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Editorial
Digital Technology in Clinical Medicine: From Calculators to ChatGPT

Article
Coagulation Abnormalities in Severe Scrub Typhus and Their Association with Complications

Review Article
A Review on Vitamin D Deficiency and Related Disorders: What is the Right Serum Vitamin D Level?

Drug Corner
Naftifine: A Topical Allylamine for Superficial Dermatophytosis

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Digital Technology in Clinical Medicine: From Calculators to ChatGPT

Shriram V Kulkarni1*, Sagar Sinha2, Ramakrishnan Dindigal Narasimhan3

INTRODUCTION

The healthcare industry has always strived to utilise the latest advances in technology and communication to bring about meaningful progress in people’s daily lives. We have harnessed the power of semiconductors to ensure an magnetic resonance imaging scan can travel the world in seconds; a type 1 diabetic patient can lead an active lifestyle or detect life-threatening arrhythmias just on our wrists.

Despite all of these advancements, the pace of our progress and the lives of our patients clearly tells us there is a lot more we can do. Digital technology remains underutilised, underappreciated, and underestimated. The potential to develop and utilise technologies that can help patients manage their health conditions judiciously, diagnose diseases quicker, and measure the impact of prescribed therapies on health is immense.

BACKGROUND

Digital technology and its applications infiltrated medicine way back in 1972 in the form of electronic health records. The primary goal of digitising our healthcare systems has only continued to be refined since then. Modern systems now have vastly improved access to healthcare, massively reduced inefficiencies, lowered the cost of access, improved the quality of care and, above all, introduced personalisation for patients.

The domain of digital technology has been everexpanding since and now includes software algorithms, improved connectivity devices, and integrated sensors. Doctors are now aided in their diagnostic and clinical decision-making skills by not just the Bluetooth-connected stethoscope or chip-based ultrasound probes, but also by mobile applications which determine the prognostic scores has been made possible by advancements in software development.

Wearable devices have redefined the outlook on lifestyle disorders. A vast array of sensors have now enabled patients and their physicians to collect physiological data in real time and perform timely interventions. Behavioral modifications have now been gamified by great enthusiasm from physicians managing such patients.

Coronavirus disease of 2019 introduced a paradigm shift in the delivery of healthcare by means of telemedicine. Patients could now experience frictionless access to their physicians and completely avoid the waiting line at the clinic. But telemedicine did bring about challenges of its own, especially for the physician gathering crucial data from the oldest trick in the book—the thorough clinical examination. This unnerving complete loss of tactile input has dampened the eagerness that came during the early adoption of this technology. A reevaluation of its utility is certainly due as we have returned to our offices.

Our biggest challenge in the digital age of medicine has now reared its ugly head. Widespread internet access combined with fear, uncertainty and gullibility has ensured that medical misinformation tends to wear down even the most astute clinician. While it is acceptable to have a disagreement in a community as educated and large as ours, having such disagreements in public forums where it may be amplified in an improper context poses novel challenges. As research provides us with newer ways to tackle the disease, we must find a way to navigate these treacherous paths, take advantage of mass communication platforms and ensure the right information is delivered to our patients through the right mediums.

A crucial event sparked when “OpenAI” announced Chat Generative Pretrained Transformer (GPT).

Generative Pretrained Transformer (GPT) language model on 1st December 2022. A state-of-the-art natural language processing and machine learning (ML) system designed to assist with a wide range of language-based tasks.

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CURRENT EVIDENCE

Regulatory bodies have recognised the growing impact of digital technology in the delivery of healthcare and are actively advocating for betterment through clinical trials. The World Health Organization published the recommendations on digital interventions for health system strengthening in 2019 and provided a framework for interventions by classifying the interventions into four target groups, namely clients, health workers, health systems managers and data services and subsequently identifying the major challenges encountered in the propagation of digital health systems in each of these groups.

The Food and Drug Administration’s Digital Health Center of Excellence has several ongoing projects involving all major stakeholders in the healthcare industry. It is currently evaluating digital biomarkers, artificial intelligence (AI)/ML software, and augmented reality/virtual reality devices targeted towards improved delivery of healthcare services.

The Indian government announced a major stride towards the adoption and implementation of digital health services via the Ayushman Bharat Digital Mission in 2021. The mission seeks to provide a unified platform to enable ease of access to medical services across India by means of provider and hospital registries, among many other objectives.

CONTROVERSIES

As the digitisation of health proceeds at a breakneck speed, it is essential for us to repeatedly remind ourselves of a core

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Digital Technology in Clinical Medicine: From Calculators to ChatGPT

principle of medicine—primum non nocere. Our pursuit of glamorous technology must never deter our focus from patient care. These advancements must come with inbuilt checks and balances to ensure absolute patient privacy and counter the ever-growing threat of cyberwarfare. The exposure of personal health records and data can have devastating consequences, and these potential downsides must be considered at every step of development. There is now a mounting body of evidence to suggest the detrimental effects of the overuse of digital interfaces on physical and mental health, and physicians must be wary of these before proceeding to become over-reliant on these technologies.

However exciting, it may appear superficially that ChatGPT will not make much of a change in crucial aspects of the medical field. As professionals, we need to listen to history; in physical evaluation need to feel, auscultate, integrate the necessary investigations, come down to a provisional diagnosis, and plan the therapy. No question about AI will not have skills of physical examination, empathy of communication, dexterity of procedures and a humane way of crisis management. An adverse effect of over-reliance on technology and unregulated use has the capacity to moronize the young generation, who might look for easier solutions. Will it cause a sort of cognitive aplasia and suppress creativity and rational thinking? Will it produce a new syndrome of functional dementia?

Making the best option a technosavvy, technoacquired clinician is the right answer and is the best option. Balanced and regulated use can enhance productivity and performance in conferences and teaching.

We all physicians must embrace, adopt, and practice technology.

Publishers and preprint servers contacted by Nature’s news team agree that AIs such as ChatGPT do not fulfil the criteria for a study author because they cannot take responsibility for the content and integrity of scientific papers.6

SUMMARY

Mankind has been a witness to four social revolutions, from hunter-gatherers, horticultural, agrarian, and industrial to the present fifth digital knowledge and technology-based one. This fifth revolution has changed the way in which we think, live, create, and use various factors of production. Digital technology in medicine has certainly progressed a long way—we’ve moved from the era of calculators to now having ChatGPT clear the United States Medical Licensing Examination.

As responsible clinicians, we must reap the benefits of these advancements and help improve our patients’ lives while at the same time being careful enough not to tilt the boat too much, lest we capsize the sacred doctor-patient covenant. The future is very glorious if a proper balance between technology, clinical skills, and humane values is achieved.

REFERENCES

6. https://www.nature.com/articles/d41586-023-00107-z

Announcement

Association of Physicians of India (API) is launching Membership drive starting from 15th April to 15th August 2023.

Life membership of API is being offered to all eligible physicians at a discounted membership fee of `8,850/- inclusive of GST against the existing fee of `13,098/-.

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Thyroid Function in Newly Diagnosed HIV-positive Patients

Soutrik Kumar Dutta1*, Bipul Chandra Kalita2

Received: 22 December 2022; Accepted: 16 February 2023

Abstract

Background: As of 2019, the highest prevalence of human immunodeficiency virus (HIV) in India is seen in the Northeastern states. Endocrine and metabolic disturbances can occur in HIV infection. Thyroid dysfunction is one of the common endocrinopathies. In HIV infection, thyroid function abnormalities are seen in about 4–35% of adult patients. Thyroid function abnormalities range from overt hypothyroidism, subclinical hypothyroidism, and sick euthyroid syndrome to overt hyperthyroidism. Among them, subclinical hypothyroidism is the commonest abnormality. To our knowledge, there have been no studies from Northeastern India done in this regard.

Aims and objectives: To study the thyroid function in newly diagnosed cases of HIV infection attending anti-retroviral therapy (ART) center, Assam Medical College.

To estimate the prevalence and types of thyroid dysfunction in newly diagnosed HIV-infected individuals.

To study thyroid dysfunctions with respect to age, sex, and cluster of differentiation (CD) 4 count.

Materials and methods: Hospital-based observational study was done at a tertiary care centre of upper Assam on newly diagnosed HIV-positive patients who were not started on antiretroviral therapy and who attended the ART centre, Assam Medical College during the period of our study. History, examinations and laboratory investigations, including thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), and CD4 count, are done in all such patients, and only those who fulfilled the inclusion and exclusion criteria of our study are taken as study participants, and their findings tabulated.

Results and observations: A total of 95 newly diagnosed HIV-positive patients fulfilling the inclusion and exclusion criteria of our study were taken. In our study, a total of 36.84% of the patients had thyroid dysfunction. We got subclinical hypothyroidism, overt hypothyroidism, sick euthyroid syndrome, and overt hyperthyroidism as the types of thyroid dysfunction. Among all the types of thyroid dysfunction, subclinical hypothyroidism was the commonest abnormality in our study. Under sick euthyroid syndrome, we got only low FT3 as the biochemical abnormality. Thyroid dysfunctions were more common in females (42.3%) than males (35.8%) and were more common in the age group of 30–39 years. In the present study, among patients with thyroid dysfunction, it was seen that 51.43% of the patients had a CD4 cell count in the range 101–200 cells/mm³, whereas only 11.43% of patients had a CD4 cell count in the range <50 cells/mm³ and no patient had a CD4 cell count >500 cells/mm³.

Conclusion: In our study, we found that thyroid dysfunctions were common in newly diagnosed HIV-positive patients, the prevalence of which was much higher in the general population. Thyroid dysfunction was present in all the stages of the HIV disease.

AIM

To study the thyroid function in newly diagnosed cases of HIV infection attending ART center, Assam Medical College.

OBJECTIVES

• To estimate the prevalence and types of thyroid dysfunction in newly diagnosed HIV-infected individuals.

• To study thyroid dysfunctions with respect to age, sex, and CD4 count.

INTRODUCTION

Human Immunodeficiency virus (HIV) is a retrovirus that affects the immune system of the body. HIV is grouped into the genus Lentivirus and has two subtypes—HIV-1 and HIV-2. It is HIV-1 which causes most of the infections around the world. HIV infection is a global pandemic with significant morbidity and mortality, which has claimed 36.3 million lives so far. Globally in 2020, around 1.5 million people acquired HIV. In the case of India, there are about 23 lakh people living with HIV infection as of 2021. As of 2019, the highest prevalence of HIV in India is seen in the Northeastern states. Though Assam doesn’t count as one, it has an annual incidence of 1.33 thousand new infections estimated in 2019. Clinical manifestations in HIV infection are due to immunodeficiency as well as due to the effects of the virus itself. CD4 T cells are selectively infected by HIV. A patient’s CD4 count is regarded as a reliable measure of his or her immunologic state. Endocrine and metabolic disturbances can occur in HIV infection. Though adrenal insufficiency is the most common HIV endocrinopathy, thyroid dysfunction is also one of the common endocrinopathies. HIV infection and the endocrine system interact in a complex way that ranges from modest biochemical and hormonal abnormalities to overt glandular failure. Thyroid dysfunction can affect multiple systems of the body and can have varied clinical manifestations, which can affect the quality of life. In HIV infection, thyroid function abnormalities are seen in about 4–35% of adult patients. Thyroid function abnormalities range from overt hypothyroidism, subclinical hypothyroidism, and sick euthyroid syndrome to overt hyperthyroidism. Among them, subclinical hypothyroidism is the commonest abnormality. This is true for both highly active antiretroviral therapy (HAART) naïve and HAART-treated patients. Numerous studies have suggested that as the disease progresses, thyroid function abnormalities appear. Immunodeficiency correlates with thyroid function abnormalities. Though the prevalence of overt glandular failure in HIV patients is similar to that in the general population, the prevalence of subclinical hypothyroidism as well as subtle other biochemical thyroid abnormalities, is high in HIV-infected individuals. Numerous studies have demonstrated a relationship between CD4 count, a marker of immunodeficiency in HIV-infected individuals and thyroid dysfunctions. There have been only a few studies across India from eastern and northern parts of the country which assessed the prevalence and types of thyroid function abnormalities in newly diagnosed HIV-infected patients. To our knowledge, there have been no studies from Northeastern India done in this regard.
Northeastern India consists of the three most highly prevalent states for HIV, and Assam, being surrounded by all these highly prevalent states, receives a considerable number of patients to its various hospitals. This made us think about conducting this study.

**Materials and Methods**

- **Study place:** Assam Medical College and Hospital, Dibrugarh.
- **Study design:** Hospital-based observational study.
- **Period of study:** The study was conducted over a period of 1 year, from 1st June 2020 to 31st May 2021.

**Study Population**

All patients who were newly diagnosed as HIV positive at the Integrated and Counseling Testing Centre (ICTC) of Assam Medical College according to the National HIV guidelines and attended the ART centre of Assam Medical College and Hospital, Dibrugarh.

**Inclusion Criteria**

All cases newly diagnosed as HIV positive at the ICTC center of Assam Medical College and attended the ART centre of Assam Medical College and Hospital, Dibrugarh and were not on antiretroviral therapy.

- Patients with age >12 years.
- Patients willing to give written informed consent.

**Exclusion Criteria**

- Patients with preexisting diagnosed thyroid disorder with or without treatment or with the presence of thyroid enlargement.
- Patients with coexisting hepatitis B/C coinfection.
- Patients having kidney disease, liver disease, and diabetes mellitus.
- Pregnant patients.
- Patients on drugs known to interfere with thyroid hormones or thyroid function indices.
- Patients who underwent radiation therapy.

Ethical clearance was taken from the Institutional Ethics Committee before starting the study.

