent Global health concern, affects a quarter of the population, with an increasing incidence among young adults. In India, approximately 27 million young adults grapple with hypertension but awareness, treatment, and control remain low. Early-onset hypertension significantly elevates cardiovascular risks in later life, necessitating a paradigm shift in management approaches. The combination of nebivolol, a third-generation ß1-selective ß-blocker and telmisartan, an Angiotensin Receptor Blocker (ARB), emerges as a promising therapeutic strategy. The complementary mechanisms of these drugs on the Sympathetic Nervous System (SNS) and the Renin-angiotensin-aldosterone System (RAAS) prove crucial for robust Blood Pressure (BP) control and cardiovascular risk reduction. Nebivolol's unique vasodilatory effects, minimal metabolic impact, and telmisartan's distinct pharmacokinetic properties present complementary mechanisms for BPcontrol. Various clinical trials underscore the efficacy of this combination in reducing mean systolic and diastolic BP, heart rate and cardiovascular events.This review also highlights the potential benefits of combination therapy in populations with comorbidities such as obesity, insulin resistance, dyslipidemia, asthma, Chronic Obstructive Pulmonary Disease (COPD) and Erectile Dysfunction (ED). Furthermore, the additive effects of nebivolol and telmisartan, as well as the reduced pill burden through fixed-dose combinations, enhance patient adherence and overall hypertension management. In conclusion, the nebivolol and telmisartan combination provides a holistic and promising approach to hypertension management, emphasising the need for continued research to uncover its long-term benefits and broaden its application in tailored treatment strategies for hypertension in young adults.

[*J Indian Med Assoc* 2024; **122(3):** 69-74]

Key words **: Hypertension, Nebivolol, Telmisartan, Cardiovascular Risk, Young adults, ARBs, Beta-blocker.**

Hypertension, a major risk factor for all-cause mortality, morbidity and cardiovascular disease, affects one-quarter of the Global population and is common among young people, affecting 1 in 8 adults aged between 20-40 years. India, with 32% of its 1.2 billion people being young adults according to the 2011 census, assumes a prevalence rate of around 27 million young adults with hypertension. The awareness, treatment and control of high BP among young adults with hypertension are notably low and pre-hypertension serves as a significant precursor for developing hypertension and CV disease later in life. Despite this, there is a lack of screening for pre-hypertension and hypertension among young individuals and healthcare professionals are less likely to prescribe anti-hypertensive drugs to young adults with hypertension compared to older patients. Previously, age has been a significant factor in treatment decisions, emphasising those with the highest 10-year risk of CV events, but young hypertension increases the risk of CV events in middle age, contributing to the earlier development of heart failure, coronary heart disease, transient ischemic attacks and stroke. Although good national guidelines exist, they do not serve low-risk young hypertensive patients as effectively as older patients[1-3].

Hypertension, even in young adults, can have harmful health effects and is associated with higher rates of left ventricular hypertrophy and changes in brain volume and white matter hyperintensity volume. Studies such as the Strong Heart Study and the Coronary Artery Risk Development in Young Adults (CARDIA) longitudinal study emphasise the importance of early-life risk factors.In the Strong Heart Study, 1940 Native Americans aged 14 to 39 years were examined for clinical and echocardiographic features and showed higher rates of left ventricular hypertrophy in individuals with pre-hypertension (blood pressure120-139/80-89mmHg) and hypertension (blood pressuree ≥140/90 or taking antihypertensive medications) compared to those with normotensive individuals of the same age[1,4]. The CARDIA longitudinal study, which included a cohort of 5115 young adults aged 18 to 30 years, demonstrated that elevated SBP at baseline predicted the presence of coronary artery calcium 15 years later and emphasised the role of early-life risk factors in the development of coronary

[1]MD (Medicine), DM (Cardiology), FISE, FESC, FSCAI, Interventional Cardiologist, Jupiter Hospital, Thane, Maharashtra 400601 and Jay Anand Hospital for acute MI management, Thane, Maharashtra 400602

Received on : 06/03/2024
Accepted on : 07/03/2024

heart disease in later life. Moreover, a retrospective analysis of CARDIA data demonstrated that individuals under 40 years old at baseline who had hypertension as defined by the 2017 ACC/AHA guidelines had a significantly higher risk of CV disease compared to those with normal blood pressure (<120/80mmHg)[5,6].

Despite significant progress in understanding the complex pathophysiological mechanisms of hypertension, lowering BP through the use of all major antihypertensive drug classes Angiotensin-converting Enzyme (ACE) inhibitors, Angiotensin Receptor Blockers (ARBs), ß-blockers, calcium channel blockers (CCBs) and diuretics)remains the best strategy to reduce cardiovascular risk associated with hypertension. According to the most recent international ESC/ESH guidelines, ß-blockers maintain a central role in the management of hypertension, being recommended at any treatment step when there is a specific indication, such as heart failure, angina, post-acute myocardial infarction, atrial fibrillation or pregnancy. In particular, nebivolol, a third-generation ß1-selective ß-blocker, has demonstrated advantages over other ß-blockers, including vasodilatory properties, neutral metabolic effects and good tolerability, making the drug suitable for a wide range of hypertensive patients with or without co-morbidities[7,8].

Around 75% of hypertensive patients require combination therapy for BP control due to multiple pathophysiological pathways and counter regulatory responses. In India, dual and triple therapies often involve ARBs with telmisartan being a preferred choice among physiciansdue to its sustained effectiveness, morning BP surge control and its role in preventing complications like microalbuminuria, nephropathy, cardiovascular morbidity and mortality. A cross-sectional observational survey conducted by Jadhav U, *et al* using a structured questionnaire showed that among young hypertensive patients, ARBs and beta-blockers were the preferred drug classes, with 61.6% choosing ARBs and 15.8% opting for beta-blockers (Fig 1). Calcium channel blockers, diuretics and ACE inhibitors were selected by 10.4%, 7.6%, and 4.6% of respondents, respectively[9,10]. Combining anti-hypertensive drugs with complementary mechanisms of action enhances efficacy, reduces side effects, and provides a broader approach to blood pressure control through additive drug effects[11]. This review delves into the mechanisms, clinical evidence and potential benefits of this synergistic combination, highlighting its advantages over individual use.

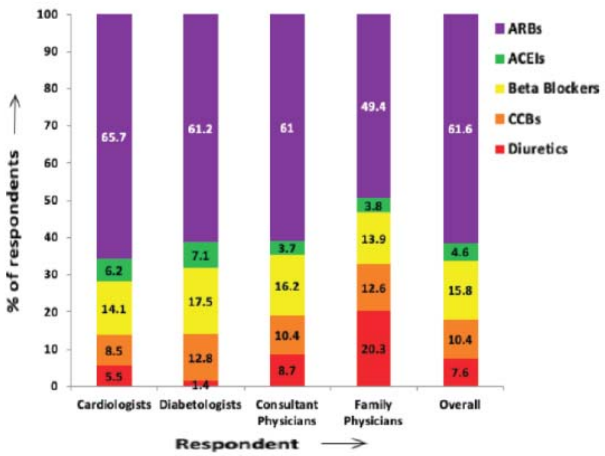


Fig 1 — Drug class preference for the management of hypertension in young adults

Complimentary Action of SNS and RAAS : A Duet of Mechanisms

The combination of Nebivolol (ß-blockers) and Telmisartan (ARBs) offers distinct and complementary mechanisms for controlling BP and is of particular interest due to their complementary effects on the Renin-angiotensin-aldosterone System (RAAS) and the Sympathetic Nervous System (SNS), two interconnected pathways that affect cardiovascular risk and disease outcomes.

Nebivolol, a third-generation $ß_1$ adrenoreceptor antagonist, exhibits unique characteristics, including Nitric Oxide (NO)-mediated vasodilation through $ß_3$ receptor agonism and reduced oxidative stress, distinguishing it from conventional non-vasodilatory ß-blockers such as atenolol as well as from vasodilatory ß-blockers like carvedilol and labetalol, which act through α_1 adrenergic antagonism. It also offers a better tolerability profile and reduced metabolic effects, along with aldosterone reduction for potential blood pressure control[9,11].

The renin-angiotensin system plays a crucial role in blood pressure regulation and volume homeostasis. The angiotensin receptor blockers control high blood pressure by blocking the binding of angiotensin II to the angiotensin subtype 1 receptor, which is believed to be responsible for the majority of the physiologic actions of angiotensin II relevant to the regulation of blood pressure. Telmisartan, a widely used ARB, possesses distinct pharmacokinetic and pharmaco-dynamic properties, including partial Peroxisome Proliferator-activated Receptor (PPAR)γ agonism and a long duration of action.Telmisartan has a higher affinity for the angiotensin type 1 receptor (more than 3000 times) than the angiotensin type 2 receptor,

potentially allowing angiotensin II to have beneficial effects via this receptor. This could lead to increased bradykinin production, vasodilation, andendothelial dysfunction. Nebivolol may counter-regulate this increase in renin, allowing a dual RAAS blockade. ARBs may also lead to a reactive increase in aldosterone caused by angiotensin II blockade, which could potentially be mitigated with combination therapy, resulting in improved efficacy[9,12].

Cardiovascular (CV) Benefits : Insights from Clinical Trials and Studies

Guideline Evolution on Combination Therapy:

According to epidemiological data, BP reduction at the population level is beneficial. The careful monitoring of BP from early adulthood to later life and the detection of cardiovascular and brain changes in young adults with hypertension support the argument that young people with high BP should be treated in the same way as older adults. However, there is a lack of data assessing pharmacological intervention in this young age group[1]. There is now general agreement that monotherapy is less likely to be adequate to achieve optimal BP control in the majority of patients and combination therapy involving two or more anti-hypertensive drugs is typically necessary for targeted BP accomplishment and CV risk reduction. Moreover, according to JNC 7 guidelines and the guidelines put forth jointly by the International Society of Hypertension and the European Society of Hypertension, BP-lowering treatment should be initiated with a combination of two drugs in patients with multiple CV risk factors such as metabolic syndrome, diabetes and heart and renal disease, as well as in patients with a systolic pressure higher than 20 mmHg and/or diastolic pressure higher than 10 mmHg of the targeted goal[13].

Effects on Blood Pressure (BP) :

The Giles, *et al* study demonstrated that nebivolol monotherapy is an effective and well-tolerated treatment option for the phenotype of a younger adult with diastolic hypertension, a patient population that is often overlooked. Furthermore, a high proportion of patients with a Diastolic Blood Pressure (DBP) reduction $\geq$8 mm Hg is encouraging because DBP is a stronger predictor of coronary heart disease than SBP or pulse pressure in individuals younger than 50 years[14].

Another study conducted by Sharpe M, *et al* demonstrated that telmisartan is an effective anti-hypertensive agent that significantly reduces blood pressure in patients with mild to moderate hypertension, with maximum reduction observed at a dosage of 40 to 80 mg/day. Telmisartan is associated with a significantly lower incidence of dry, persistent cough compared to lisinopril and is comparable in efficacy to other major classes of antihypertensive agents, such as amlodipine, atenolol, enalapril and lisinopril. Thus, for the treatment of hypertensive patients, telmisartan is a valuable therapeutic choice.[15]

Effects on Heart Rate (HR) :

The BENEFIT KOREA study, led by Jinho S, *et al* demonstrated that once-daily nebivolol, either as monotherapy or add-on therapy, significantly reduced mean SBP and DBP in 3011 adult South Korean patients with essential hypertension with or without co-morbidities. Additionally, a significant decrease in HR was also noted. The reductions in SBP and DBP were significantly greater when nebivolol was used as monotherapy in de novo patients and as add-on therapy to existing anti-hypertensives (angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers)[16].

The VALUE trial demonstrated that elevated heart rate is an important factor in cardiovascular risk even when individual BP is well controlled,suggesting that both BP and heart rate must be lowered for optimal risk reduction. Elevated heart rate is now recognised as a key variable influencing cardiovascular risk in hypertension patients and provides a strong rationale for the use of interventions that target heart rate by modulating the SNS. In combination therapy, a beta-blocker component is essential to achieve optimal control caused by sympathetic overdrive, particularly with a selective beta-1 blocker, preserving beta-2-mediated vasodilation, inhibiting sympathetic activity in the heart and kidney and minimising adverse effects associated with beta-2 receptor blockade in the lungs and peripheral tissues[17].

Effects on Left Ventricular Hypertrophy (LVH) :

Left Ventricular Hypertrophy (LVH) is a risk factor for cardiovascular mortality and morbidity and its regression is important for patient outcomes.In a study involving controlled hypertensive patients with Left Ventricular Hypertrophy (LVH), Fountoulaki, *et al* compared the effects of nebivolol (2.5-5 mg) and telmisartan (40-80 mg) on Blood Pressure (BP) control and Left Ventricular Mass (LVM). Both groups exhibited similar reductions in BP and a 14g/m^2 decrease in LVM, possibly due to different mechanisms[18].

Degirmenci, *et al* conducted a prospective cohort study to assess the long-term effects of irbesartan, an ARB and new-generation beta-blockers (such as nebivolol and carvedilol) on LVH associated with essential hypertension. The results showed that both

new-generation beta-blockers were more effective than irbesartan in the regression of LVH, with notable improvements observed 3 months after nebivolol treatment and 6 months following irbesartan and carvedilol treatments[19]. In a study by Misra, *et al* telmisartan proved to be more effective than atenolol in achieving LVH regression, resulting in a substantial 27.49% reduction in Left Ventricular Mass Index (LVMI) with a higher proportion of patients achieving the target LVMI value[20].

Effects on Cardiovascular (CV) Protection :

Elevated SBP or DBP increases cardiovascular risk and even small reductions in severe hypertension can have a significant positive impact. The ONTARGET study showed that the ARB telmisartan preserved 95% of the vascular protective properties of the ACE iramipril when administered at similar doses to a similar patient group. The TRANSCEND study demonstrated benefits in a patient in tolerant to ACEi, with a trend towards a combined secondary end point of cardiovascular death, MI and stroke. Despite the primary endpoint being neutral, with excellent tolerance of the ARB,the reductions in the risk of stroke, myocardial infarction, and CV death were 19%, 14% and 35%, respectively. These studies suggest that an ARB can be used as an alternative to an ACEi for vascular protection in high-risk individuals. For individuals with a high risk of cardiovascular disease, telmisartan is the only ARB that has been demonstrated to reduce cardiovascular risk[12,21].

The INTERHEART study revealed that hypertension increases the risk of a myocardial infarction by 25%. Lowering BP has a positive impact on myocardial infarction risk, with a 17% reduction in Coronary Artery Disease (CAD) for every 10 mmHg reduction in SBP, as evidenced by a recent meta-analysis of Randomised Controlled Trials (RCTs) of anti-hypertensive therapy. In hypertensive patients with CAD, the preferred components of the antihypertensive drug treatment strategy are ß-blockers, either in combination with blockers of the Renin-angiotensin System (RAS) or CCBs[8].

Effects on Mortality :

The European Trial on Reduction of Cardiac Events with Perindopril in Patients with Stable Coronary Artery Disease (EUROPA), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) and Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trials demonstrated that the addition of RAAS inhibitors to a preexisting ß-blocker treatment resulted in a 20% reduction in the relative risk of the primary end point, a 23% reduction in non-fatal myocardial infarction, and a 22% reduction in all-cause mortality compared to placebo[22]. Nebivolol significantly reduces all-cause mortality or cardiovascular hospitalisation compared to placebo,as reported by the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS)[8].

Dual-Class Indications :

Nebivolol and telmisartan may be beneficial for patients with indications for both drug classes. While nebivolol is not a first-line option for HTN, it may be considered for specific populations, like post-myocardial infarction patients. In individuals with metabolic syndrome or diabetes requiring a ß-blocker, nebivolol's metabolically neutral profile might offer benefits over other ß-blockers. For patients with chronic kidney disease or diabetes who are unable to tolerate ACE inhibitors, the nebivolol/telmisartan combination becomes a favourable option[9].

Hypertension with Comorbidities :

Obesity :

Obesity-related hypertension involves multiple systems, such as the SNS and the RAAS. Lifestyle changes alone may not be enough to control BP. A study by Manrique C, *et al* examined the effects of nebivolol, a β-blocker, on blood pressure control in obese and non-obese hypertensive patients. Nebivolol significantly lowered diastolic blood pressure in both groups and systolic blood pressure in non-obese patients. The drug also had neutral effects on lipid and carbohydrate metabolism, making it apotential option for controlling blood pressurein moderately obese individuals[23]. Another post hoc analysis by Mende C, *et al* found that a Single-pill Combination (SPC) of nebivolol (ß-blocker) and valsartan (ARBs) is effective in lowering BP in individuals regardless of their obesity status. This combination significantly lowered blood pressure and aldosterone levels in both obese and nonobese participants compared to placebo and was more effective than nebivolol or valsartan monotherapies.[24]

Insulin Resistance, Lipid Profile and Dyslipidemia:

Many antihypertensive medications negatively impact metabolism, making blood pressure control difficult in hypertensive patients with metabolic abnormalities. Nebivolol, a third-generation vasodilatory β-blocker, significantly lowers blood sugar, HbA1c, total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol compared to atenolol and improves serum lipid profile and glycemic control[25].

Telmisartan, compared to other ARBs, is superior in improving insulin resistance, reducing fasting insulin and fasting blood glucose, decreasing diastolic blood pressure and significantly reducing serum triglycerides, VLDL-C, LDL-C and cholesterol levels while increasing HDL-C levels in hypertensive patients with dyslipidemia. Furthermore, in these patients, telmisartan effectively reduced both systolic and diastolic blood pressure[26].