**Sample Size**

Considering a 95% confidence interval with an absolute precision of 10% and a proportion of newly diagnosed HIV-infected individuals with thyroid dysfunction to be 60.4%, as observed in the study by Tripathy et al.,25 a sample size calculated to be 95 was estimated for the present study.

A detailed clinical history, physical examination, and investigations were conducted in all the consecutive newly diagnosed HIV-infected patients who tested positive at the ICTC centre of Assam Medical College and subsequently attended the ART centre of Assam Medical College. These details were then filled up in a predesigned proforma.

A detailed history of the patients was taken at the time of presentation. Present history was elaborated with an emphasis on symptoms of thyroid disorder (if any) and also the duration of the presenting symptoms. Past history was elaborated with emphasis on any history of thyroid disorder, any presence of neck swelling, any history of diabetes mellitus, any history of liver and kidney disease, any history of opportunistic infections in HIV and malignancies, any history of blood transfusions, radiation therapy, or any surgical procedures. In personal history, subjects were enquired about the risk factors for transmission of HIV, including any use of intravenous drugs. In family history, patients were enquired about the health status of their family members, especially regarding anyone in the family living with HIV/hepatitis B or C positive status. History of intake of thyraxine, antithyroid drugs, antibiotics, anti-tubercular therapy or any drugs which are known to affect thyroid hormones were also enquired about and documented. In female patients, menstrual and obstetrical history was enquired about. A detailed general and systemic examination was done in all the patients with arthrometric measurements and with special emphasis on the presence of any thyroid enlargement and with regard to the various signs of thyroid dysfunction.

<table>
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<th>FT4</th>
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<tr>
<td>Subclinical hyperthyroidism</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Secondary hypothyroidism</td>
<td>Low/normal</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Secondary hyperthyroidism</td>
<td>High/normal</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

In literature reviews and studies, it was seen that a typical healthy HIV-negative patient has a CD4 count of >500 cells/mm³, and a CD4 cell count ≤50 cells/mm³ in HIV patients is associated with substantial mortality and morbidity. CD4 count greater than 500 cells/mm³ in HIV patients is associated with a lower risk of complications and opportunistic infections. Thus, the CD4 distribution in our study was done with these absolute values of CD4 count in mind.30

**Laboratory Parameters**

**Serum Thyroid Stimulating Hormone**

Principle used—immunometric with VITROS 5600 immunodiagnostic autoanalyzer system.

Reference range—0.47–4.68 µIU/mL.31

**Serum Free T3**

Principle used—direct competitive immunoassay technique by using VITROS 5600 immunodiagnostic autoanalyzer system.
Thyroid Function in Newly Diagnosed HIV-positive Patients

Reference range—2.77–5.27 pg/mL. 32

**Serum Free T4**
Principle used—direct competitive immunoassay technique by using VITROS 5600 immunodiagnostic system.
Reference range—0.78–2.19 ng/dL. 33

**Blood CD4 Count** 34
Technique used—flow cytometry in CD4 easy count kit by using Sysmex Partec Cyflow Counter IVD flow cytometer.

In the case of HIV patients, the absolute number of CD4 cells is more important in assessing the disease progression rather than any reference range of CD4 count calculated in the laboratory.

### Statistical Analysis
Data were collected and recorded with predesigned proforma, which were then tabulated to prepare a master chart. The statistical analysis of data was performed using the computer program Statistical Package for the Social Sciences (SPSS) (SPSS for Windows, version 21.0 Chicago, SPSS Inc.) and Microsoft Excel 2019. Results on continuous measurements were presented as mean ± SD.

### Results and Observations
A total of 95 newly diagnosed HIV-positive patients fulfilling the inclusion and exclusion criteria of our study were taken, and detailed clinical history, physical examination, and necessary laboratory investigations were done for the evaluation of the patients.

The major findings of the study are summarized below.

The mean age in our study was found to be 35.85 ± 8.89 years, with the most common age group being 30–39 years (Fig. 1).

In our study, the majority of the patients were male. The male-female ratio was 2.39:1 (Fig. 2).

In our study, mean ± standard deviation (SD) of the CD4 distribution, FT3, FT4 and TSH values was 230.82 ± 144 cells/mm³, 3.71 ± 1.13 pg/mL, 1.62 ± 0.54 ng/mL, and 3.91 ± 2.75 µIU/mL, respectively.

The maximum number of patients had a CD4 cell count in the range of 201–300 cells/mm³ (Fig. 3).

In our study, a total of 36.84% of the patients had thyroid dysfunction (Fig. 4).

We got subclinical hypothyroidism, overt hypothyroidism, sick euthyroid syndrome and overt hyperthyroidism as the types of thyroid dysfunction. Among all the types of thyroid dysfunction, subclinical hypothyroidism was the commonest abnormality in our study, followed by sick euthyroid syndrome and, subsequently, overt hypothyroidism and hyperthyroidism. None of the patients with thyroid dysfunction, including overt hyperthyroidism, had any signs and symptoms of thyroid dysfunction at the time of the study.

In our study, among the patients with thyroid dysfunction, 71.43% of the patients had subclinical hypothyroidism (i.e., 26.31% of all our study participants). A total of 8.57% of the patients had overt hypothyroidism (i.e., 3.16% of all our study subjects). 2.86% of the patients had overt hyperthyroidism (i.e., 1.05% of all our study subjects). Around 17.14% of the patients had sick euthyroid syndrome (i.e., 6.32% of all our study subjects). Under sick euthyroid syndrome, we got only low FT3 as the biochemical abnormality.

Thyroid dysfunctions were more common in females (42.3%) than males (35.8%).

<table>
<thead>
<tr>
<th>Types of thyroid dysfunction</th>
<th>Number of Males</th>
<th>Number of females</th>
<th>Total number of patients (n)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overt hypothyroidism</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>8.57</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>15</td>
<td>10</td>
<td>25</td>
<td>71.43</td>
</tr>
<tr>
<td>Overt hyperthyroidism</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2.86</td>
</tr>
<tr>
<td>Subclinical Hyperthyroidism</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Sick euthyroid syndrome (low FT3)</td>
<td>5</td>
<td>1</td>
<td>6</td>
<td>17.14</td>
</tr>
<tr>
<td>Secondary hypothyroidism</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Secondary hyperthyroidism</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>11</td>
<td>35</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Types of thyroid dysfunction</th>
<th>Patients with age group (in years) (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;20</td>
</tr>
<tr>
<td>Overt hypothyroidism</td>
<td>0</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>0</td>
</tr>
<tr>
<td>Overt hyperthyroidism</td>
<td>0</td>
</tr>
<tr>
<td>Subclinical Hyperthyroidism</td>
<td>0</td>
</tr>
<tr>
<td>Sick euthyroid syndrome (low FT3)</td>
<td>0</td>
</tr>
<tr>
<td>Secondary hypothyroidism</td>
<td>0</td>
</tr>
<tr>
<td>Secondary hyperthyroidism</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Types of thyroid dysfunction</th>
<th>Patients with CD4 cell count (cells/mm³) (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤50</td>
</tr>
<tr>
<td>Overt hypothyroidism</td>
<td>2</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>2</td>
</tr>
<tr>
<td>Overt hyperthyroidism</td>
<td>0</td>
</tr>
<tr>
<td>Subclinical Hyperthyroidism</td>
<td>0</td>
</tr>
<tr>
<td>Sick euthyroid syndrome (low FT3)</td>
<td>0</td>
</tr>
<tr>
<td>Secondary hypothyroidism</td>
<td>0</td>
</tr>
<tr>
<td>Secondary hyperthyroidism</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
</tr>
</tbody>
</table>

Fig. 1: Age-wise distribution
Thyroid Function in Newly Diagnosed HIV-positive Patients

In our study, in the case of patients with thyroid dysfunction, the majority (48.57%) of the patients were in the age group of 30–39 years.

In our study, out of the patients with thyroid dysfunction, 51.43% of patients had a CD4 cell count in the range of 101–200 cells/mm³.

**Discussion**

In our study, 36.84% of the patients had thyroid dysfunction. We got subclinical hypothyroidism, overt hypothyroidism, sick euthyroid syndrome and overt hyperthyroidism as types of thyroid dysfunction, among which subclinical hypothyroidism was the commonest abnormality. Thus, it can be seen that the prevalence of thyroid dysfunction was more in HIV-positive patients as compared to the general population, where it is 5% in women and 0.5% in men.35 Even comparing a population-based study in India, which estimated thyroid dysfunction as high as 19%,36 our study found a higher prevalence of thyroid dysfunction in HIV patients. Saha et al.,23 in their observational study on newly diagnosed HIV-positive patients conducted in India, found similar prevalence and similar types of thyroid dysfunctions except for sick euthyroid syndrome. They also found subclinical hypothyroidism to be the commonest. However, Dev et al.,18 in their study on newly diagnosed HIV-positive patients done in India, found a higher prevalence of thyroid dysfunctions but with similar types except for overt hyperthyroidism. They also found subclinical hypothyroidism to be the commonest. Variation in pattern and prevalence may be due to the selection of patients with different rates of disease progression, other comorbid conditions and different clinical stages in different studies.

Among patients with thyroid dysfunction, 26.31% of the study participants had subclinical hypothyroidism. Saha et al.,23 Meena et al.,37 and Dev et al.,18 in their studies observed similar results. 3.16% of the patients had overt hypothyroidism. This is similar to that observed in the studies done by Midha et al.,34 Noureldeen et al.,38 1.05% of the patients had overt hyperthyroidism. This is similar to the observations made by Noureldeen et al.38 In European studies done on the general population, overt hyperthyroidism was 0.8% in women and 0.48% in men.39 So, the prevalence of hyperthyroidism found in HIV patients is not much different from what is observed in the general population. 6.32% of the patients had sick euthyroid syndrome. In sick euthyroid syndrome, we got only low FT3 as the biochemical abnormality. This is similar to the studies done by Noureldeen et al.,38 and Dev et al.18

In our study, thyroid dysfunctions were more common in females than males in our study. This finding is similar to the observations made in the general population, where thyroid dysfunctions, in general, are seen more commonly in females than males.35 In the studies by Qurino et al.17 and Vohra et al.,40 it was seen that thyroid dysfunctions were more common in females than males. However, Saha et al.,23 in their study found no association of gender with any of the thyroid dysfunctions. Thus, large case-control studies are needed to ascertain the association of gender with thyroid dysfunction.

In our present study, 48.57% of the patients with thyroid dysfunction were aged between 30 and 39 years. In studies by Parihar et al.,21 and Vohra et al.,40 similar findings were noted. However, Saha et al.,23 and Nelson et al.41 in their studies found no association of age with thyroid dysfunctions. Thus, large case-control studies are needed to ascertain the association of age with thyroid dysfunction.

In the present study, among patients with thyroid dysfunction, it was seen that 51.43% of the patients had a CD4 cell count in the range of 101–200 cells/mm³, followed by 25.71% of patients in the CD4 cell count range 51–100 cells/mm³ whereas only 11.43% patients had CD4 cell count in the range <50 cells/mm³ and no patient had a CD4 cell count >500 cells/mm³. In the case of overt hypothyroidism, 66.66% of the patients had CD4 cell counts ≤50 cells/mm³. In the case of subclinical hypothyroidism, 60% of the patients had a CD4 cell count in the range of 101–200 cells/mm³. In the case of sick euthyroid syndrome, 50% of the patients had a CD4 cell count in the range of 101–200 cells/mm³. In studies by Saha et al.,23 and Parihar et al.,21 they found the majority of the patients with thyroid dysfunction had a CD4 cell count below 250 cells/mm³. They also observed that most of the patients with subclinical hypothyroidism had a CD4 cell count below 250 cells/mm³. In studies by Ji et al.16 and Sachdeva et al.,42 it was observed that the CD4 cell counts in cases of overt hypothyroidism were the lowest among all other thyroid dysfunctions. They also showed that CD4 cell counts were high in cases of hyperthyroidism when compared with hypothyroidism. However, a prospective study by Nelson et al.41 done on HIV patients had not found any association between thyroid function and CD4 cell counts.

**Conclusion**

In our study, we found that thyroid dysfunctions were common in newly diagnosed HIV-positive patients, the prevalence of which was much higher in the general population. Thyroid dysfunction was present in all the stages of the HIV disease. We found subclinical hypothyroidism, overt hypothyroidism, overt hyperthyroidism, and sick euthyroid syndrome as the principal types, among which subclinical hypothyroidism was the most common.

Low CD4 cell count was an important indicator of the risk of thyroid dysfunction in our study. Thyroid dysfunction, which may be subclinical in the early stages of the disease, may become overt and symptomatic with the fall of CD4 cell count.

As subclinical hypothyroidism remains the most common thyroid abnormality in patients with HIV infection, we recommend screening thyroid function in patients with HIV infection with severe immunodeficiency. HIV is here
Thyroid Function in Newly Diagnosed HIV-positive Patients

to stay, but we should aim that individuals should be free of any morbidity owing to the complications like thyroid dysfunctions. Thus, we should invest our efforts to improve the quality of life.

REFERENCES

34. Sysmex Partec. Instructions for Use CD4 easy count kit. Munster:Sysmex Partec Gmbh;2008
A Study of Thyroid Profile and Lipid Profile in Patients with Chronic Kidney Disease with or without Hemodialysis in a Tertiary Care Hospital

Nikhil Gupta1, Sulakshna Dahiya2, Pankaj Bansal3, Satish Kumar4, Ashok K Agarwal5

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ABSTRACT

Background: Chronic kidney disease (CKD), due to increasing frequency and prevalence, has become one of the leading public health issues. The Kidney Disease Outcome Quality Initiative (KDOQI) defines CKD as kidney injury or a reduction in the glomerular filtration rate (GFR) to <60 mL/minute/1.73 m² for at least 3 months. This study aims to compare the effects of decreased renal function on thyroid profile and lipid profile in CKD patients.