Asthma and/or Chronic Obstructive Pulmonary Disease (COPD) :

Beta-blockers are recommended for COPD patients due to their cardio-protective properties, lower heart rate and improved systolic function. However, they are underutilised in heart failure and post-myocardial infarction due to concerns about bronchoconstriction, even with cardio-selective drugs. Retrospective observational studies have demonstrated significant reductions in exacerbations and mortality conferred by beta-blockers in COPD. Beta-1-selective antagonists such as bisoprolol, nebivolol and metoprolol are preferred over non-selective carvedilolas they are less likely to cause broncho-constriction in COPD patients.Studies have shown that nebivolol exhibits greater in vitro beta-1/2 receptor selectivity and suppresses endothelial nitric oxide more effectively than bisoprolol in the human myocardium[27].

For patients with asthma and hypertension, ARBs may be the preferred drugs that act on the renin-angiotensin system. In patients with severe asthma during exacerbations, levels of circulating angiotensin II and renin were found to be increased as compared with those without exacerbations.Inhibition of angiotensin II type 1 receptors has led to a slight decrease in bronchial hyperresponsiveness.ARBs target pathways that can address both hypertension and asthma without inducing coughing, making them safe for patients with asthma or COPD. In a small trial, ARBs were found to be well tolerated and did not increase cough or bronchial hyperreactivity in hypertensive patients with asthma, similar to calcium channel blockers[28].

Erectile Dysfunction (ED) :

Beta-blockers are linked to Erectile Dysfunction (ED), which is more common in men with hypertension. Compared to other beta-blockers, nebivolol, a beta-blocker with vasodilating properties, may offer an advantage in improving erectile function. The study conducted by Sharp, *et al* found that when a practitioner specifically wants to use a beta blocker as an add-on antihypertensive treatment, nebivolol may be useful in patients who have or are at risk of developing ED[29].

Additive Effect :

Combining antihypertensive drugs can be more effective than increasing monotherapy doses for treating hypertension. Current guidelines have recognized this and provided enhanced support for initial combination therapy in hypertensive patients, although it has been limited by patient compliance and cost.The combination of ß-blockers and RAAS inhibitors has been deemed 'less effective' due to partially overlapping mechanisms of action and limited evidence.A randomized Phase 3 trial (NAC-MD-01; 4161) has provided convincing evidence that at least one ß-blocker/RAAS inhibitor combination, comprising the $ß_1$-selective adrenergic blocker with agonistic vasodilatory properties, Nebivolol,and the $ß_3$ Angiotensin II Receptor Blocker (ARB), valsartan, is more effective in reducing BP than their monotherapies. Based on the results of this study, the US Food and Drug Administration has approved the 5/80-mg/day Neb/valsartan Single-pill Combination (SPC) for hypertension treatment[30].

Combining drugs with different, yet complementary, mechanisms of action is the most effective approach for achieving additive BP-lowering effects. However, it is important to note that not all combinations of drugs from complementary drug classes produce strong additive effects. In a study conducted by Ishak, *et al* the combination of a specific ß-blocker (nebivolol) and RAAS inhibitor (valsartan) demonstrated additive effects, which may be attributed to the multi-modal effects of nebivolol, making it unique from other ß-blockers. Nebivolol has a better tolerability profile than other ß-blockers, which may be explained by differences in receptor affinity and vasodilatory pathways and may also explain why the ß-blocker nebivolol/RAAS inhibitor combination has demonstrated greater additivity than other non-vasodilatory or non-$ß_1$-selective ß-blocker and RAAS inhibitor combinations in previous hypertension trials[11].

Fixed-Dose Combination Reduces Pill Burden :

In addition, combination antihypertensives can increase adherence by decreasing pill burden and dosing frequency, resulting in improved HTN management and subsequent patient outcomes. According to one meta-analysis, a 26% improvement in adherence was found with single-pill combination antihypertensives, especially if this is accomplished cost-effectively[9]. ß-blocker nebivolol and ARB telmisartan reduce BP through complementary mechanisms. When used in combination, their efficacy surpasses that of component monotherapies[30].

Conclusion :

Hypertension among young adults is a significant health concern with long-term implications for cardiovascular health and the synergistic combination of nebivolol and telmisartan emerges as a promising strategy for its management. The dual action of the SNS and the RAAS contributes to robust blood pressure control, cardiovascular protection, and reduced left ventricular hypertrophy. The benefits extend to specific populations, including those with comorbidities, showcasing the versatility of this combination. Notably, the combination's efficacy, tolerability and potential to reduce pill burden underscore its clinical significance. However, further research is warranted for comprehensive validation of long-term outcomes and safety profiles in diverse patient cohorts. Overall, the combination of nebivolol and telmisartan represents a promising and personalized approach to hypertension, addressing the complex interplay of physiological pathways associated with cardiovascular health.

Funding : None

Conflict of Interest : None

References

1 Hinton TC, Adams ZH, Baker RP — Investigation and Treatment of High Blood Pressure in Young People: Too Much Medicine or Appropriate Risk Reduction? *Hypertension* 2020; **75(1):** 16-22.
2 Geevar Z, Krishnan MN, Venugopal K — Prevalence, Awareness, Treatment, and Control of Hypertension in Young Adults (20-39 Years) in Kerala, South India. *Front Cardiovasc Med* 2022; **18;9:** 765442.
3 Meher M, Pradhan S, Pradhan S — Risk Factors Associated With Hypertension in Young Adults: A Systematic Review. *Cureus* 2023; **15(4):** e37467.
4 Drukteinis JS, Roman MJ, Fabsitz RR — Cardiac and systemic hemodynamic characteristics of hypertension and prehypertension in adolescents and young adults: the Strong Heart Study. *Circulation* 2007; **115:** 221-7.
5 Yano Y, Reis JP, Colangelo LA — Association of Blood Pressure Classification in Young Adults Using the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline With Cardiovascular Events Later in Life. *JAMA* 2018; **320(17):** 1774-82.
6 Loria CM, Liu K, Lewis CE — Early adult risk factor levels and subsequent coronary artery calcification: the CARDIA Study. *J Am Coll Cardiol* 2007; **49(20):** 2013-20.
7 Williams B, Mancia G, Spiering W — 2018 ESC/ESH guidelines for the management of arterial hypertension. J Hypertens 2018; **36:** 1953-2041.
8 Ferri C — The role of nebivolol in the management of hypertensive patients: from pharmacological profile to treatment guidelines. *Future Cardiol* 2021; **17(8):** 1421-33.
9 Battise D, Boland CL, Nuzum DS — Nebivolol/Valsartan: A Novel Antihypertensive Fixed-Dose Combination Tablet. *Annals of Pharmacotherapy* 2019; **53(4):** 402-12.
10 Jadhav U, Tiwaskar M, Khan A — Hypertension in Young Adults in India: Perspectives and Therapeutic Options amongst Clinician's in a Cross Sectional Observational Study. *J Assoc Physicians India* 2021; **69(11):** 11-2.
11 Ishak J, Rael M, Punzi H — Additivity of nebivolol/valsartan single-pill combinations versus other single-pill combinations for hypertension. *J Clin Hypertens* 2018; **20:** 14-9.
12 Unger T, Schupp M — Telmisartan: from lowering blood pressure to end-organ protection. *Future Cardiol* 2005; **1(1):** 7-15.
13 Varagic J, Punzi H, Ferrario CM — Clinical utility of fixed-dose combinations in hypertension: evidence for the potential of nebivolol/valsartan. *Integr Blood Press Control* 2014; **7:** 61-70.
14 Giles TD, Khan BV, Lato J — Nebivolol monotherapy in younger adults (younger than 55 years) with hypertension: a randomized, placebo-controlled trial. *J Clin Hypertens (Greenwich)* 2013; **15(9):** 687-93.
15 Sharpe M, Jarvis B, Goa KL — Telmisartan: a review of its use in hypertension. *Drugs* 2001; **61(10):** 1501-29.
16 Shin J, Choi YJ, Hong GR — Real-world efficacy and safety of nebivolol in Korean patients with hypertension from the BENEFIT KOREA study. *J Hypertens* 2020; **38(3):** 527-35.
17 Strauss MH, Hall AS, Narkiewicz K — The Combination of Beta-Blockers and ACE Inhibitors Across the Spectrum of Cardiovascular Diseases. *Cardiovasc Drugs Ther* 2023; **37(4):** 757-70.
18 Fountoulaki K, Dimopoulos V, Giannakoulis J — Left ventricular mass and mechanics in mild-to-moderate hypertension: effect of nebivolol versus telmisartan. *Am J Hypertens* 2005; **18:** 171-7.
19 Degirmenci H, Açikel M, Bakirci EM — Comparison of effects of nebivolol, carvedilol and irbesartan on left ventricular hypertrophy associated with hypertension. *Eur Rev Med Pharmacol Sci* 2014; **18(5):** 630-7.
20 Misra KH, Das MC, Ramani YR — Effect of telmisartan on the regression of the left ventricular hypertrophy in the patients of essential hypertension. *J Clin Diagn Res* 2013; **7(7):** 1352-5.
21 Fitchett D — Results of the ONTARGET and TRANSCEND studies: An update and discussion. *Vascular Health and Risk Management* 2009; **5:** 21-9.
22 Brugts JJ, Bertrand M, Remme W — The treatment effect of an ACE-inhibitor based regimen with perindopril in relation to beta-blocker use in 29,463 patients with vascular disease: a combined analysis of individual data of ADVANCE, EUROPA and PROGRESS trials. *Cardiovasc Drugs Ther* 2017; **31(4):** 391-400.
23 Manrique C, Whaley-Connell A, Sowers JR — Nebivolol in obese and non-obese hypertensive patients. *J Clin Hypertens (Greenwich)* 2009; **11(6):** 309-15.
24 Mende CW, Giles TD, Bharucha DB — Efficacy of nebivolol-valsartan single-pill combination in obese and nonobese patients with hypertension. *J Clin Hypertens (Greenwich)* 2017; **19(6):** 632-639.
25 Majid A, Javed A, Hussain M — Effect of nebivolol beneficial on lipid profile and glycemic control in comparison with Atenolol in patients with type 2 DM with concomitant hypertension. *Pak J Pharm Sci* 2021; **34(5(Supplementary):** 1891-5.
26 Wang Y, Qiao S, Han DW — Telmisartan Improves Insulin Resistance: A Meta-Analysis. *Am J Ther* 2018; **25(6):** e642-e651.
27 Lipworth B, Wedzicha J, Devereux G — Beta-blockers in COPD: time for reappraisal. *Eur Respir J* 2016; **48(3):** 880-8.
28 Christiansen SC, Zuraw BL — Treatment of Hypertension in Patients with Asthma. *N Engl J Med* 2019; **381(11):** 1046-57.
29 Sharp RP, Gales BJ — Nebivolol versus other beta blockers in patients with hypertension and erectile dysfunction. *Ther Adv Urol* 2017; **9(2):** 59-63.
30 Giles TD, Cockcroft JR, Pitt B — Rationale for nebivolol/valsartan combination for hypertension: review of preclinical and clinical data. *J Hypertens* 2017; **35:** 1758-67.