Materials and methods: This is a prospective cross-sectional observational study conducted among the patients attending Outpatient Department/Inpatient Department (OPD/IPD) at the School of Medical Sciences & Research, Sharda Hospital, Greater Noida, Uttar Pradesh, India, in known cases of CKD, irrespective of the treatment/stage of CKD. All patients of >18 years of age with CKD were included in the study.

Result: A total of 200 patients who met the inclusion criteria were included after obtaining detailed informed consent, of which 100 were cases and 100 were controls. The mean age of patients in the study was 47.74 years, with the mean age in patients with CKD 52 years, and the control was 43 years. The mean level of triglycerides (TGs) was significantly higher among the cases, and the high-density lipoprotein (HDL) was significantly lower among cases compared to controls (p < 0.05). Pearson's correlation between thyroid-stimulating hormone (TSH) with creatinine showed a weak albeit significant positive association (r = 0.200; p < 0.05).

Conclusion: Our study shows a higher incidence of alteration in thyroid profile and dyslipidemia among the patients with CKD compared to controls. There is a necessary need to screen routinely for hypothyroidism and dyslipidemia among patients with CKD. Importantly, thyroid hormone levels and their effects on the progression of CKD have not been studied exhaustively.

Introduction

As a consequence of ever-rising life expectancy, CKD has become one of the foremost challenges to the public health system. Its frequency and prevalence have increased over the past decades. K/DQOI defines CKD as kidney injury or a decrease in GFR of <60 mL/minute/1.73 m² for a period of 3 months. Chronic kidney disease (CKD) patients, especially those who have end-stage renal disease (ESRD) and who are managed with either intermittent hemodialysis (HD), peritoneal dialysis, or renal transplantation, have a greater risk of developing cardiovascular disease (CVD). Patients with CKD are more likely to die because of CVD than due to complications arising out of ESRD and renal replacement therapy (RRT).

When compared to the general population, the incidence of CVD is significantly higher in patients with CKD. This is due to numerous risk factors frequently associated with CKD. The risk factors can be the ones that are usually linked with CVD in the universal population, like age, gender, diabetes, obesity, hypertension, and dyslipidemia. There are also certain risk factors that are exclusive to patients of CKD; these are uremia, anemia, hyperhomocysteinemia, mineral bone disease-CKD with hyperparathyroidism, increased oxidative stress, hypoalbuminemia, and chronic inflammation.

It has been frequently observed that a decrease in renal function usually affects the function of the thyroid gland. However, the association between thyroid hormone levels and the progression of CKD has not been studied exhaustively. CKD disrupts the working of the hypothalamus-pituitary-thyroid axis and also affects the peripheral metabolism of thyroid hormone. Previous studies have shown that a low triiodothyronine (T3) and subclinical hypothyroidism are the most frequent thyroid gland disorder which is seen in patients of CKD.

Another common complication of CKD is dyslipidemia. Lipid profile is greatly affected by the grade of kidney function (GFR) and the extent of proteinuria. Hypertriglyceridemia due to an increase in TG-rich lipoproteins (very-low-density lipoprotein (VLDL), chylomicrons, and their fragments) is typically seen in patients with CKD.

The mechanism which is most prominent in the raised levels of TG is delayed catabolism which occurs because the action of hepatic TG lipase and peripheral lipoprotein lipase is reduced. An increase in hepatic production of TG-rich lipoproteins also contributes to hypertriglyceridemia.

Low-density lipoprotein (LDL) particles that are smaller, denser, and more atherogenic are not usually elevated in patients with CKD. However, oxidized LDL and intermediate-density lipoproteins, which are atherogenic, are increased.

Materials and Methods

Study Type
Prospective cross-sectional observational study.

Study Site
Patients attending the School of Medical Sciences and Research, Sharda Hospital, Greater Noida, Uttar Pradesh, India.

Study Duration

Study Participants
A total of 100 newly diagnosed and known CKD cases were involved in the study, along with an equivalent number of controls after taking informed consent from the patients (cases) and the controls.

After the approval of the Institutional Ethics Committee, this study was conducted on different age groups of patients who have...
A Study of Thyroid Profile and Lipid Profile in Patients with CKD

Inclusion Criteria
- All patients of CKD aged >18 years with a history of or newly diagnosed CKD.
- CKD patients on either HD or conservative management.

Exclusion Criteria
- Patients with acute kidney injury or a history of renal transplantation.
- History of any hematological disorder.
- Patients with a history of any renal malignancy or on chemotherapy.
- Patients with autoimmune disorders.
- Patients in any stage of pregnancy.
- Patients with a history of use of nephrotoxic drugs/lipid-lowering agents/thyroid hormone-altering medications.

Statistical Analysis
All the patient’s data was recorded in a patient pro forma sheet and entered in Microsoft Excel. The demographic details of the patients were summarized as frequency, percentage, mean, and standard deviation (SD). The data is represented using tables, figures, etc., as per need (Table 1). The statistical difference between the continuous variable was analyzed using the student’s t-test, and categorical variables were analyzed using the Chi-squared test. Pearson’s correlation was used to analyze the strength of the association between the continuous variables. A p-value of <0.05 was considered statistically noteworthy, and all the statistical analysis was executed by means of Statistical Package for the Social Sciences version 21, operating on Windows 10.

Results
A total of 200 subjects were enrolled after obtaining informed consent which included 100 patients with CKD and 100 healthy controls. The average age of subjects in the present study was 47.74 years, with the mean age in patients with CKD being 52 years and for control was 43 years (Table 2 and Fig. 1).

In studying the gender distribution among the study subjects, it was found that among the enrolled subjects, 40.5% were females, and 59.5% were males (Fig. 2).

The distribution of CKD patients in the study according to the mode of management with or without HD. Among the 100 enrolled cases of CKD, 44 patients were on maintenance HD, while 66 patients were taking medical management (Table 3).

On comparing the mean of urea and creatinine between the two study groups, it was observed that a higher proportion of patients with CKD had raised urea and creatinine values as equated with the control group (Table 4 and Fig. 3).

On comparing the thyroid profile between the study groups, the mean value of T3, thyroxine (T4), and TSH was found to be 3.3 ng/mL, 9.9 µg/mL, and 6.6 µIU/mL, respectively, in the CKD patients (Table 5 and Fig. 4).

On comparing the lipid profile between the two study groups, dyslipidemia was more prevalent amongst the patients with CKD as compared to the control group (Table 6 and Fig. 5).

Table 1: CKD classification based upon GFR and albuminuria

<table>
<thead>
<tr>
<th>GFR stages</th>
<th>GFR (mL/minute/1.73 m²)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>≥90</td>
<td>Normal or high</td>
</tr>
<tr>
<td>G2</td>
<td>60–89</td>
<td>Mildly decreased</td>
</tr>
<tr>
<td>G3a</td>
<td>45–59</td>
<td>Mildly to moderately decreased</td>
</tr>
<tr>
<td>G3b</td>
<td>30–44</td>
<td>Moderately to severely decreased</td>
</tr>
<tr>
<td>G4</td>
<td>15–29</td>
<td>Severely decreased</td>
</tr>
<tr>
<td>G5</td>
<td>&lt;15</td>
<td>Kidney failure (add D if treated by dialysis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Albuminuria stages</th>
<th>AER (mg/day)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>&lt;30</td>
<td>Normal to mildly increased (may be subdivided for risk prediction)</td>
</tr>
<tr>
<td>A2</td>
<td>30–300</td>
<td>Moderately increased</td>
</tr>
<tr>
<td>A3</td>
<td>&gt;300</td>
<td>Severely increased (may be subdivided into nephrotic and nonnephrotic for differential diagnosis, management, and risk prediction)</td>
</tr>
</tbody>
</table>

Table 2: Showing the mean age of patients

<table>
<thead>
<tr>
<th></th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>200</td>
<td>18</td>
<td>80</td>
<td>47.74</td>
</tr>
</tbody>
</table>
A Study of Thyroid Profile and Lipid Profile in Patients with CKD

Table 3: Table showing the distribution of CKD patients according to the mode of management

<table>
<thead>
<tr>
<th>Patients on maintenance HD</th>
<th>Patients not on maintenance HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>44</td>
<td>66</td>
</tr>
</tbody>
</table>

Table 4: Comparison of mean of urea and creatinine between the study groups

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Mean</th>
<th>SD</th>
<th>Cases</th>
<th>Mean</th>
<th>SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea in mg/dL</td>
<td></td>
<td>22.39</td>
<td>0.07</td>
<td>66.34</td>
<td>50.65</td>
<td></td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Creatinine in mg/dL</td>
<td></td>
<td>0.88</td>
<td>0.29</td>
<td>4.75</td>
<td>3.23</td>
<td></td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

**, statistically significant

Table 5: Comparison of the thyroid profile between the study groups

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Mean</th>
<th>SD</th>
<th>Cases</th>
<th>Mean</th>
<th>SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3</td>
<td></td>
<td>115.5</td>
<td>29.0</td>
<td>3.3</td>
<td>1.4</td>
<td></td>
<td>0.01**</td>
</tr>
<tr>
<td>T4</td>
<td></td>
<td>9.3</td>
<td>2.4</td>
<td>9.9</td>
<td>3.6</td>
<td></td>
<td>0.146</td>
</tr>
<tr>
<td>TSH</td>
<td></td>
<td>7.6</td>
<td>1.4</td>
<td>6.6</td>
<td>2.9</td>
<td></td>
<td>0.01**</td>
</tr>
</tbody>
</table>

**, statistically significant

Table 6: Comparison of lipid profile between the two study groups

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Mean</th>
<th>SD</th>
<th>Cases</th>
<th>Mean</th>
<th>SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol in mg/dL</td>
<td></td>
<td>171</td>
<td>13</td>
<td>171</td>
<td>46</td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td>TGs in mg/dL</td>
<td></td>
<td>136</td>
<td>19</td>
<td>287</td>
<td>99</td>
<td></td>
<td>0.01**</td>
</tr>
<tr>
<td>LDL in mg/dL</td>
<td></td>
<td>83</td>
<td>7</td>
<td>47</td>
<td>11</td>
<td></td>
<td>0.01**</td>
</tr>
<tr>
<td>HDL in mg/dL</td>
<td></td>
<td>51</td>
<td>8</td>
<td>26</td>
<td>7</td>
<td></td>
<td>0.01**</td>
</tr>
<tr>
<td>VLDL</td>
<td></td>
<td>25</td>
<td>3</td>
<td>16</td>
<td>7</td>
<td></td>
<td>0.01**</td>
</tr>
</tbody>
</table>

**, statistically significant

and controls were 100 healthy controls. The mean age of participants in the present study was 47.74 years. The mean age was 51.18 ± 11.03 and 62.52 ± 11.95 years in control and CKD patients, respectively. Among 100 CKD patients, 40% (n = 40) were females, and 60% (n = 60) were males.

Among the study participants (cases and controls), the majority were male patients (59.5%), and 40.5% were female patients. The male-to-female ratio was found to be 1.46:1. The levels of urea and creatinine increased significantly in CKD patients when compared to the control population. Blood urea in CKD patients was 66.34 ± 50.65 mg/dL (p < 0.0001), and serum creatinine was 4.75 ± 3.23 mg/dL (p < 0.0001), whereas, in control, blood urea was 22.39 ± 0.07 mg/dL and serum creatinine was 0.88 ± 0.29 mg/dL. Serum proteins were also significantly decreased in the CKD group 5.40 ± 7.03 gm/dL (p < 0.0001) vs 7.44 ± 0.53 gm/dL in controls.

In studying the correlation between the lipid profile amongst CKD patients to healthy controls in the current study, we found that there was a greater occurrence of dyslipidemia in the patients diagnosed with CKD. The value of TGs in the controls (mean value 136 ± 19) was found to be lower as compared to patients with CKD (mean value 287 ± 99) (p > 0.05).

On studying the thyroid profile in the two study groups, it was concluded that a positive correlation exists between thyroid dysfunction and CKD (low T3 levels in the CKD patients with a mean value of 3.3 ± 1.4, p < 0.01) as compared to the study subjects (mean value of T3 in the study subjects 115.5 ± 29).