Drug Corner

Advancements in Vitamin D3 Formulations : A Review of UNS D3 Ultra Nano 60 Thousand

K J Reddy[1], Jayram Reddy[1], Siva Reddy[1], Anish Desai[2], Manish R Garg[3]

Vitamin D plays a crucial role in maintaining calcium balance, bone health and various non-calcemic processes in the body. However, factors like reduced sun exposure and dietary habits lead to widespread deficiencies, impacting skeletal and non-skeletal health. Traditional fat-soluble Vitamin D formulations have poor bioavailability, necessitating high supplemental levels that may pose risks. Nanotechnology offers a solution with nanoemulsions improving bioavailability and stability. The UNS D3 Ultra Nano 60 Thousand utilizes En-Infi™ nanotechnology, delivering stable, uniform ultra-fine nanoparticles for enhanced absorption. Clinical studies show its superior efficacy and safety compared to conventional formulations. The formulation's innovative use of C3 CURA™ adds further benefits, improving immunity and metabolic wellness. Future advancements may focus on targeted delivery and innovative nanoparticle formulations to further enhance Vitamin D3's bioavailability and effectiveness. Overall, UNS D3 presents a promising solution to combat Vitamin D deficiencies, offering a reliable and effective supplementation method.

[*J Indian Med Assoc* 2024; **122(3):** 75-8]

Key words **: Vitamin D Deficiency / drug therapy, Biological Availability, Cholecalciferol, Healthy Volunteers, Administration, Oral.**

Vitamin D, a fat-soluble vitamin, is crucial for maintaining calcium balance and bone health[1]. It also influences various non-calcemic processes in different body tissues, including the cardiovascular system, metabolism, type 2 diabetes, multiple cancers and immune function[2-4]. The primary source of Vitamin D for humans is through the skin's synthesis upon exposure to ultraviolet B radiation (Fig 1) provides an overview of the Vitamin D metabolism. However, due to factors such as reduced sun exposure, lifestyle changes, pollution, dietary habits and specific dietary components, many people require Vitamin D supplements to meet their needs[5,6]. Vitamin D deficiency can lead to skeletal issues like rickets in children and osteomalacia and osteoporosis in adults, as well as impact non-skeletal health. Addressing these factors and ensuring adequate Vitamin D intake is essential for overall health and well-being[6].

Vitamin D deficiency/insufficiency has become a pandemic and a widely untreated and underdiagnosed issue Worldwide. Approximately one billion individuals worldwide experience a deficiency in Vitamin D[7,8]. In India, Vitamin D deficiency is widespread[6], with deficiency rates ranging from 40% to 99% across both urban and rural areas, irrespective of Socio-economic factors, gender, age, geographical regions, environmental conditions or profession[7,8]. However, the clinically diagnosed cases represent only the tip of

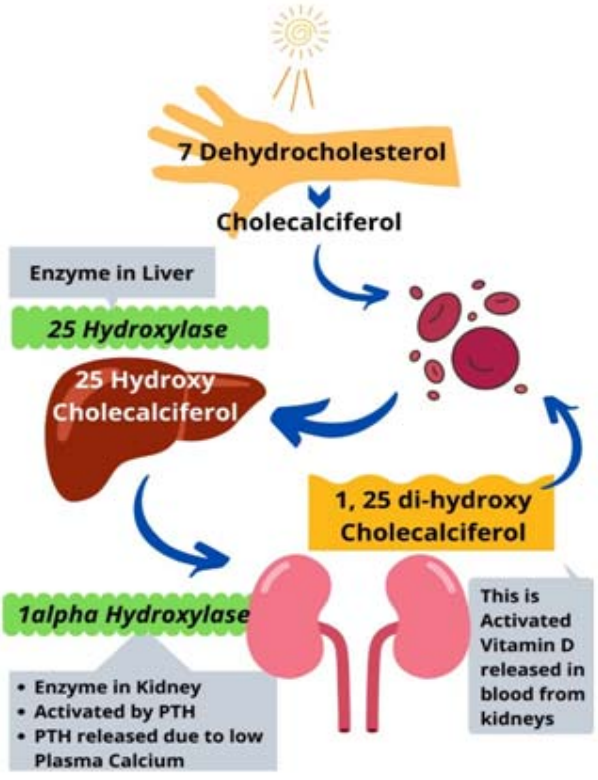


Fig 1 — Process of Vitamin D metabolism

[1]Orthopedician, Department of Orthopaedics, SVS Medical College, Mehboob Nagar, Telangana 509001
[2]MD, FCP, PGDHEP, Clinical Pharmacologist and Pharmaceutical Physician, Director, Intelli Med Healthcare Solutions, Mumbai
[3]MD, Clinical Pharmacologist, Head – Medical Affairs, Universal NutriSciences Pvt Ltd, Mumbai
Received on : 05/03/2024
Accepted on : 07/03/2024

the iceberg. Considering the numerous implications it may cause, the burden posed by this silent epidemic on the country's development is substantial. Therefore, addressing Vitamin D deficiency demands significant attention and decisive action[6].

Traditional Vitamin D3 Formulations :

The bioavailability of Vitamin D is typically relatively low because its strong hydrophobicity leads to a low solubility in aqueous fluids, such as those in the Gastrointestinal Tract (GIT). Therefore, Vitamin D is often delivered in an oil-in-water emulsion that is specifically designed to enhance its bioaccessibility by improving its solubility and the formation of mixed micelles. Several fat-soluble nutrients and dietary bioactive components exhibit a "U" shaped pattern, with potential risks associated with both low and high levels of intake. Therefore, to improve Vitamin D status, we cannot unlimitedly increase the supplemental level. Otherwise, it may put a subgroup of the population at risk of exposure to high levels of Vitamin D. Indeed, it has been estimated that around 1% of the population in the US may be at a possibly harmful level (>125 nmol/L)[9]. Also, most available formulations in the Indian market are traditional fat-soluble preparations, which have poor bioavailability due to their low solubility in the Gastrointestinal tract (GIT)[10]. Thus, to improve oral Vitamin D bioavailability and to reduce the variation of Vitamin D absorption, rather than simply increasing the supplemental level, there should be a better strategy to improve Vitamin D status for public health[9].

Nanotechnology has witnessed rapid growth in recent decades and along with the emergence of nanotechnology, the utilization of nanoemulsion (d< 200 nm) over conventional coarse emulsion (d >200 nm) as delivery vehicles for lipophilic nutrients and bioactives has received substantial attention in nutrition and food industry[9]. These nanoemulsions are a novel type of colloidal delivery system that may encapsulate, safeguard, and transport lipophilic bioactive compounds. Compared to conventional delivery systems, the droplets in these liquid dispersions are more minor, ranging in size from 50 to 500 nm. The nanoemulsions exhibit improved bioavailability, stability against phase separation and hydrophobic chemical absorption capacity[11]. Physiochemical advantages include lesser aggregation and higher optical clarity. Additionally, lipid nanoparticles tend to undergo quicker digestion within the Gastro-intestinal tract due to their smaller size and extensive surface area. Studies have shown that reducing lipid nanoparticle size increases the bioaccessibility of hydrophobic components, eg, curcumin and carotenoid[9].

It has been demonstrated that the cholecalciferol nanoemulsion formulation (D<200/ nm) exhibits higher bioavailability and homogeneity when compared to the conventional coarse emulsion with particle diameters >200/ nm[11].

Based on histopathological findings and improved biochemical profile, it was found that Vitamin D nanoemulsion is more hepatoprotective compared to conventional Vitamin D supplements when anti-inflammatory and anti-oxidant properties of Vitamin D nanoemulsion were studiedin animal models of Non-alcoholic Fatty Liver Disease (NAFLD)[11].

For the following reasons, the nanoemulsions are likely to be better than conventional Vitamin D preparations:

- It has a better compliance rate.
- It has a better therapeutic role in patients with malabsorption syndromes caused by inflammatory bowel disease, celiac disease, short bowel syndrome, hepatobiliary disorders, pancreatic insufficiency and bariatric surgery who suffer from deficiencies of essential fatty acids and fat-soluble vitamins, including Vitamin D.
- Improved hepatoprotective effect than conventional formulation[11]

Introduction to UNS D3 Ultra Nano 60 Thousand :

UNS D3™ Oral Solution is prepared using patented nanotechnology. This internationally patented En-Infi™ nanotechnology – precision engineered used in the formulation offers a stable, uniform ultra-fine nanoparticle of average 26.01 nm particle size, which is evenly interspersed and thoroughly water miscible. This formulation contains a natural colorant, C3 Cura™, which enhances immunity and enables metabolic wellness. Free from sugar; safe for diabetic and Cardiovascular (CVD) patients.

The UNS D3 Nano 60 thousand formulations, designed using En-Infi™ nanotechnology, encapsulates solubilized Vitamin D3 within a nano-lipid system. This system features a stable hydrophilic surface that shields the nanoparticles from breakdown in the presence of high concentrations of bile and lipases during transit through the Gastro-intestinal Tract (GIT). Consequently, it delivers Vitamin D3 directly at the absorption site without relying on the lipid digestion process, as seen in conventional systems.

Also, this novel formulation uniquely utilizes another proprietary technology comprising C3 CURA™. Curcuma drops (Curcumin) are a natural colorant at adequate concentration levels. As opposed to other colorants used by different brands, for instance, Tartrazine. It is highly bioavailable (500 times more

bioavailable) and has faster and easier absorption of curcumin in the body. C3 Cura™ is comprised of active constituents of curcumin and helps reduce dosage to 1/100th of marketed products (Fig 2). Apart from being a natural colorant, C3 CURA™ adds value to the formulation as a stabilizing agent and provides practical clinical outcomes by supplementing the Immunity profile of Vitamin D3 and enabling metabolic wellness.

The combination of C3 Cura™ and Vitamin D3 in UNS D3 Nano Formulation offers:

- Protection from lipase enzymes
- Protects against enzymatic degradation
- Enhanced stability
- Prevents agglomeration
- Maintains structural integrity

Efficacy and Safety of UNS D3 Ultra Nano 60 Thousand :

An open-label, balanced, randomized, single-dose, three-treatment, single-period, parallel-design bioequivalence study was conducted to compare the efficacy of UNS D3 to other marketed formulations in a group of healthy adult subjects under fasting conditions. The test formulation, 60000 IU Vitamin D3 Oral Solution of Universal NutriSciencePvt. Ltd., India, was compared with reference products: DePURA, 60000 IU Vitamin D3 Oral Solution of Sanofi India Limited (R1) and Uprise®- D3 60K Cholecalciferol Capsule USP of Alkem Laboratories, India (R2). Each group consisted of 10 subjects.

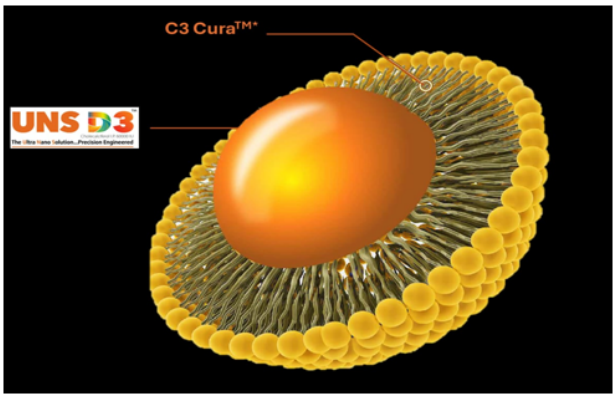


Fig 2 — Micelle structure of UNS D3 Ultra Nano 60 Thousand

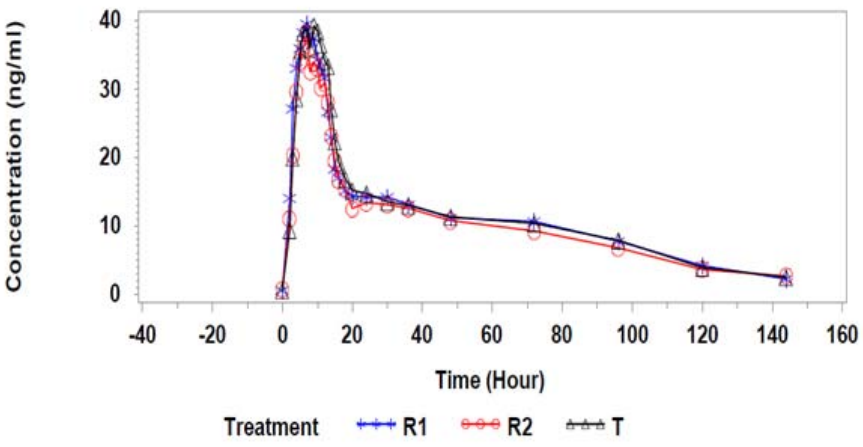


Fig 3 — Linear plot of mean serum concentration of baseline corrected 25-hydroxy Vitamin D3 *versus* time for test product (T), reference product 1 (R1), and reference product 2 (R2) (N=30)

Among the 30 participants, the C_{max} of serum 25(OH) D from the test formulation was higher than that of R2 by 14.94%. The area under the concentration-time curve up to 144 h (AUC_{0-144h}) of serum 25(OH)D3 from the test formulation was higher than that of R2 by 20.52% (Fig 3). The C_{max} and AUC_{0-144h} of serum 25(OH)D3 levels from the test formulation were comparable to that of R1. Thus, the test formulation is bioequivalent to R1 and shows a trend of superiority over R2. T_{max} of 25(OH)D3 was found to be 8.3602 hr, 6.4674 hr, and 7.3419 hr for test formulation, R1 and R2 respectively (Table 1). The test formulation was safe and well tolerated, as no adverse events were reported.

The test formulation, formulated with En-Infi™ nanotechnology, exhibited higher C_{max} and AUC_{0-144h} compared to the R2, showed bioequivalence to the R1, and was well tolerated. These elevated metabolite levels [serum 25(OH)D] are likely attributed to the superior rate and extent of absorption of Vitamin D3 from the test compared to R2. The comparable data confirms the advantages of En-Infi™ nanotechnology and underscores the benefits of ultra-nanoparticles utilized in the test formulation.

Table 1 — *Descriptive statistics of formulation means for 25-hydroxy Vitamin D3 obtained by a non-compartmental model (N = 30)*

Pharmacokinetic Parameters (Units)	Test product (T)	Reference product (R1)	Reference product (R2)
C_{max} (ng/mL)	46.4529	45.2277	40.4148
AUC_{0-144h} (ng.hr/mL)	1557.593	1567.735	1292.363
T_{max} (hr)	8.3602	6.4674	7.3419

The nanoformulation process facilitates smooth paracellular, transcellular and persorption pathways of Vitamin D through the intestinal mucus layer, ensuring higher bioavailability compared to conventional formulations, regardless of the fat content in the gut. It also offers improved compliance as it does not necessitate the consumption of milk or clarified butter for absorption[12].

Conclusion and Future Directions :

Thus, the UNS D3™ presents a promising and innovative solution utilizing advanced nanotechnology, offering improved bioavailability, stability and potential health benefits. This product is a viable option to combat the widespread deficiency of Vitamin D3, catering to a range of health-conscious consumers seeking a reliable and effective supplementation method. This will help the patient reach a sufficiency level from a deficiency or insufficiency level faster than other nano-marketed formulations.