In a 2013 study conducted by Rajagopalan et al., it was found that in patients with CKD, the levels of T3 and T4 were significantly reduced, while the TSH levels remained unchanged when compared to healthy controls. In this study, they also found that there was a significant negative association between thyroid hormones and blood urea and creatinine levels.13

In another study conducted by Khatiwada et al. in Nepal, it was found that patients with CKD had abnormal thyroid functions. In this study, subclinical hypothyroidism was found to be strongly associated with CKD. This study also found a significant association between the progression of CKD and abnormalities of thyroid function.14

In another study conducted by Rajeev et al., it was found that in patients with CKD,
A Study of Thyroid Profile and Lipid Profile in Patients with CKD

Table 7: Showing Pearson’s correlation between TSH and creatinine among the study participants

<table>
<thead>
<tr>
<th>TSH</th>
<th>Pearson’s correlation</th>
<th>Creatinine in mg/DL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Significant</td>
<td>0.004</td>
</tr>
</tbody>
</table>

**, statistically significant

The levels of total T3, total T4, albumin, and serum protein are significantly reduced when compared to controls. TSH levels were found to be significantly raised in the same study. These results are similar to the present study. We concur that patients with CKD have significant thyroid abnormalities, and these should be interpreted carefully.15

In the present study, the Pearson’s correlation of TSH with creatinine was found to be a weak significant positive association, with \( r = 0.200, p < 0.05 \) (Table 7). In the study by Srivastava et al., Pearson’s correlation coefficient revealed a nonsignificant relationship between the levels of urea in blood and serum TSH \( (r = 0.236, p = 0.069) \) and the creatinine clearance and serum TSH \( (r = 0.206, p = 0.114) \). There is a weak positive association between creatinine levels and TSH \( (r = 0.248, p = 0.049) \). Thyroid hormone levels were found to be significantly lower in nondialyzed CKD patients compared to healthy controls.16

Dyslipidaemia was seen among the patients with CKD. The mean level of TGs was significantly higher among the cases, and the HDL was significantly lower among the cases as compared to controls \( (p < 0.05) \). In the study by Aryee et al., the TG, total count, LDL, HDL, VLDL, and TSH levels did not show any significant difference among the stages of CKD among the study subjects. However, the free-T4 (FT4) and free-T3 (FT3) levels were meaningfully different between the stages of CKD. The study concluded that higher levels of FT3 and FT4 were associated with the occurrence of CKD and estimated GFR decline among the patients with CKD.17

In a 2013 study conducted by Chen et al., it was found that dyslipidaemias and their certain levels were independently associated with a need for RRT and rapid progression of CKD in stages 3–5. This study which was conducted on 1,080 subjects, concluded that an assessment of lipid profile might help to identify patients at risk of developing a rapidly progressive renal dysfunction.18

Strengths of Study

Dyslipidaemia and thyroid hormone dysfunction are major contributors to the early progression and increased complications in patients with CKD. These are two easily attainable parameters and, therefore, if managed timely, can slow the progression of the disease.

The presence of an equal number of healthy subjects provides more credibility to the observations made.

Limitations of Study

Small sample size and single-centric study. The study has large potential to globalize the findings and strengthen the results by conducting similar observations at multiple centers with a larger sample size which includes an equal number of males and females.

Conclusion

A prospective cross-sectional study was conducted on a total of 200 study subjects at the School of Medical Sciences and Research, Sharda Hospital, Greater Noida, Uttar Pradesh, India, on 100 CKD patients and 100 healthy controls.

Blood samples for thyroid profile, lipid profile, and kidney function test were taken. The study documented a higher incidence of alteration in thyroid profile and dyslipidemia among the patients with CKD compared to controls.

Clinicians must exercise extreme caution in patients with CKD, and regular screening for thyroid dysfunction and dyslipidemia should be carried out. This, in turn, may contribute to decreased CVD risk in patients with CKD so that timely intervention and proper preventive measures can be undertaken.

References

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Program to Enhance Well-being and Psychospiritual Understanding Implications in Indian Medical Care Perspective

Anirban Pal1,*, Puranava Mukhopadhyay2, Nidhi Dawar Pal3

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Abstract

Background: Spirituality is an important dimension of life. The medical practitioner’s well-being is an under-appreciated priority in India. As research on spirituality is minimal, this study attempts to introduce an online 6-week Eastern spirituality-based educational program for physicians. The primary aim was to see the effects of the intervention on the well-being of the participants. The secondary aim was to form an opinion about an extension to medical practice.

Materials and methods: A total of 60 medical practitioners were randomized into two groups—one attended the spirituality sessions while the other placebo “self-care” sessions. Quantitative outcome measures were Warwick-Edinburg Mental Well-being Scale (WEMWBS) and World Health Organization (WHO) Well-being Index (WHO-5) noted pre and postprogram. Qualitative data was collected to support the quantitative outcomes. Statistical tests used were unpaired and paired t-tests for quantitative data. A 5-point Likert scale and Cochran’s Q test were used for the qualitative data.

Results: In the spirituality group, postsession WEMWBS and WHO-5 scores improved with p < 0.0001 and p = 0.0033, respectively. Regarding qualitative data, 94.44% of physicians “agreed/strongly agreed” in favor of the benefits of sessions with p = 0.0242 and Q = 5.0793. A total of 86.67% of physicians felt the sessions have helped them to understand other’s spirituality-related problems and made them more confident to discuss spirituality with others.

Conclusion: The online Eastern spirituality program had a positive impact on the well-being of Indian medical practitioners. There appears to be a potential for extension to the medical care setting. The results need to be substantiated by further studies.

Introduction

Spirituality is an important dimension of human existence. Spirituality is a complex construct made up of multiple aspects as diverse as beliefs, rituals, coping, relationship with the transcendent, the meaning of life, and much more.1 Previously spirituality was thought to unfold within a religious context but now it is a separate construct itself. Eastern spirituality is a distinct entity with practically no similarity with its Western counterpart. In the extended biopsychosocial model of medical care, spirituality forms the fourth dimension.2 In this research work, we refer to spirituality as “the aspect of humanity that refers to the way individuals seek and express meaning and purpose and the way they experience their connectedness to the moment, to self, to others, to nature and to the significant or sacred.” (United States Consensus Committee 2009).3

Spirituality plays a prime role in the lives of millions of Indians. There is a wide variation in the ways spirituality is understood and practiced throughout India. In the Indian scenario, eastern spirituality is not a single entity but an assembly of concepts, affiliations, practices, cultural influences, and perspectives influencing day-to-day lives. Spirituality can help one to find hope, purpose, and meaning in life and improve emotional adjustment.4 A high proportion of doctors in India experience occupational stress and depression.5 The clinician’s well-being is an underappreciated priority in this subcontinent. Indian physicians may find spirituality significant and fulfilling in their own lives.6 In addition to achieving personal well-being, there can be a unique benefit of spirituality for physicians. A better psychospiritual understanding may help them to support their patients to find meaning and acceptance amid their suffering.7 The medical training in India neither involves spirituality nor any structured programs available to orient physicians to Eastern spirituality. But nearly 90% of medical institutions in Western countries have something about spirituality in their curricula.8 Unfortunately, the Western psychospiritual educational models have no practical implications from the Indian perspective. The lack of understanding, unavailability of training, personal reservations, and apprehension in addressing spiritual issues make Indian physicians stressed, uncomfortable, and insecure in real-life situations. Being a very sensitive and emotionally charged issue, research with practical application of Eastern spirituality-based interventions in the Indian medical care perspective remains limited.

The researchers are physicians with in-depth knowledge of spirituality and this study is an early attempt to introduce a semi-structured time-limited Eastern spirituality-based educational group program for the peers. An online mode of delivery that can be attended from home, clinic, or hospital was deliberately chosen to respect the time management aspect of professionally burdened Indian physicians. The primary aim of the study was to see the effects of the program on the well-being of participants using the WEMWBS and WHO Well-being Index (WHO-5). Qualitative data was used to support the quantitative outcomes and indirectly reflect the psychospiritual understanding. The secondary aim was to form an opinion about an extension to medical practice settings.

Materials and Methods

Study Design and Setting

This prospective randomized trial was conducted from October to December 2021. The study was conducted by a medical institution in collaboration with a meditation center based in West Bengal, India. Institutional Ethical Approval was obtained and the study was registered in the Clinical Trial Registry of India.

Sample Size Calculation

From the previous available studies using WEMWBS and WHO-5, we calculated our sample size to detect a standard deviation (SD) of 8.6 and 14.2 of the expected difference...
of means in the above scales, respectively, with a power of 80% to detect this difference using unpaired t-test and paired t-test with type I error (α) of <5%. The calculated minimum sample size in each group was 26 using WEMWBS and 21 using WHO-5. The overall minimum size in each group was 26 using both instruments. Hence, we started our study with 60 participants.

### Study Participants

The physicians and practitioners involved in primary care were informed about the study. Those interested to attend the program were asked to contact the study coordinators. A total of 60 participants were recruited based on inclusion and exclusion criteria. Inclusion criteria—(1) age 18–65 years, (2) have access to an electronic device with an internet connection, and (3) not suffering from any psychiatric illness. Exclusion criteria—(1) have a significant medical illness or comorbidity and (2) have previous experience of attending an Eastern spirituality course.

Informed consent was obtained from all participants via e-mails. The participants were subjected to an online interview with a clinical psychologist to exclude any significant mental health issues which escaped screening. If found, they were not included in the study. The participants were randomized into two groups. Group S attended online spirituality sessions while Group C attended “self-care” sessions (Flowchart 1). The “self-care” sessions were placebo sessions with the same facilitator of similar duration, excluding the concepts of Spirituality. It included discussions on ways of dealing with professional stress, the importance of taking work breaks, effective ways of utilization of spare time, and different relaxation techniques. Candidates of Group C were later offered to join the online spirituality sessions after the study period, which is beyond the scope of the present discussion.

### Intervention

The educational program was an online 6-week psychospiritual intervention. The goal was to use spirituality to develop positive spiritual coping and achieve wellness in life. A nonreligious, secular method was adopted based on the core principles of Hinduism and Buddhism, devoid of any particular rituals. The focus of the intervention was to help participants understand their problems from a spiritual perspective, to gain a greater sense of hope, accept responsibility for their actions, and to experience a sense of self-worth. Positive virtues like compassion, gratitude, and acceptance were advised to be applied in daily life situations. Compassion was given utmost importance as it helps to promote well-being. Group activities included informal talk, discussions, and meditations. Daily 10 minutes of home practice of meditations were encouraged as it produced a calming effect. A physician having adept knowledge of spirituality and meditations served as a facilitator. There were six online group sessions in the program each of 1.5 hours duration every week. The details of the program are given in Table 1. At the end of the session, participants were encouraged to share their experiences and newer understanding regarding spirituality. The participants maintained a daily practice log and were monitored by the facilitator through a social media app. Any participant experiencing any discomfort/side effects was instructed to report to the facilitator.

### Outcome Variables

Demographic data was collected before the program. The data of the participants included the person’s age, gender, and religious affiliation. In terms of religious affiliation, all the participants were incidentally found to be Hindus. Quantitative variables were noted twice, before, and after the program. Qualitative data was collected from Group S at the end of the program. All the data were collected via e-mails. The researcher who noted the outcome variables had no idea of the patient’s allocation and the intervention received.

### Quantitative Variables

The researchers wanted to explore the well-being of the physicians, mostly the psychological aspect. WEMWBS is a measure of mental well-being focusing on positive aspects of mental health. WEMWBS is a tool commonly used in previous studies.
on spirituality. In addition, the 5-item World Health Organization Well-Being Index (WHO-5) was used to assess subjective psychological well-being.

**Qualitative Variable**

A questionnaire was formed with six questions—(1) this spirituality course is helpful to deal with my life problems, (2) this spirituality course is helpful to reach my peace of mind, (3) this spirituality course has made my concepts more clear, (4) this spirituality course has made me more confident to discuss spirituality with others, (5) this spirituality course is helpful to understand others’ spirituality-related problems, and (6) spirituality course like this is very much needed for the well-being of our society. The responses are noted on a 5-point Likert scale—strongly disagree = 1, disagree = 2, neither disagree nor agree = 3, agree = 4, and strongly agree = 5.

**Statistical Analysis**

Data from WEMWBS and WHO-5 scales were treated as continuous. Data were tested for equality of variance using Levene’s test. Normality was tested using the Shapiro–Wilk test. The analysis of continuous data was performed using unpaired and paired t-tests. Baseline characteristics (age and sex) were tested using unpaired t-tests for age and Chi-squared ($\chi^2$) test. Qualitative data via a 5-point Likert scale was collected in response to a 6-point questionnaire in Group M postsession. This Likert scale was analyzed via dichotomous division: “agree/strongly agree” and neither agree nor disagree/disagree” and interpreted via Cochrans’ Q test. The statistical software used was Statistical Package for the Social Sciences statistics for Windows 7® version 18.0.0 (Chicago, Illinois 60606-6412), GraphPad Prism® InStat version 5.0 (California 92037-3219) and Microsoft® Office Excel 2010 (Washington: Microsoft). Results were presented in mean (SD) and percentage format. $p < 0.05$ was considered statistically significant.

**RESULTS**

Baseline characteristics (age and sex) were similar between the cases (Group S) compared to the controls (Group C) (Table 2).

**Quantitative Variables**

By unpaired t-test, the mean scores in Group S when compared to Group C in postsession increased significantly in both WEMWBS and WHO-5 scales with $p < 0.0001$ and $p = 0.0033$, respectively. Effect size (measured by Cohen’s d) was $d = 1.2827$ for WEMWBS and $d = 0.7909$ for WHO-5, respectively (Table 3).

Within Group S comparison by paired t-test showed that the postsession scores increased significantly in both WEMWBS and WHO-5 scales with $p < 0.0001$ in each respectively. Effect size (measured by Cohen’s d) was $d = 1.0025$ for WEMWBS and $d = 0.7290$ for WHO-5, respectively (Table 3).

The difference in mean scores in Group S was not significant when compared to Group C before the session by unpaired t-test; as also within Group C pre and postsession comparison by paired t-test.

**Qualitative Variables**

The Group S postsession 6-point questionnaire yielded the following results—only two responses out of 30 (6.67%) to questions 3 and 4; and four responses out of 30 (13.33%) to question 5 have remained “neither agree nor disagree.” Only two responses out of 30 (6.67%) “disagreed” only in question four of the postsession questionnaire (Fig. 1). Around 100% of responses (30/30) to questions 1, 2, and 6 have either “agreed” or “strongly agreed” in favor of meditation sessions. A total of 86.67% of responses (26/30) to questions 4 and 5 and 93.33% of responses (28/30) to question 3 have either “agreed” or “strongly agreed” in favor of spirituality sessions (Fig. 1).

Overall 94.44% (170/180) of responses have either “agreed” or “strongly agreed” to all questions taken cumulatively and only 5.56% (10/180) of responses have either remained “neither agree nor disagree” or “disagreed” with the postsession questions. The above dichotomous proportions, when compared by nonparametric Cochrans’ Q test showed that the proportion of responses (94.44%) who “agreed/strongly agreed” in favor of spirituality session was significantly greater
The primary aim of the study was to see the effects of an online Eastern spirituality-based program on the well-being of the participants. The postsession mean scores of both WEMWBS and WHO-5 in the spirituality group improved significantly with \( p < 0.0001 \) and \( p = 0.0033 \), respectively compared to control groups. So the spirituality program significantly affected the well-being of the physicians.

The qualitative data asked about making the spiritual concepts clearer, getting the confidence to discuss spirituality with others, and understanding others’ spirituality-related problems. A major proportion (94.44%) of participants “agreed/strongly agreed” in favor of the benefits of a spiritual educational program with \( p = 0.0242 \) and \( Q = 5.0793 \). While 86.67% of physicians felt the sessions helped them to understand other’s spirituality-related problems and made them more confident to discuss spirituality with others. The secondary aim was a scope of extension to medical practice settings. It is difficult to form a definitive opinion with the parameters studied in this particular research work but the quantitative and qualitative outcomes indirectly see a potential for extension to medical practice settings.

The study results are in line with previous studies conducted in other countries. A study concluded that spirituality among healthy individuals was associated with higher health-related quality of life.11 Even in persons with chronic health problems spirituality can be beneficial.12 Previous study results on physicians are quite encouraging. There are possible protective associations of certain dimensions of spirituality on the maladaptive behaviors of physicians.13 Spirituality-based wellness practices for physicians can negate negative behavioral effects of the profession.14 Attention to health including spiritual health helps physicians to protect against burnout and enhances both coping and caregiving abilities.15 A review comments that the better spiritual well-being of resident physicians was associated with a better sense of work accomplishment, overall health, decreased burnout, and depressive symptoms.16 A systemic review showed consistent independent associations between spiritual well-being and quality of life.17 Another systemic review found Spirituality to have benefited by improving quality of life and promoting health behaviors.18

**Eastern Spirituality as a Distinct Construct**

Eastern spirituality differs significantly from spirituality practiced in the Western world. In Eastern spirituality, the concept of human

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### Table 3: Representation of WEMWBS and WHO Well-being Index (WHO-5) Scores pre and postsession in Group S and Group C

<table>
<thead>
<tr>
<th></th>
<th>Group S (N = 30) Mean (SD)</th>
<th>Group C (N = 30) Mean (SD)</th>
<th>Group S vs C pre vs postsession</th>
<th>Group S (pre vs postsession)</th>
<th>Group C (pre vs postsession)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unpaired ( t )</td>
<td>Unpaired ( t )</td>
<td>Paired ( t )</td>
<td>Paired ( t )</td>
<td>Paired ( t )</td>
</tr>
<tr>
<td><strong>WEMWBS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presession</td>
<td>50.1333 (9.1942)</td>
<td>49.3000 (8.9178)</td>
<td>( p = 0.7229 )</td>
<td>( p &lt; 0.0001^* )</td>
<td>( p &lt; 0.0001^* )</td>
</tr>
<tr>
<td>Postsession</td>
<td>58.2667 (6.8628)</td>
<td>48.7667 (7.9119)</td>
<td>( t = 0.3564 )</td>
<td>( t = 4.9680 )</td>
<td>( t = 5.2332 )</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( df = 58 )</td>
<td>( df = 58 )</td>
<td>( df = 29 )</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( 95% CI = -3.85 to 5.51 )</td>
<td>( 95% CI = 5.67 to 13.33 )</td>
<td>( 95% CI = 5.11 to 13.80 )</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( d = 0.0920 )</td>
<td>( d = 1.2827^{**} )</td>
<td>( d = 0.1002^{**} )</td>
</tr>
<tr>
<td><strong>WHO-5</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presession</td>
<td>62.9333 (15.1109)</td>
<td>61.0667 (13.9331)</td>
<td>( p = 0.6208 )</td>
<td>( p = 0.0033^* )</td>
<td>( p &lt; 0.0001^* )</td>
</tr>
<tr>
<td>Postsession</td>
<td>74.0000 (15.2496)</td>
<td>61.8667 (15.4289)</td>
<td>( t = 0.4974 )</td>
<td>( t = 3.0635 )</td>
<td>( t = 4.8478 )</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( df = 58 )</td>
<td>( df = 58 )</td>
<td>( df = 29 )</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( 95% CI = -5.65 to 9.38 )</td>
<td>( 95% CI = 4.21 to 20.06 )</td>
<td>( 95% CI = -15.74 to -6.40 )</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( d = 0.1284 )</td>
<td>( d = 0.7909^{**} )</td>
<td>( d = 0.0729 )</td>
</tr>
</tbody>
</table>

Columns 2 and 3 show the presession and postsession mean (SD) scores of WEMWBS and WHO-5 scores for Group S (case group) and Group C (control group), respectively. Column 4 shows the \( p \)-value of unpaired \( t \)-test comparison of Groups S and C prior to the beginning of the session. Column 5 shows the \( p \)-value of the unpaired \( t \)-test comparison of Groups S and C after the session. Column 6 shows within group S paired \( t \)-test comparison pre vs postsession. Column 7 shows within Group C paired \( t \)-test comparison pre vs postsession. *\( p \)-values are statistically significant. **Cohen’s \( d \) values have a large effect size.

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**Fig. 1:** Post session responses of participants regarding their views of the spirituality program

The qualitative data asked about making the spiritual concepts clearer, getting the confidence to discuss spirituality with others, and understanding others’ spirituality-related problems. A major proportion (94.44%) of participants “agreed/strongly agreed” in favor of the benefits of a spiritual educational program with \( p = 0.0242 \) and \( Q = 5.0793 \). While 86.67% of physicians felt the sessions helped them to understand other’s spirituality-related problems and made them more confident to discuss spirituality with others. The secondary aim was a scope of extension to medical practice settings. It is difficult to form a definitive opinion with the parameters studied in this particular research work but the quantitative and qualitative outcomes indirectly see a potential for extension to medical practice settings.

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### Discussion

The primary aim of the study was to see the effects of an online Eastern spirituality-based program on the well-being of the participants. The postsession mean scores of both WEMWBS and WHO-5 in the spirituality group improved significantly with \( p < 0.0001 \) and \( p = 0.0033 \), respectively compared to control groups. So the spirituality program significantly affected the well-being of the physicians.

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Eastern Spirituality as a Distinct Construct

Eastern spirituality differs significantly from spirituality practiced in the Western world. In Eastern spirituality, the concept of human
existence is based on the understanding that the human soul is from the divine. Life is a continuum and the purpose of life is liberation from the surroundings (mâyá) of this world and union with the divine. Here death is not a termination of existence but a passage to the divine. The core principles of spirituality are “union with the divine,” “being at peace,” and “preserving dignity.” The core aspects of Indian spirituality were included in the program, but a lot of concepts were not covered as considered confusing or superfluous. It is practically not possible for a simple 6-week program to capture all the diverse dimensions of Eastern spirituality.

**Indian Medical Care and Spirituality**

There is a paucity of literature and a lack of understanding about the interplay of Spirituality with health and medicine in the Indian scenario. Traditionally Western modern medicine did not incorporate spirituality, and it was considered a symptom of mental illness. Many practitioners of modern medicine in India still consider patients’ beliefs and practices as irrelevant and as problematic superstitions. Now in medical literature, there is a growing appreciation of the impact of spirituality on health as well as influencing recovery from illness. The unfamiliarity of Indian healthcare providers with spirituality is compromising the holistic goal of healthcare. A lot of Indian medical professionals still consider religion and spirituality synonymous. Programs incorporating spirituality into clinical practice are available in Western countries. But the use of chaplains, pastors, and priests for spirituality is not a practical idea in the Indian scenario. Turning to ritualistic religious practitioners for healthcare needs can be no less than a disaster. Negative religious coping can lead to greater spiritual distress, including greater anxiety, depression, and lower self-esteem. So a group of physicians with adept spiritual understanding needs to be included in the program, but a lot of concepts were not covered as considered confusing or superfluous. It is practically not possible for a simple 6-week program to capture all the diverse dimensions of Eastern spirituality.

Despite these limitations, this program provides a rudimentary framework to guide future work on Eastern spirituality in the Indian medical fraternity. This intervention can be a forerunner of more structured and standardized programs or curriculums custom-made for the healthcare community. This study opens up new gateways for further research on the integration of spirituality with medical care in the Indian context toward achieving a holistic healthcare goal.

**Conclusion**

The online Eastern spirituality-based educational program shows promising results in influencing the well-being of Indian medical practitioners. There appears a potential for extension to medical care practice. Further studies will be needed to substantiate the results.

**References**


Coagulation Abnormalities in Severe Scrub Typhus and Their Association with Complications

Deepti Singla1, Balraj Singh2, Komal Ahire3, Sanjay K Mahajan4

Received: 08 October 2022; Accepted: 11 February 2023

A B S T R A C T

Aim: To describe coagulation abnormalities and their association with complications in patients with severe scrub typhus.

Materials and methods: A cohort study was conducted among all patients of severe scrub typhus (immunoglobulin M (IgM) positive) who reported to this facility from 1st August 2019 to 31st July 2020 and met our inclusion criteria. We estimated the incidence of severe thrombocytopenia (<50,000/μL) and overt disseminated intravascular coagulation (DIC) (DIC score of ≥5). We determined the association (risk (RR) ratios) of these abnormalities with complications of scrub typhus, namely—septic shock, multiple organ dysfunction syndrome (MODS), and septic shock with MODS.

Results: In total, 71 patients were studied with a mean age of 50 ± 15.5 years, of which 45 (63.4%) were females. On presentation, fever 70 (98.5%), myalgias 22 (31.0%), loose stools 13 (18.3%), cough, vomiting, headache 11 (15.5%), altered sensorium 10 (14.1%), and pain abdomen 9 (12.7%) were main symptoms. On examination, hypotension 31 (43.7%), eschar 25 (35.2%), icterus 17 (23.9%), and rash 16 (22.5%) were noted.

The d-dimer (>0.5 μg/mL) levels were increased in all (100%) patients. Thrombocytopenia (91.5%) was the commonest hematological abnormality and 31 (43.6%) of them had severe thrombocytopenia, 25 (35.2%) patients had low fibrinogen levels (<200 mg/dL) and prothrombin time (PT >16.7 seconds) was prolonged in 20 (28.1%).

A total of 42 (59.1%) patients developed MODS, 33 (46.4%) developed septic shock, 24 (33.8%) had MODS with septic shock (17 (23.9%) developed overt DIC, and eight (11.2%) died. Severe thrombocytopenia (p = 0.028) and overt DIC (p = 0.045) were significantly associated with septic shock development.

Conclusion: In the patients admitted with severe scrub typhus; thrombocytopenia was the commonest hematological abnormality. The development of septic shock was significantly associated with severe thrombocytopenia and overt DIC.

Introduction

Scrub typhus, caused by Orientia tsutsugamushi, is an endemic disease in the “tsutsugamushi triangle,” extending from north part of Japan to Northern Australia in the South, the far eastern part of Russia in the North, and to Pakistan in the Western part.1 The recombinant enzyme-linked immunosorbent assay (ELISA) used for the detection of IgM antibodies for O. tsutsugamushi has sensitivity and specificity of 97 and 100%, respectively.2

On the basis of histopathologic studies, scrub typhus causes disseminated vasculitis with perivascularitis. O. tsutsugamushi multiplies at the inoculation site leading to necrosis of the skin, forming an eschar with regional lymph node enlargement. O. tsutsugamushi infection causes elevation of interferon α, interleukin-18 (IL-18), and IL-15 levels associated with a type 1 immune response.3 The dissemination of O. tsutsugamushi infection to vascular endothelium results in vascular injury affecting multiple organs leading to DIC with platelet consumption, vascular leak, shock, dysfunction of kidneys, liver, pulmonary edema, and meningoencephalitis.3

Pathophysiology of DIC in Sepsis

The development of sepsis is commonly associated with hemostatic abnormalities, which can range from insignificant laboratory derangements to severe DIC.3 All patients with sepsis have coagulation abnormalities ranging from mild thrombocytopenia, subclinical prolongation of clotting time to fulminant DIC.5

The intravascular activation of coagulation with a specific localization characterizes DIC. O. tsutsugamushi induces a very strong procoagulant activity leading to an excess of thrombin formation overpowering the mechanisms responsible for maintaining the anticoagulant state maintained due to the effects of protein C, antithrombin, and the tissue factor pathway inhibitor, which results into thrombosis throughout the vasculature. It also causes “consumption coagulopathy,” which includes prolonged PT and PT/international normalized ratio (INR), thrombocytopenia, hypofibrinogenemia, and an increase in D-dimer. DIC can be a hypercoagulable state initially manifesting clinically as thrombosis, embolism, and microvascular occlusion by fibrin thrombi causing tissue ischemia leading to dysfunction of multiple organs (MODS) and simultaneously a hemorrhagic disorder also due to platelets depletion, consumption of various coagulation factors, and/or accelerated plasmin formation manifesting as both thrombosis and bleeding disorders in the same patient.3

The availability of literature on the prevalence of coagulation abnormalities in scrub typhus is rather sparse.3–11

Materials and Methods

The study was conducted from 1st August 2019 to 31st July 2020 on 71 patients admitted with severe scrub typhus

Inclusion Criteria

• Age of >18 years.
• A clinically suspected scrub typhus patient with IgM antibodies positive by ELISA for O. tsutsugamushi and fulfilling criteria of severe sepsis or septic shock or MODS.

Exclusion Criteria

The patients were not willing to participate in the study.