Potential future advancements in Vitamin D3 formulations may involve ongoing exploration of nanotechnology-based delivery systems, similar to the En-Infi™ nanotechnology utilized in UNS D3 Ultra Nano 60 Thousand. Such endeavors could result in enhanced bioavailability and effectiveness of Vitamin D3 formulations. This may involve refining current nanoemulsion-based platforms or investigating innovative nanoparticle formulations. Furthermore, foundational research into targeted delivery using nanoemulsions presents promising prospects in enabling lower doses of Vitamin D3 to achieve therapeutic effects, reducing the risk of toxicity.

Declaration : Article is not published / submitted in any other journal.

Acknowledgments : The authors thank all the study investigators, study coordinators and other study personnel who participated in the study, for their contributions.

Conflict of Interest : No

References

1 Habib AM, Nagi K, Thillaiappan NB, Sukumaran V, Akhtar S — Vitamin D and Its Potential Interplay With Pain Signaling Pathways. Frontiers in Immunology. 2020 May 28;11.

2 Adams JS, Hewison M. Update in Vitamin D — *The Journal of Clinical Endocrinology & Metabolism* 2010; **95(2):** 471-8.

3 Rosen CJ — Vitamin D Insufficiency. *New England Journal of Medicine* 2011; **364(3):** 248-54.

4 Bener A, Al-Hamaq A, Saleh N — Association between vitamin D insufficiency and adverse pregnancy outcome: global comparisons. International Journal of Women's Health. 2013 Sep; 523.

5 Silva MC, Furlanetto TW — Intestinal absorption of vitamin D: a systematic review. *Nutrition Reviews* 2017; **76(1):** 60-76.

6 Aparna P, Muthathal S, Nongkynrih B, Gupta SK — Vitamin D deficiency in India. *Journal of Family Medicine and Primary Care [Internet]* 2018; **7(2):** 324-30. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6060930/

7 Shah P, Kulkarni S, Narayani S, Sureka D, Dutta S, Vipat AS, *et al* — Prevalence Study of Vitamin D Deficiency and to Evaluate the Efficacy of Vitamin D3 Granules 60,000 IU Supplementation in Vitamin D Deficient Apparently Healthy Adults. pesquisabvsaludorg [Internet]. 2013 [cited 2024 Mar 1]; Available from: https://pesquisa.bvsalud.org/portal/resource/pt/sea-182562

8 Kuchay MS, Mithal A — Vitamin D deficiency in India. *J Indian Med Assoc [Internet]* 2018 [cited 2024 Jan 31]; **116(10):** 41-44+55.

9 Kadappan AS, Guo C, Gumus CE, Bessey A, Wood RJ, McClements DJ, *et al* — The Efficacy of Nanoemulsion-Based Delivery to Improve Vitamin D Absorption: Comparison of In Vitro and In Vivo Studies. *Molecular Nutrition & Food Research [Internet]* 2018 Feb 1 [cited 2024 Mar 1];62(4). Available from: https://pubmed.ncbi.nlm.nih.gov/29266712/

10 Chugh P, Lhamo Y, Tripathi C — Vitamin D supplements in the Indian Market. *Indian Journal of Pharmaceutical Sciences* 2016; **78(1):** 41.

11 Marwaha RK, Dabas A — Bioavailability of nanoemulsion formulations vs conventional fat soluble preparations of cholecalciferol (D3) – An overview. *Journal of Clinical Orthopaedics and Trauma* 2019; **10(6):** 1094-6.

12 Marwaha RK, Yenamandra VK, Ganie MA, Sethuraman G, Sreenivas V, Ramakrishnan L, *et al* — Efficacy of micellized vs. fat-soluble vitamin D3 supplementation in healthy school children from Northern India. *Journal of Pediatric Endocrinology and Metabolism* 2016; **29(12)**.

Letters to the Editor

[The Editor is not responsible for the views expressed by the correspondents]

Association between Sleep Quality and Different Aspects of Memory along with Assessment of Post Exercise and Post Meditation Effects

Sir, — Recently I read the Original Article, titled "Association between Sleep Quality and Different Aspects of Memory along with Assessment of Post Exercise and Post Meditation Effects" by Mohita Singh, *et al*[1]. The study was done in two phases. In the first phase they have assessed different components of sleepquality and memory thoroughly by using Pittsburgh sleep quality index and PGI memory test respectively. Based on memory scores, both male and female subjects were divided into five groups like, excellent, above average, average, below average and low level of memory. Various sleep quality components were studied in these memory groups. The finding was very interesting that memory scores were improved with better sleep quality in both males and females.

This study has reported that women have better sleep quality compared with men and various previous studies also have reported the same[2]. In the second phase of this study, they have divided both the male and female subjects into two groups and studied the effects of moderate intensity exercise and meditation on both sleep and memory. In this phase also they have reported that there was improvement in sleep quality and memory scores in both males and females after exercise and meditation interventions.

In today's competitive World psychological problems are increasing and various studies have shown that daily meditation can help in enhancing attention, memory and mood[3]. Some studies have reported that lack of sleep in middle age may increase risk of dementia[4,5].

This study will be very helpful to the society, as its not only reporting that sleep quality and memory are interrelated but also proved that moderate intensity exercise and meditation will help in improving sleep quality and memory. But in the second phase of the study, if they would have divided both males and females in five groups on levels of memory like phase one and studied the effects of these interventions in each group separately, we would have got clear idea about whether moderate intensity exercise and meditation can improve memory directly or it has positive effect on sleep quality which in turn improves memory.

References

1 Singh M, Sachdev S, Manhas M, Raj D — Association between Sleep Quality and Different Aspects of Memory along with Assessment of Post Exercise and Post Meditation Effects. *J Indian Med Assoc* 2023; **121(1):** 19-23.

2 Krishnan V, Collop NA — Gender differences in sleep disorders. *Curr Opin Pulm Med* 2006; **12(6):** 383-89.

3 Basso JC, McHale A, Ende V, Oberlin DJ, Suzuki W — Brief daily meditation enhances attention, memory, mood and emotional regulation in non- experienced meditators. *Behav Brain Res* 2019; **356:** 208-20.

4 Rana BK, Panizzon MS, Franz CE, Spoon KM, Jacobson KC, Xian H, *et al* — Association of sleep quality on memory related executive functions in middle age. *J Intl Neuropsychol Soc* 2018; **24(1)**: 67-76.

5 Sabia S, Fayosse A, Dumurgier J, van Hees VT, Paquet C, Sommerlad A, Kivimäki M, *et al* — Association of sleep duration in middle and old age with incidence of dementia. *Nat Commun* 2021; **12(1):** 2289.

Department of Biochemistry,
Dr D Y Patil Medical College,
Maharashtra 411018
[1]MD, Associate Professor
[2]MSc, PhD, Professor

Anita Deepak Deshmukh[1]
Sarita Anil Shinde[2]
Pradnya Jay Phalak[1]

Successful Use of Total Parenteral Nutrition in Patients with Paraquat Poisoning

Sir, — Paraquat (1,10-dimethy l-4, 40-bipyridinium dichloride) is an effective, nonselective herbicide that is widely used in many parts of India. It is also the most frequently used herbicide in the rural part of West Bengal. Dermal or spray exposure generally causes limited, localised injury, whereas intentional ingestion of this compound for suicide has an extremely high case fatality rate[1]. A paraquat dose of 30mg/kg may be fatal which is equivalent to 7-8 mL of the 24.6% solution sold commercially[2]. This compound is absorbed by the intestine and accumulates inside the cells of different organ where it undergoes redox cycling and the production of Reactive Oxygen Species (ROS). Which results in subsequent inflammatory responses mediated by various inflammatory cytokines such as Interleukin (IL)-1, IL-6, IL-8, tumour necrosis factor (TNF)-a, TNF-b, interferon-1, transforming growth factor (TGF)-b and nuclear factor (NF)-kappa b[3]. Clinical features include oral ulceration with gastro-intestinal tract injury, acute kidney injury, acute lung injury (subsequently progressive pulmonary fibrosis), acute liver failure, metabolic acidosis and leucocytosis. Till now, there has been no effective targeted antidote for paraquat poisoning. Many centres have tried a combination of cyclophosphamide, steroids, antioxidants, charcoal haemoperfusion and early haemodialysis[4]. But still, the case fatality rate is very high.

Clinically, most patients with paraquat poisoning who have excessive upper GI mucosal injury have been found to develop feeding difficulties and Total Parenteral Nutrition (TPN) is needed to reduce nutritional deficit. Studies have shown previously about the beneficial role

of ω-3 fish oil containing TPN as an anti-inflammatory agent in the case of paraquat poisoning (decreases 4-series leukotrienes and increases production of anti-inflammatory cytokines like TGF-β)[5]. Based on the above findings, we have used TPN (peripheral) both as pharmacological and nutritional therapy in two patients with paraquat poisoning, with very good early recovery.