Case Definitions

Case—a clinically suspected scrub typhus patient with IgM antibodies positive by ELISA

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Coagulation Abnormalities in Severe Scrub Typhus

Severe Scrub Typhus
A case of scrub typhus with severe sepsis or septic shock or MODS. The systemic response to proven or suspected infection plus some degree of organ hypofunction that is:

- Cardiovascular: Systolic blood pressure (SBP) of ≤90 mm Hg or mean arterial pressure (MAP) of <70 mm Hg that responds to the administration of intravenous fluids.
- Renal: Urine output <0.5 mL/kg/hour for 1 hour despite adequate fluid resuscitation.
- Respiratory: Partial pressure of oxygen/fraction of inspired oxygen of ≤250 or, if the lung is the only dysfunctional organ, <200.
- Hematological: Platelet count of <80,000/µL or 50% decrease in platelet count from the highest value recorded over the previous 3 days.
- Unexplained metabolic acidosis: pH of ≤7.30 or base deficit of ≥5 mEq/L and plasma lactate levels >1.5 times the upper limit of normal.

Septic Shock
Sepsis with hypotension (SBP of <90 mm Hg) for at least 1 hour despite fluid resuscitation or need for vasopressors to maintain SBP of >90 mm Hg or MAP of >70 mm Hg. 12

Multiple Organs Dysfunction Syndrome (MODS)
The presence of sepsis causing potentially reversible physiological derangement involving two or more organ systems was defined as MODS. 13

The patients were included in the present study after obtaining consent. A detailed clinical examination, hematological investigations, including platelet counts and biochemical investigations, were performed. All patients were treated with anti-rickettsial drugs empirically.

The following special hematological investigations were included:

- Prothrombin time (PT): Normal for PT—11.4–13.7 seconds, prolonged PT was defined as prolongation by >3 seconds.
- International normalized ratio (INR)
- D-dimer: Normal levels—<0.5 µg/mL, >0.5–<4 µg/mL were defined as moderately increased, and levels of >4 µg/mL were defined as markedly increased.
- Serum fibrinogen: Serum fibrinogen <200 mg/dL was defined as low fibrinogen. The values of serum fibrinogen were calculated as mg/dL and the calculation used was serum fibrinogen levels 100/dL = 1 gm/L.
- Platelet count: Range—normal range >1,50,000/µL, platelets count 1,50,000/µL or less was defined as thrombocytopenia, and platelet counts of <50,000/µL was defined as severe thrombocytopenia.
- Serum ferritin levels >2000 ng/mL were defined as raised levels in the study.

The DIC score was calculated as per the diagnostic scoring system for DIC proposed by the International Society for Thrombosis and Hemostasis (ISTH). 14

### Diagnostic Scoring System for DIC

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Value</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>&gt;1,00,000/µL</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>50,000–1,00,000/µL</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&lt;50,000/µL</td>
<td>2</td>
</tr>
<tr>
<td>PT prolongation</td>
<td>&gt;3 seconds</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;3–&lt; 6 seconds</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;6 seconds</td>
<td>2</td>
</tr>
<tr>
<td>Fibrinogen levels</td>
<td>&gt;1 g/L</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;1 g/L</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&lt;1 g/L</td>
<td>3</td>
</tr>
<tr>
<td>D-dimer</td>
<td>No increase</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Moderate increase</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Marked increase</td>
<td>3</td>
</tr>
</tbody>
</table>

A calculated DIC score of ≥5 was defined as overt DIC.

The data obtained was entered on a Microsoft Excel spreadsheet and Epi Info 7.1.5 for windows was used for data analysis. The patients were classified based on operational definitions. The p-value of <0.05 was considered statistically significant. This study was approved by Institutional Ethics Committee.

### Results
A total of 71 patients, ranging from 18 to 80 years (mean age was 50 ± 15.5 years), were studied. Forty five (63.4%) were females, 26 (36.6%) were males (male to female ratio 1:1.7). A total of 36 (50.7%) were aged <50 years and the majority (91.5%) patients were involved in agricultural activities, and 70 (98.5%) cases were observed during monsoon and postmonsoon season.

The details of the main clinical features noted in the study population are given in Table 1. In biochemical investigations, transaminits in 63 (87.7%), hypoalbuminemia in 62 (87.3%), hyperbilirubinemia in 34 (49.7%), hyponatremia in 30 (42.3%), and raised serum creatinine in 29 (40.8%) patients were observed.

In hematological investigations, severe thrombocytopenia (platelets <50,000/µL) was observed in 30 (42.2%) and 25 (35.2%) had leucocyte abnormalities. Of the total 71 patients, d-dimer (>0.5 µg/mL) levels were raised in all patients, PT (PT of >16.7 seconds) was prolonged in 20 (28.1%), and low fibrinogen levels (<200 mg/dL) were noted in 25 (35.2%) patients. The raised serum ferritin levels (>2000 ng/mL) were observed in 44 (61.9%) patients. The details of special hematological investigations in patients included in the study are given in Table 2.

Of the total 71 patients, only two patients required intensive care unit and 8 (11.2%) died. The details of various complications, that is, septic shock, MODS, septic shock with MODS

### Table 1: Clinical features among the study population

<table>
<thead>
<tr>
<th>Serial no</th>
<th>Clinical feature</th>
<th>Total n = 71 (%)</th>
<th>Female n = 45 (%)</th>
<th>Male n = 26 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fever</td>
<td>70 (98.5)</td>
<td>44 (97.7)</td>
<td>26 (100)</td>
</tr>
<tr>
<td>2</td>
<td>Myalgia</td>
<td>22 (31.0)</td>
<td>12 (26.7)</td>
<td>10 (38.5)</td>
</tr>
<tr>
<td>3</td>
<td>Loose stools</td>
<td>13 (18.3)</td>
<td>5 (11.1)</td>
<td>8 (30.8)</td>
</tr>
<tr>
<td>4</td>
<td>Vomiting</td>
<td>11 (15.5)</td>
<td>6 (13.3)</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td>5</td>
<td>Cough</td>
<td>11 (15.5)</td>
<td>7 (15.6)</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td>6</td>
<td>Headache</td>
<td>11 (15.5)</td>
<td>8 (17.8)</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>7</td>
<td>Altered sensorium</td>
<td>10 (14.1)</td>
<td>6 (13.3)</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td>8</td>
<td>Pain abdomen</td>
<td>9 (12.7)</td>
<td>4 (8.9)</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td>9</td>
<td>Seizure</td>
<td>2 (2.8)</td>
<td>1 (2.2)</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>10</td>
<td>Myalgia</td>
<td>22 (31.0)</td>
<td>12 (26.7)</td>
<td>10 (38.5)</td>
</tr>
<tr>
<td>11</td>
<td>Loose stools</td>
<td>13 (18.3)</td>
<td>5 (11.1)</td>
<td>8 (30.8)</td>
</tr>
<tr>
<td>12</td>
<td>Hypotension</td>
<td>31 (43.6)</td>
<td>15 (33.3)</td>
<td>16 (61.5)</td>
</tr>
<tr>
<td>13</td>
<td>Eschar</td>
<td>25 (35.2)</td>
<td>14 (31.1)</td>
<td>11 (42.3)</td>
</tr>
<tr>
<td>14</td>
<td>Icterus</td>
<td>17 (23.9)</td>
<td>8 (17.7)</td>
<td>9 (34.6)</td>
</tr>
<tr>
<td>15</td>
<td>Rash</td>
<td>16 (22.5)</td>
<td>15 (33.3)</td>
<td>1 (3.8)</td>
</tr>
</tbody>
</table>
and overt DIC, observed in the patients in the study are given in Table 3.

The relationship between various complications observed in the study population with the hematological abnormalities studied in the present study is given in Table 4. The elevated serum ferritin levels (>2000 ng/mL) were not associated with the complications studied. Thrombocytopenia was the commonest hematological abnormality. There was a significant association between the development of septic shock with overt DIC ($p = 0.045$) and severe thrombocytopenia ($p = 0.028$).

**DISCUSSION**

This study was conducted, among admitted patients of scrub typhus, to describe the association of coagulation abnormalities with the development of various complications.

Of the total 71 patients in the study, 45 (63.4%) were females and 26 (36.6%) were males. Sharma et al. and Griffith et al. also reported a higher incidence of scrub typhus in females.$^{15,2}$ The higher incidence in females may be due to the fact that in this region of our country, the females involved in agriculture work with bare hands in a sitting position, and hence their chances of exposure to mites are much higher. The majority of patients in our study were noted in the monsoon and postmonsoon months of September and October, which was similar to a study by Subbalaxmi et al.$^{16}$

In this study, fever was present in 98.5% of cases, myalgias were noted in 22 (31.0%), loose stools in 13 (18.3%), headache, cough, and vomiting in 11 (15.5%), altered sensorium in 10 (14.1%). Similar findings of our study are similar to those noted by Tsay and Chang and Mahajan et al.$^{2,17}$ In the present study, eschar was observed in 32 (35.9%), whereas a study by Griffith et al. and Tsay and Chang reported eschar in 41.6% and 60% respectively in patients of scrub typhus.$^{15,2}$

Of the total 71 patients, thrombocytopenia (<1.5 lakhs/dL) was a major finding observed in 41.6% of cases, and hence their chances of exposure to mites are much higher. The majority of patients in our study were noted in the monsoon and postmonsoon months of September and October, which was similar to a study by Subbalaxmi et al.$^{16}$

Of the total 71 patients, thrombocytopenia (<1.5 lakhs/dL) was a major finding observed in 60% of patients. Similar findings of our study are similar to those noted by Tsay and Chang and Mahajan et al.$^{2,17}$ In the present study, eschar was observed in 32 (35.9%), whereas a study by Griffith et al. and Tsay and Chang reported eschar in 41.6% and 60% respectively in patients of scrub typhus.$^{15,2}$

**Table 2**: Special hematological investigations among the study population

<table>
<thead>
<tr>
<th>Serial no</th>
<th>Investigation</th>
<th>Total</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$n = 71($%</td>
<td>$n = 45($%</td>
<td>$n = 26($%</td>
</tr>
<tr>
<td>1</td>
<td>PT (seconds)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;16.7</td>
<td>20 (28.1)</td>
<td>11 (24.4)</td>
<td>9 (34.6)</td>
</tr>
<tr>
<td></td>
<td>&gt;19.7</td>
<td>4 (5.6)</td>
<td>3 (6.6)</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>2</td>
<td>D-dimer (μg/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;0.5</td>
<td>71 (100)</td>
<td>45 (100)</td>
<td>26 (100)</td>
</tr>
<tr>
<td></td>
<td>&gt;1.0–&lt;2</td>
<td>50 (70.4)</td>
<td>40 (88.8)</td>
<td>10 (38.4)</td>
</tr>
<tr>
<td></td>
<td>&gt;2.0–&lt;4</td>
<td>10 (14.0)</td>
<td>5 (11.1)</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td></td>
<td>&gt;4</td>
<td>3 (4.2)</td>
<td>2 (4.4)</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>3</td>
<td>Serum fibrinogen (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;200</td>
<td>46 (64.7)</td>
<td>29 (64.4)</td>
<td>18 (69.2)</td>
</tr>
<tr>
<td></td>
<td>&lt;200</td>
<td>25 (35.2)</td>
<td>17 (37.7)</td>
<td>8 (30.7)</td>
</tr>
<tr>
<td></td>
<td>&lt;100</td>
<td>8 (11.2)</td>
<td>7 (15.5)</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>4</td>
<td>Platelet (/µL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;1,50,000</td>
<td>6 (8.4)</td>
<td>3 (6.6)</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td></td>
<td>&lt;1,50,000</td>
<td>65 (91.5)</td>
<td>43 (95.5)</td>
<td>22 (84.6)</td>
</tr>
<tr>
<td></td>
<td>&lt;50,000</td>
<td>27 (38.0)</td>
<td>19 (42.2)</td>
<td>8 (30.7)</td>
</tr>
<tr>
<td></td>
<td>&lt;5,000</td>
<td>31 (43.6)</td>
<td>18 (40.0)</td>
<td>13 (50.0)</td>
</tr>
<tr>
<td>5</td>
<td>Serum ferritin (ng/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;2000</td>
<td>46 (64.7)</td>
<td>29 (64.4)</td>
<td>18 (69.2)</td>
</tr>
<tr>
<td></td>
<td>&gt;2000</td>
<td>44 (62.8)</td>
<td>31 (68.8)</td>
<td>13 (52.0)</td>
</tr>
</tbody>
</table>

**Table 3**: The complications observed among the study population

<table>
<thead>
<tr>
<th>Serial no</th>
<th>Findings</th>
<th>Total</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$n = 71($%</td>
<td>$n = 45($%</td>
<td>$n = 26($%</td>
</tr>
<tr>
<td>1</td>
<td>MODS</td>
<td>42 (59.1)</td>
<td>28 (62.2)</td>
<td>14 (53.8)</td>
</tr>
<tr>
<td>2</td>
<td>Septic shock</td>
<td>33 (46.4)</td>
<td>22 (48.8)</td>
<td>11 (42.3)</td>
</tr>
<tr>
<td>3</td>
<td>Septic shock with MODS</td>
<td>24 (33.8)</td>
<td>13 (28.8)</td>
<td>11 (42.3)</td>
</tr>
<tr>
<td>4</td>
<td>DIC score ≥ 5</td>
<td>17 (23.9)</td>
<td>11 (24.4)</td>
<td>6 (23.0)</td>
</tr>
</tbody>
</table>

**Table 4**: The association between hematological abnormalities and complications studied ($n = 71$)$^\text{1}$

<table>
<thead>
<tr>
<th>Exposure/risk factor</th>
<th>Incidence</th>
<th>RR (%)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Among exposed</td>
<td>Among unexposed</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>Total</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Platelet count &lt;50,000</td>
<td>19</td>
<td>30</td>
<td>63.3</td>
<td>14</td>
</tr>
<tr>
<td>DIC score ≥5</td>
<td>12</td>
<td>17</td>
<td>70.6</td>
<td>21</td>
</tr>
<tr>
<td>Serum ferritin &gt;2000 (n = 70)</td>
<td>24</td>
<td>44</td>
<td>54.5</td>
<td>9</td>
</tr>
</tbody>
</table>

Association between MODS and hematological abnormalities among the study population

|                      | No. | Total | % | No. | Total | % | p-value |
| Platelets count <50,000 | 30 | 70.0 | 21 | 41 | 51.2 | 1.4 | 0.9–2.0 | 0.178 |
| DIC score ≥5 | 17 | 6.5 | 29 | 54 | 53.7 | 1.4 | 1.0–2.0 | 0.167 |
| Serum ferritin >2000 (n = 70) | 24 | 63.6 | 14 | 26 | 53.8 | 1.2 | 0.8–1.8 | 0.579 |

Association between septic shock with MODS and hematological abnormalities among the study population

|                      | No. | Total | % | No. | Total | % | p-value |
| Platelets count <50,000 | 14 | 46.7 | 10 | 41 | 24.4 | 1.9 | 1.0–3.7 | 0.088 |
| DIC score ≥5 | 17 | 52.9 | 15 | 54 | 27.8 | 1.9 | 1.0–3.5 | 0.105 |
| Serum ferritin >2000 (n = 70) | 19 | 43.2 | 5 | 26 | 19.2 | 2.2 | 1.0–5.3 | 0.075 |

Association between mortality and hematological abnormalities among the study population

|                      | No. | Total | % | No. | Total | % | p-value |
| Platelets count <50,000 | 3 | 10.0 | 4 | 41 | 9.8 | 1.0 | 0.2–4.2 | 0.712 |
| DIC score ≥5 | 2 | 11.8 | 5 | 54 | 9.3 | 1.3 | 0.3–6.0 | 0.870 |
| Serum ferritin >2000 (n = 70) | 4 | 9.1 | 3 | 26 | 11.5 | 0.8 | 0.2–3.2 | 0.934 |
occurrence of thrombocytopenia has been reported from 61 to 86% in patients of scrub typhus.\(^{15,18}\) A retrospective study reported the presence of lower platelet count than the control population and platelets <100,000 /mm\(^3\) were observed more frequently in patients of scrub typhus with bleeding and severe illness.\(^{11}\)

In our study, septic shock was present in 33 (46.4%) patients, MODS was observed in 42 (59.1%) patients, and septic shock with MODS was noted in 24 (33.8%). In a study conducted in Meghalaya,\(^{19}\) MODS were reported in 14.4% of patients. Of the total 71 patients in the present study, 8 (11.2%) patients died; however, Griffith et al. reported mortality in 24.1% of patients with scrub typhus.\(^{15}\) A study by Thap et al. reported that scrub typhus with septic shock resulted in organ failure and respiratory failure.\(^{18}\) A retrospective study done in Korea reported MODS in 57.7% of patients.\(^{11}\)

In the present study, 60 (84.5%) patients had moderately increased d-dimer and three of them had markedly raised d-dimer levels; 20 (28.1%) patients had prolonged PT, and low fibrinogen levels (<1 g/mL) were noted in eight (11.2%) patients. The levels of coagulation factors and the presence of DIC in patients with scrub typhus were evaluated in a retrospective study. In total, 365 patients and 36 healthy controls were evaluated for DIC scores. The comparison was done between patients and healthy controls (p < 0.001 for all tests) by comparing median concentrations of fibrinogen, d-dimer, and fibrin/fibrinogen degradation products. PT was prolonged in patients of scrub typhus than the controls. When compared, the patients of severe scrub typhus were associated more significantly with PT prolongation, increased d-dimer levels along with fibrinogen degradation products and decreased fibrinogen levels in comparison to less severe scrub typhus.\(^{11}\)

In our study, overt DIC was observed in 17 (23.9%) patients. A study by Thap et al. documented the occurrence of DIC in patients with scrub typhus.\(^{20}\) In a retrospective study, the DIC scores (ISTH criteria) were calculated in 365 patients of scrub typhus, 51 patients fulfilled the criteria of severe scrub typhus, and the remaining 314 were in nonsevere group. Overt DIC was observed in 13.7% of patients with severe scrub typhus, whereas only 2.7% of patients in nonsevere group had overt DIC; it concluded that coagulation system activation was an important feature of scrub typhus and it also correlated with the severity of scrub typhus.\(^{11}\)

Voves et al. calculated the DIC score (ISTH criteria) in patients with severe sepsis (32 patients) and those with septic shock (eight patients). The DIC scores calculated for nonsurvivors group and those in the septic shock group were significantly higher in comparison to the survivor’s group and severe sepsis group. The presence of overt DIC had a significantly higher risk of death and septic shock. The prolongations of the PT and platelet counts were strongly linked to the DIC score. They concluded that the DIC score was very useful in identifying patients with activation of coagulation cascade hence predicting disease severity and fatality.\(^{21}\)

In the present study, septic shock (p = 0.028, RR 1.9, and 95% confidence interval (CI) 1.1–3.1) was significantly associated with severe thrombocytopenia. The associations of severe thrombocytopenia with other complications studied, MODS (p = 0.178) and septic shock with MODS (p = 0.088), were not significant; however, higher risk ratios of 1.4 and 1.9 were observed with these complications, respectively. The presence of overt DIC was also significantly associated with the development of septic shock (p = 0.045, RR 1.9, and 95% CI 1.2–2.9), but overt DIC was not significantly associated, but higher risk ratios were observed with the development of MODS (1.4), septic shock with MODS (1.9) and death (1.3).

The study was underpowered to detect associations between severe thrombocytopenia and overt DIC with the development of MODS and septic shock with MODS due to the smaller sample size of the study population.

**Conclusion**

In patients admitted with severe scrub typhus, thrombocytopenia was the commonest hematological abnormality noted, and the presence of severe thrombocytopenia and overt DIC were associated with the development of septic shock.

**Acknowledgments**

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**References**


Knowledge, Attitudes, and Practices regarding Oral Fluid, Electrolyte, and Energy Management in Acute Nondiarrheal Illnesses among Physicians in India

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ABSTRACT

Background: Fluid, electrolytes, and energy (FEE) management is important in the treatment of acute nondiarrheal illnesses. However, the use of FEE drinks in managing such illnesses is not well-documented.

Objective: This study aimed to understand physicians’ knowledge, attitude, and practices (KAP) and perceived patient outcomes in treating FEE deficits in acute nondiarrheal illnesses using FEE drinks in India.

Materials and methods: A cross-sectional respondent-blinded survey was designed and administered among practicing physicians across various specialties and prescribing statuses in India. KAP among groups of physicians was assessed, and the correlations between knowledge–attitudes, knowledge–practice, and knowledge–perceived outcomes were explored.

Results: A total of 494 physicians participated in the study from September to October 2021. Overall, knowledge scores were moderate. Prescribers had a higher average knowledge score and more proactive attitudes and practices as compared to nonprescribers. Most physicians agreed that FEE management recommendations could improve patients’ recovery speed. There were significant positive correlations between knowledge scores and physicians’ attitudes toward the importance of FEE management awareness, the importance of FEE management for patient recovery, and a physician’s perception that FEE drinks improved patients’ recovery time. There was no significant correlation between knowledge score and practices.

Conclusion: There may be benefits from improving the knowledge of physicians in India in FEE management and developing guidelines for the use of FEE drinks in acute nondiarrheal illnesses. Further research exploring the knowledge–practice gap and evaluating the clinical benefit of FEE drinks in acute nondiarrheal illnesses should also be undertaken to develop such guidelines.

INTRODUCTION

Adequate water intake is essential to maintain several physiological functions and cellular homeostasis.1 Accordingly, dehydration, which can be defined as a complex condition resulting in a reduction in total body water, can lead to a worsening health status.1 Hydration is; therefore, a key aspect of disease management, especially across acute conditions, and the prescription of fluid and electrolyte therapy is a key tool in addressing this. Treating dehydration due to diarrheal diseases is well-documented, and there are well-established hydration guidelines by the World Health Organisation (WHO). The WHO and United Nations Children’s Fund even jointly developed official guidelines for the manufacture of oral rehydration solutions (ORS) in 1969 and included it in the WHO’s model list of essential medicines.2,3

Additionally, there may also be instances in acute nondiarrheal illnesses when there is overt or subclinical dehydration and where rehydration and electrolyte repletion is important. Conditions associated with such dehydration may include fever (due to diseases such as dengue, malaria, and typhoid), nausea, vomiting, heat-related illnesses, and infections such as upper respiratory tract infections and urinary tract infections. These can be further exacerbated in the elderly or children due to their physiology.1,4 In such cases, physicians may also find it important to prescribe fluid and electrolyte therapy. However, as there are no formal guidelines in the management of dehydration linked to these conditions, physicians often extrapolate clinical management from diarrheal illnesses to nondiarrheal illnesses and prescribe the WHO ORS.

The composition of a typical ORS used for diarrhea mostly includes fluids and electrolytes (sodium and potassium). A small amount of glucose is added, and the synergistic combination of these ingredients facilitates the absorption of sodium and water in the small intestine and replaces essential ions that are lost.1 However, with other acute nondiarrheal illnesses, there may be a need for an extra energy component due to the hypermetabolic response to such illnesses.5 Also, patients may experience anorexia during such illnesses.6 Hence, the extrapolation of ORS use to nondiarrheal illnesses is likely inadequate and represents a potential management gap. Recommendations to eat solids to obtain additional calories may also result in lower compliance as patients may find it easier to consume fluids instead during periods of anorexia.7 Patients may also find the WHO ORS unpalatable due to the reported strong salty taste.8,9 The addition of added energy (glucose) to fluid and electrolytes drinks could therefore improve palatability and patient compliance.10 A ready-to-drink (RTD) format may also have the added advantage of being more convenient to consume and being sterile packed.11

The use of ORS in acute diarrhea, its prescription trend, and the knowledge and practices by healthcare providers are well-evaluated and reported in India.12-14 However, in acute nondiarrheal illnesses, the need to prevent and treat dehydration as well as energy management may often be overlooked, and there are no data describing the utilization of drinks that contain FEE in nondiarrheal illnesses in India. This study will therefore be the first to provide data on the use of FEE drinks in nondiarrheal illnesses. The objectives were to evaluate physicians’ KAP regarding the treatment of...
FEE deficits in patients with acute nondiarrheal illness and to examine if there are differences amongst different groups of physicians in India. Physicians’ reported impact of FEE management on the speed of patients’ recovery was also explored.

**Materials and Methods**

**Questionnaire Design**

A cross-sectional online questionnaire was developed to assess the KAP of physicians in treating FEE deficits in patients with acute nondiarrheal illness using FEE drinks in India. The questionnaire consists of four domains. The first domain of knowledge aimed to obtain information on the awareness of FEE deficits, knowledge about dehydration, definitions, clinical challenges, signs, symptoms, and biomarkers. The second domain evaluated a physician's attitude toward the use of FEE drinks in different clinical situations. The third domain assessed the physician's current practice, including FEE drink prescription and recommendation behaviors. The fourth domain evaluated physician-perceived patient outcomes with questions surrounding the impact of FEE management on a patient’s recovery.

**Figure 1** illustrates the questionnaire design process. A multi-phase approach was used to develop the questionnaire to optimize the validity of the study. The first phase included a literature review and a focus group discussion consisting of key opinion leaders (KOLs) in India with a deep understanding of the fluid and electrolyte management landscape. Four KOLs were recruited, and topics such as the dehydration landscape, guidelines and best practices, and fluid recommendation protocols were discussed. The second phase included the development of the questionnaire based on information obtained during the focus group. Finally, the third phase involved questionnaire dissemination to the KOLs in obtaining feedback and comments. Iterative changes were then made to the questionnaire, and the final version was approved by all KOLs. The final questionnaire administered is provided in the appendix.

**Questionnaire Administration**

The questionnaire was administered through an online platform from September to October 2021. Verified physicians were recruited to participate and remained anonymous. Informed consent was obtained prior to the questionnaire administration. Ethics approval was not required as this was an anonymous survey, and no identifiable information, patient data, and no personal information were obtained. Quota sampling was used to recruit participants based on prescribing status, clinical specialty, and area of practice. This allowed us to examine the differences in KAP amongst different groups of physicians. Prescribers were defined as physicians who give formal written or electronic prescriptions of FEE drinks to 50% or more of their eligible patients for FEE deficit management, whilst nonprescribers do not give formal written or electronic prescriptions of such products. As there were no specific guidelines nor literature that defined prescribers and nonprescribers, the criterion of a 50% or more prescription rate was obtained after discussions with the KOLs. During the questionnaire development phase, it was also suggested that questions should be tailored according to the physician’s specialty and prescribing status. Therefore, the online platform was designed to distribute customized questions to the participants based on their clinical specialty and prescribing status. For example, a pediatrician will receive pediatric-specific knowledge questions about hydration in children and infants, while an obstetrician-gynecologist will receive questions about hydration in pregnant and lactating women. Wordings were also tweaked to make them appropriate to the specialty and prescribing status. Details of the differences are shown in the questionnaire provided in the appendix.

**Statistical Analysis**

Knowledge scores were summed into a total maximum score of 6. We used a two-sample t-test to analyze the differences in knowledge scores between prescribers and nonprescribers. Results were illustrated in mean [standard deviation (SD)]. Pearson’s Chi-squared test was used to evaluate the difference in attitude between prescribers and nonprescribers, and results were illustrated in proportions. Correlation analysis was used to measure the strength and direction of the associations that existed between knowledge score and attitude, practices, and perceived patient outcomes. The corresponding correlation coefficients were reported.