Case 1 : A 21-year-old female presented to the emergency room (Day 3) with a history of paraquat ingestion (approx 20ml) two days earlier. Clinical examination has revealed extensive oral mucosal ulceration and icterus. On admission, her renal and hepatic functions were altered, her total leucocyte count was elevated (Table 1) and her urine output was also reduced. Based on KDIGO guidelines for acute kidney injury, haemodialysis was initiated on day 4. Total parenteral nutrition (1000 mL) supplementation was initiated on day 5. On days 6, 8, and 10, three episodes of dialysis were given. From day 8 onward, the patient's renal functions had started to improve along with increased urine output. On days 9 and 12, two more units of TPN (1000 mL) were given. Subsequently, all the haematological and biochemical parameters had improved. We had discharged the patient on day 17 with an almost normal renal function and liver function report (Table 1).

Table 1 — *Comparison between hematological and biochemical parameters of Patient 1 on Day3, Day 8,Day14 and Day 17 (discharge day)*

Parameters	Day 3	Day 8	Day 14	Day 17
Hemoglobin	10.6	9.8	10.5	11.0
TLC	23,300	13,900	11,200	10,200
Urea	169	105	76	36
Creatinine	6.1	3.6	2.1	1.2
Total Bilirubin	4.6	3.0	2.6	1.4
ALT	345	123	99	56
AST	258	97	56	33

Case 2 : This 28-year-old male was referred to our institution from the nearest sub-divisional hospital with altered sensorium and acute kidney injury. He had taken paraquat poison (>15 mL) 6 days prior, according to his history. At the sub-divisional hospital, the patient had undergone 2 episodes of haemodialysis. After admission (Day 7), his renal function and liver function were found to be abnormal (serum creatinine 17 mg/dl and total bilirubin 12.5 mg/dl). Haemodialysis was restarted, and as in a resource-poor setting, alternate-day dialysis was given. We had transfused 4 units of total parenteral nutrition (1000 mL) along with 3 units of blood transfusion in between alternate-day dialysis. A total of 16 episodes of haemodialysis were given. Patient's condition started improving from day 21, and he was discharged after 32 days of admission with normal renal and liver functions. The gradual changes are depicted in Table 2.

Table 2 — *Comparison between hematological and biochemical parameters of Patient 2 on Day 7, Day 14, Day 21, Day 28, Day 35 and Day 39 (discharge day)*

Parameters	Day 7	Day 14	Day 21	Day 28	Day 35	Day 39
Hemoglobin	7.8	8.3	9.5	9.1	10.5	11.1
TLC	26700	19800	12000	16500	13000	9800
Urea	257	198	166	110	67	42
Creatinine	17	15.3	11.8	8.7	3.5	1.4
Total Bilirubin	12.5	11.2	9.7	6.5	3.3	1.8
ALT	356	234	200	156	99	66
AST	455	266	213	177	105	78

From the above-mentioned data, it is evident that both patients improved despite having AKI and acute liver failure on presentation. The first patient required fewer amount of hemodialysis with early recovery as she had presented early. In spite of her relatively late presentation, the second patient also survived. One possible explanation may be that patient had received large quantities of antioxidant molecules through total parenteral nutrition, which had reversed the detrimental oxidative damage caused by paraquat and its metabolites .Early haemodialysis is therapeutic option for the paraquat poisoning patients as per literature but in our patient, dialysis was given as a supportive care.Urine paraquat level can not be measured in this resource poor settings, proof of direct improvement after TPN therapy cannot be elicited. Thus, further studies are needed to find the definitive therapeutic roles of TPN in cases of paraquat poisoning.

References

1 Dinis-Oliveira RJ, Duarte JA, Sánchez-Navarro A, Remião F, Bastos ML, Carvalho F — Paraquat poisonings: mechanisms of lung toxicity, clinical features, and treatment. *Crit Rev Toxicol* 2008; **38(1):** 13-71. doi: 10.1080/10408440701669959. PMID: 18161502.

2 Suntres ZE — Role of antioxidants in paraquat toxicity. *Toxicology* 2002; **180(1):** 65-77. doi: 10.1016/s0300-483x(02)00382-7. PMID: 12324200.

3 Cavalli RD, Fletcher K — An effective treatment for paraquat poisoning. In: Autor A.P., editor. Biochemical Mechanisms of Paraquat Toxicity. New York: Academic Press; 1977. 213-34.

4 Zhang Q, Wu WZ, Lu YQ, Wang JZ, Shang AD, Yao F, *et al* — Successful treatment of patients with paraquat intoxication: three case reports and review of the literature. *J Zhejiang Univ Sci B* 2012; **13(5):** 413-8. doi: 10.1631/jzus.B1200008. PMID: 22556181; PMCID: PMC3348234.

5 Meng Z, Dong Y, Gao H, Yao D, Gong Y, Meng Q, *et al* — The effects of ω-3 fish oil emulsion-based parenteral nutrition plus combination treatment for acute paraquat poisoning. J Int Med Res. 2019 Feb;47(2):600-614.

Department of Medicine,
Burdwan Medical College & Hospital,
West Bengal 713104

Uttam Biswas[1]
Arpan Mukhopadhyay[2]
Saumik Datta[3]

[1]MBBS, MD (Medicine), MRCP (UK), Associate Professor
[2]MBBS, Junior Resident
[3]MBBS, MD (Medicine), DM (Endocrinology) Professor and Head

Are Deep Learning Algorithms Changing the Landscape of AI-Assisted LV-GLS Analysis in Cardiology, Offering Hope for Early Disease Detection?

Sir, — The fusion of Artificial Intelligence (AI) and Deep Learning (DL) in cardiology, particularly in Left Ventricular Global Longitudinal Strain (LV-GLS) analysis via echocardiography, heralds a transformative epoch in cardiac healthcare[1]. This integration promises to reshape cardiac healthcare by revolutionizing early detection, risk assessment, and therapy evaluation, offering substantial benefits for patients and healthcare providers.

The heart, a vital yet vulnerable organ, necessitates timely detection and intervention in conditions like heart failure and myocardial infarction. Traditionally, LV-GLS measurement involved manual calculations and subjective interpretations, leading to delayed diagnoses and inconsistent results. The advent of AI-driven LV-GLS analysis powered by DL has revolutionized this approach. DL, a subset of AI, harnesses artificial neural networks to independently process intricate patterns within datasets, significantly augmenting the precision and efficiency of cardiac evaluations.

This groundbreaking technology provides precise and consistently reliable LV-GLS measurements, even in nuanced cases of cardiac dysfunction. AI empowers independent acquisition of pattern combinations within datasets, enhancing standard section identification of cardiac anatomical structures, automatic recognition, and segmentation of cardiac structures, expediting disease diagnosis[2]. Leveraging neural networks and extensive datasets, DL algorithms process and analyze LV-GLS data with remarkable precision and speed, performing specific tasks in echocardiographic image analysis such as view classification, time to events, and image segmentation[3].

Automating LV-GLS analysis accelerates processes, freeing healthcare professionals to focus on the art of medicine and patient care rather than manual calculations. Furthermore, fully automated strain measurements rooted in DL hold the promise of reducing manual intervention while significantly enhancing result reproducibility. The rapid processing speed of these learning-based algorithms opens the door to conducting real-time on-screen measurements during image capture[4]. Such heightened precision is invaluable for early detection and diagnosis, saving time and streamlining patient care while extending the reach of advanced cardiac diagnostics across diverse healthcare settings.

AI pipelines' ability to categorize cardiac views, time cardiac events, track myocardium, and swiftly measure GLS allows for early detection of cardiac dysfunction, offering a critical intervention window[4]. These systems analyze vast data, yielding deeper insights into cardiac function and cardiovascular health factors, ultimately enhancing patient outcomes and curbing healthcare costs. This collaboration fuels ongoing research, spurring innovation in cardiology and driving the development of groundbreaking diagnostic tools and treatment strategies.

Nevertheless, while AI-driven systems hold great promise, challenges persist, such as the absence of a universally accepted gold standard for LV-GLS measurements and issues regarding model generalizability across different institutions. Ethical considerations surrounding data privacy, transparency, and accountability are paramount to ensure the responsible and ethical utilization of AI technologies[5].

In conclusion, the integration of AI-assisted LV-GLS analysis signifies a pivotal advancement in cardiology, offering a promising future for patients and healthcare professionals alike. This technological leap not only enhances the precision and efficiency of LV-GLS measurements but also holds the potential to reshape cardiac healthcare by enabling earlier detection and more accurate diagnoses. Collaborative engagement among medical practitioners, researchers, regulators, and the public is crucial to responsibly harness these innovations, ushering in an era of improved cardiac healthcare and enhanced patient well-being.

References

1 Goto S, Solanki D, John JE, Yagi R, Homilius M, Ichihara G, *et al* — Multinational federated learning approach to train ECG and echocardiogram models for hypertrophic cardiomyopathy detection. *Circulation* 2022; **146(10):** 755-69. Available from: http://dx.doi.org/10.1161/circulationaha.121.058696

2 Zhou J, Du M, Chang S, Chen Z — Artificial intelligence in echocardiography: detection, functional evaluation, and disease diagnosis. *Cardiovascular Ultrasound* 2021; **19(1).** https://doi.org/10.1186/s12947-021-00261-2

3 Salte IM, Østvik A, Smistad E, Melichova D, Nguyen TM, Karlsen S, *et al* — Artificial intelligence for automatic measurement of left ventricular strain in echocardiography. JACC. *Cardiovascular Imaging* 2021; **14(10):** 1918-28. https://doi.org/10.1016/j.jcmg.2021.04.018

4 Deng Y, Cai P, Zhang L, Cao X, Chen Y, Jiang S, *et al* — Myocardial strain analysis of echocardiography based on deep learning. *Frontiers in Cardiovascular Medicine* 2022; **9:** 1067760. https://doi.org/10.3389/fcvm.2022.1067760

5 Kusunose K — Revolution of echocardiographic reporting: the new era of artificial intelligence and natural language processing. *Journal of Echocardiography* 2023; **21(3):** 99-104. https://doi.org/10.1007/s12574-023-00611-1

Dr D Y Patil Medical College, Hospital and Research Centre Maharashtra 411018

Madhura Ajitkumar Gandhi[1]
Ajitkumar Krishna Jadhav[2]

[1]MSc Statistics, Statistician, Department of Central Research Facility
[2]MD (Cardiology), DNB, FSCAI, Assistant Professor, Department of Cardiology

JIMA Guidelines for Authors

Communications intended for publication should be sent to the Editor, Journal of the Indian Medical Association (JIMA). JIMA will consider manuscripts prepared in accordance with the **Vancouver style[1].**

Articles are considered for publication on condition that these are contributed solely to JIMA, that they have not been published previously in print and are not under consideration by another publication. In the selection of papers and in regard to priority of publication, the opinion of the Editor will be final & IMA members will be given prerogative. The Editor shall have the right to edit, condense, alter, rearrange or rewrite approved articles, before publication without reference to the authors concerned. **We Publish only online submitted articles through https://onlinejima.com**

Authorship : All persons designated as authors should **qualify for authorship.** Authorship credit should be based only on **significant contributions** to (a) conception and design, or analysisand interpretation of data; and to (b) drafting the article or revising it critically for important intellectual content; and on (c) final ap-proval of the version to be published. **Conditions (a), (b) and (c) must all be met.** Authors may include explanation of each author'scontribution separately.

Title page — The title page should include the title of the articlewhich should be concise but informative, name(s) of author(s) with his/her (their) academic qualification(s) and designation(s). Declaration regarding no conflict of interest and complete postal address including pin code of the institution(s) to which the work should be attributed. Mobile no. and email of all authors to be mentioned.

Abstract — Should carry an abstract of no morethan 250 words and should contain the purposes of the study or investigations, basic procedure, main findings and their implications along with **Key words and Take Home Message (4-5 lines).**

Text — The text of Original Articles should conform to the conventional division of Abstract, Introduction, Material and Method, Observations, Discussion, Conclusion and References. Other types of articles such as Review Articles, Case Reports, etc, are likely to need other formats.

Statistical evaluation — Description of the statistical methods used should either be given in detail in the "Material and Method" section of the article or supportive reference may be cited.

Abbreviations — Standard abbreviations should **be used and be spelt out when first used in the text.** Abbreviations should not be used in the title or abstract.

Units of measurement — Metric units should be used in scientific contributions. If the conventional units or SI units were actually followed in measurements that should be given in parentheses.

Drugs — The **generic names of the drugs (and not proprietary names)** including dose(s), route(s) and period of administration should be mentioned.

Length of manuscripts — For Originals Articles : Maximum 2200 words, 3 figures, and/or 4 tables, for Case Reports: Maximum 800 words, 2 figures, 1 table, for Letter to the Editor: upto 500 words.

Tables— Tables should be simple, self-explanatory and should supplement and not duplicate the information given in the text.

Illustrations — Graphs, charts, diagrams or pen drawings must be drawn by professional hands. Photographs should be supplied in resolution minimum 350 dpi and 5 inch wide. In case of microphotograph, stains used and magnification should be **mentioned.** Each illustration should have a minimum resolution of 350 dpi with proper labelling. All illustrations should be with suitable legends.

References — References should be **numbered in the order in which they are first mentioned in the text.** The full list of references at the end of the communication should be arranged in the order mentioned below (names and initials of all authors and/or editors up to 6; if more than 6, list the first 6 followed by *et al*):

[1]International Committee of Medical Journal Editors—Uniform Requirements for Manuscripts Submitted to Biomedical Journals. *JAMA* 1997; **277:** 927-34.

Reference from Journal :

[1]Cogo A, Lensing AWA, Koopman MMW, Piovella F, Sivagusa S, Wells PS, *et al* —Compression ultrasonography for diagnostic management of patients with clinically suspected deep vein throm-bosis: prospective cohort study. *BMJ* 1998; **316:** 17-20.

Reference from Book :

[2]Handin RI — Bleeding and thrombosis. In: Wilson JD, Braunwald E, Isselbacher KJ, Petersdorf RG, Martin JB, Fauci AS, *et al* editors—Harrison's Principles of Internal Medicine. Vol 1. 12th ed. New York: Mc Graw Hill Inc, 1991: 348-53.

Reference from Electronic Media :

[3]National Statistics Online—Trends in suicide by method in England and Wales, 1979-2001. www.statistics.gov.uk/downloads/ theme_health/ HSQ 20.pdf (accessed Jan 24, 2005): 7-18.

Only verified references against the original documents should be cited. Authors are responsible for the accuracy and completeness of their references and for correct text citation. **The number of reference should be kept limited to 20 in case of major communications and 10 for short communications.**

Dual publication : If material in a submitted article has been published previously or is to appear in part or whole in another publication, the Editor must be informed.

Forwarding letter : The covering letter accompanying the article should contain the name, complete postal address along with Mobile number & E-mail identity of one author as correspondent and must be digitally signed by all authors. The correspondent author should notify change of address, if any, in time.

Declaration : A declaration should be submitted stating that the manuscript represents valid work and that neither this manuscript nor one with substantially similar content under the present authorship has been published or is being considered for publication elsewhere and the authorship of this article will not be contested by anyone whose name (s) is/are not listed here, and that **the order of authorship as placed in the manuscript is final and accepted by the co-authors.** Declarations should be signed by all the authors in the orderin which they are mentioned in the original manuscript also **Ethical clearance letter to be send.**

- **Manuscript in Vancouver style (US spelling) in MS Word through *https://onlinejima.com***
- **Original / Review article:**
- **Case report / Current topics:**
  Max 800 words, 2 Figures, 1 Table, 10 References.
- **Letter to the Editor : 500 words**
- **Abstract :**
  Max 250 words, Keywords – 4-5 words,
  Take Home Message – Max 50 words.
- **Title Page:**
  Title of the article, Name (s) of the Author (s), Qualification, Designation, Institution, Postal Address, Email, Mobile Number & Digital Signature
- **Declaration:**
  Article is not published / submitted in any other journal.

— Hony Editor

JIMA, 53, Sir Nilratan Sirkar Sarani (Creek Row), Kolkata-700014
Phone : (033) 2237-8092,
E-mail : <jima1930@rediffmail.com> <jimaeditorial@gmail.com>
Editorial Office No.: (033) 2237-8092/ (+91) 9477493027
*Website: **https://onlinejima.com** & **www.ejima.in***

JOURNAL OF THE INDIAN MEDICAL ASSOCIATION :
Sir Nilratan Sircar IMA House, 53, Sir Nilratan Sarkar Sarani (Creek Row), Kolkata - 700 014
Phone : (033) 2237- 8092, Mobile : +919477493027; E-mail : jima1930@rediffmail.com
Website : https://onlinejima.com ; www.ima-india.org/ejima
Head office : Indian Medical Association, IMA House, Indraprastha Marg, New Delhi - 110 002
Telephones : +91-11-2337 0009, 2337 8680, Email : hsg@ima-india.org : Website : www.ima-india.org

Registration No. KOL RMS / 476 / 2023 - 2025

RNI Regd. No. 2557/1957
Vol. 68, No. 3, March 2024, Kolkata

Date of Publication : 20th March, 2024

If not delivered please return to
Journal of the IMA (JIMA)
53, Sir Nilratan Sarkar Sarani,
(Creek Row), Kolkata - 700014

Printed and Published by **Dr Sibabrata Banerjee** on behalf of Indian Medical Association and printed at Prabaha, 45, Raja Rammohan Sarani, Kolkata - 700009 and Published from Sir Nilratan Sircar IMA House, 53, Sir Nilratan Sarkar Sarani (Creek Row), Kolkata - 700014, Editor : **Dr Sanjoy Banerjee**