To describe the strength of a correlation coefficient, we defined a correlation of <0.2 as very weak, between 0.2 and 0.4 as weak, between 0.4 and 0.6 as moderate, and >0.6 as strong. We used Statistical Package for the Social Sciences 25 for all statistical analyses. All hypothesis tests were performed using a 2-sided α = 0.05.

**Results**

Participants’ demographics are described in Table 1. There was a comparable distribution of participants from various clinical specialties, prescriber status, and practice areas due to quota sampling. Results of the differences between KAP are described in Table 2.

**Knowledge**

The knowledge level of all physicians regarding dehydration and FEE management, evaluated by average knowledge score, was moderate.

**Table 1: Demographics of participants**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participants (n = 494)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of practice years, mean (SD)</td>
<td>17.8 (6.6)</td>
</tr>
<tr>
<td>No of patients a month, mean (SD)</td>
<td>536 (196.1)</td>
</tr>
<tr>
<td>Specialty, n (%)</td>
<td></td>
</tr>
<tr>
<td>• GP</td>
<td>128 (25.9)</td>
</tr>
<tr>
<td>• MD physician</td>
<td>121 (24.5)</td>
</tr>
<tr>
<td>• Pediatrician</td>
<td>123 (24.9)</td>
</tr>
<tr>
<td>• OB-GYN</td>
<td>122 (24.7)</td>
</tr>
<tr>
<td>Prescribe Status, n (%)</td>
<td></td>
</tr>
<tr>
<td>• Prescriber</td>
<td>248 (50.2)</td>
</tr>
<tr>
<td>• Nonprescriber</td>
<td>246 (49.8)</td>
</tr>
<tr>
<td>Practice Area, n (%)</td>
<td></td>
</tr>
<tr>
<td>• Metro</td>
<td>252 (51.0)</td>
</tr>
<tr>
<td>• Mini metro</td>
<td>242 (49.0)</td>
</tr>
</tbody>
</table>
Prescribers had a higher impact on health compared to nonprescribers (62.1 vs 34.2%; \(p < 0.01\)). Physicians who perceived FEE management awareness as of high importance for patient health during recovery from acute non diarrheal illness was also higher as compared to nonprescribers (65.7 vs 40.2%; \(p < 0.01\)). The proportion of prescribers who perceived FEE management as of high importance for patient health during recovery from acute non diarrheal illness was also higher as compared to nonprescribers (62.1 vs 34.2%; \(p < 0.01\)). More prescribers also felt that chronic undetected dehydration had a higher impact on health compared to nonprescribers (59.7 vs 43.1%; \(p < 0.01\)).

### Practice
Prescribers displayed a more proactive practice toward assessing dehydration, time spent providing hydration advice, and recommending FEE to patients. A higher proportion of prescribers assess patients for hydration level (72.2 vs 59.4%; \(p < 0.01\)), spend >5 minutes providing hydration advice (45.2 vs 24.4%; \(p < 0.01\)), and recommend FEE drinks to >70% of their patients (38.3 vs 21.1%; \(p < 0.01\)) as compared to nonprescribers.

### Physicians Perceived Patient Outcomes
Most physicians (87%) agreed that recommendations for FEE management would aid in improving the speed of recovery. Around 98% of the prescribers also agreed that RTD FEE drinks are more effective in shortening recovery duration as compared to non-RTD FEE drinks and that patients will recover faster if written prescriptions of RTD FEE drinks are given compared to verbal advice alone. Based on around 40% of physicians across specialties who were able to provide an estimate, the recovery duration was estimated to be shortened by 4.38 (±3.04) days and 3.83 (±2.16) days on average, respectively.

### Correlation Analysis
Table 3 describes the correlation between knowledge scores and attitude, practices, and physician-perceived patient outcomes. For attitude, there was a significant moderate positive correlation between overall knowledge score and attitude toward the importance of FEE management awareness for physicians (\(r_b = 0.41; p < 0.01\)) and attitude toward the importance of FEE management for patient recovery (\(r_b = 0.38, p < 0.01\)). For physician-perceived patient outcomes, the knowledge score was positively correlated to a physician’s perception that FEE drink recommendation improved a patient’s recovery time (\(r_b = 0.42, p < 0.01\)). Knowledge score was also positively correlated to a physician’s perception that RTD FEE drinks as compared to non-RTD FEE drinks and the provision of written prescription as compared to verbal advice improved a patient’s recovery time (\(r_b = 0.41, p = 0.03; r_b = 0.49, p < 0.01\)).

### Discussion
Fluid, electrolytes, and energy (FEE) management is important in the treatment of acute illnesses. Several studies have

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**Table 2: Differences in KAP between prescribers and nonprescribers**

<table>
<thead>
<tr>
<th>Knowledge Score (max 6 points)</th>
<th>Prescriber, mean (±SD)</th>
<th>Nonprescriber, mean (±SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge</td>
<td>3.43 (1.34)</td>
<td>3.13 (1.36)</td>
<td>(p = 0.01)</td>
</tr>
</tbody>
</table>

**Table 3: Correlation between knowledge scores and attitude, practices, and patient outcomes**

<table>
<thead>
<tr>
<th>Attitude</th>
<th>Correlation coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Importance of FEE management awareness and application for physicians in acute nondiarrheal illnesses (high, medium/low)</td>
<td>(r_b = 0.41)</td>
<td>(p &lt; 0.01)</td>
</tr>
<tr>
<td>Importance of FEE management for patient health during recovery from acute nondiarrheal illnesses (high, medium/low)</td>
<td>(r_b = 0.38)</td>
<td>(p &lt; 0.01)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Practices</th>
<th>Correlation coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of patients assessed for hydration</td>
<td>(r = 0.06)</td>
<td>(p = 0.19)</td>
</tr>
<tr>
<td>Percentage of patients recommended FEE drinks (high, medium/low)</td>
<td>(r_b = 0.20)</td>
<td>(p &lt; 0.01)</td>
</tr>
<tr>
<td>Average time spent on hydration advice (high, medium/low)</td>
<td>(r_b = 0.25)</td>
<td>(p &lt; 0.01)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient outcomes</th>
<th>Correlation coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agreement on improving the speed of recovery if recommended FEE drinks (yes, no)</td>
<td>(r_b = 0.42)</td>
<td>(p &lt; 0.01)</td>
</tr>
<tr>
<td>Agreement on improving the speed of recovery if RTD FEE drinks are recommended vs non-RTD FEE drinks (yes, no)</td>
<td>(r_b = 0.41)</td>
<td>(p = 0.03)</td>
</tr>
<tr>
<td>Agreement on improving the speed of recovery if a written prescription is given vs verbal advice</td>
<td>(r_b = 0.49)</td>
<td>(p &lt; 0.01)</td>
</tr>
</tbody>
</table>
found that dehydration amongst the elderly, especially those with concomitant infections, are associated with increased morbidity and mortality and, consequently, healthcare resource utilization.16–18 Similarly, dehydration in children is associated with increased numbers and length of hospitalizations.19,20 Metabolic changes in common chronic conditions such as diabetes may also cause patients to be more susceptible to FEE deficits.21 Oral rehydration treatment hence is an important first-line therapy for rehydration.7 Electrolyte replacements are also vital in the treatment of heat-related illnesses, particularly heat cramps and heat exhaustion.22 The imbalance in fluids and electrolytes can lead to symptoms such as malaise, vomiting, and confusion.23 RTD FEE drinks containing such electrolytes can be a useful therapy in such scenarios when treatment is time sensitive. Disease states such as fever and infections are hypermetabolic in nature, and patients with nausea or vomiting may also have a reduced appetite, which can result in inadequate fluid and energy intake.24 While recommendations to increase solid food intake can mitigate the caloric deficit, patients are unlikely to be compliant due to the satiety effect of solid food and the anorexia related to their acute illnesses.25 Calories in the form of glucose in FEE drinks can be useful in mitigating these energy deficits. A common concern with the addition of energy into ORS is that it increases its osmolarity, which can potentially exacerbate osmotic diarrhea. However, this is unlikely to be relevant in nondiarrheal cases, and the added energy component could be argued as an essential component of the FEE drink, allowing patients access to important energy sources, especially during bouts of anorexia. There is a clear differentiation between the different types of drink (FEE and ORS) that should be used to treat different dehydration profiles.

This study provides valuable insights into physicians’ current KAP in treating FEE deficits in patients with acute nondiarrheal illnesses using FEE drinks and the differences amongst different groups of physicians in India. It provides evidence of the positive and significant correlations between knowledge–attitudes and knowledge-perceived outcomes among physicians.

It was observed that there is a potential knowledge deficiency amongst physicians as the knowledge scores across all physicians are only moderate. Intervention to improve knowledge of dehydration and FEE management in acute nondiarrheal illnesses may yield better disease outcomes in the real-world setting, as it was demonstrated that higher knowledge scores are significantly associated with a more proactive attitude and perceived improved patient outcomes. Knowledge score was associated with physicians’ perception of improved recovery time for patients who recommended FEE drinks. This suggests that physicians who have better knowledge of dehydration treatment believe that the written prescription of RTD FEE drinks can shorten a patient’s recovery time which can potentially lead to reduced healthcare resource utilization. Further direct evidence can be developed from real-world outcomes research to validate the actual scale of benefit RTD FEE drinks can provide. It is also unsurprising that there are differences in KAP between prescribers and nonprescribers, with prescribers having better knowledge and more proactive attitude and practices. One will expect that those with better knowledge and a proactive attitude will be more likely to prescribe FEE drinks and spend more time providing hydration advice. With the establishment of more evidence supporting the benefit of hydration, future guidelines should include dehydration assessment and minimum time spent on hydration advice as a standard of care for patients with nondiarrheal illnesses.

Another important observation is that physicians in India perceived that FEE management recommendations, the use of RTD as compared to non-RTD FEE drinks, and written prescriptions as compared to verbal advice led to a decrease in recovery time. This suggests that physicians believe that a patient’s compliance with such FEE drinks may be improved with the use of RTD drinks and that written prescriptions reinforce their importance in recovery. Therefore, future guidelines should consider these initial findings, and further research should be conducted to evaluate the real-world differences in recovery time when given various forms of FEE drinks and prescription types.

We also noticed a gap between knowledge and practice, where we identified that a higher knowledge score does not explicitly translate to prescribing behaviors, even though it is perceived that it improved recovery time. Possible reasons for this misalignment may stem from a lack of guidelines or consensus regarding the prescription of FEE drinks for acute nondiarrheal illnesses or the lack of knowledge of available FEE drinks for the prescription. Further research may be required to elicit the reasons behind this attitude-practice gap.

This study had several limitations. Firstly, we employed a KAP questionnaire that was not psychometrically tested; latent variables such as attitude are not observable, and constructs like knowledge and practices can be difficult to assess. Secondly, when defining the respondents as a prescriber or nonprescriber, the criteria for prescriber was defined through KOL consensus. This may cause some selection bias, but it is likely to reflect real-world practice patterns, and as such, the results observed are still indicative of the patterns that were intended to investigate. Thirdly, the self-reported nature of the questionnaire may result in biases. Some respondents may choose more clinically acceptable answers, or there might be a variance in the interpretation of questions. Additionally, the design of a self-reported questionnaire with dichotomous choices and the Likert scale restricts options for selection. Such limitations will need to be taken into consideration when interpreting the results. Alternatively, more rigorous methodologies such as item-to-scale correlation testing and factor analyses can be utilized to improve the psychometric properties of the KAP questionnaire.25

Nevertheless, as the first study that evaluated FEE management and the use of FEE drinks in nondiarrheal diseases, these limitations were not entirely avoidable, and the study serves as a starting point for further evidence generation. Several mitigation strategies were also done to address the identified limitations. Although a psychometrically tested KAP questionnaire was not utilized, a targeted literature review for questionnaires with similar nature was conducted, followed by a focus group discussion that involved several KOLs. This allows us to have greater insights into the fluid replacement landscape in India and ensure that only relevant questions are included in the questionnaire and that the questions are contextually suitable. Additionally, the study surveyed a relatively large sample size of 494 participants across different specialties and areas across India. The robust sample size provides adequate power to draw insights from the statistical analyses, and the wide representation increases the external validity of the study.

**Conclusion**

In conclusion, this study evaluated physicians’ KAP in treating FEE deficits in patients with acute nondiarrheal illness in India using FEE drinks and examined if there are differences amongst different groups of physicians. This study serves as a preliminary exploration of a complex and wide-ranging disease condition, and its findings suggest there may
be benefits from improving the knowledge level of physicians in India regarding FEE management and developing guidelines for the assessment of hydration and use of FEE drinks in acute nondiarrheal illnesses. A further real-world study targeting specific conditions in acute nondiarrheal illnesses may be required to validate and investigate the shortening of illness duration when FEE drinks are aptly prescribed and complied with. This has the potential to improve the quality of life for patients and minimize healthcare resource utilization which reduces the burden for both patients and healthcare systems.

ACKNOWLEDGMENT
The authors thank Ipsos Pte Ltd, Singapore for the research and medical writing support.

REFERENCES
The Correlation of Urine Protein/osmolality and Protein/creatinine Ratio as Predictor of 24-hour Urinary Protein Excretion

Sanketkumar Balar¹, Nandkumar Beke², Dattatray Patki³, Arun Bahulikar⁴, Deepak Phalgune⁵*

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ABSTRACT

Background: The drawback of 24-hour urine collection is that it is troublesome, takes a lot of time, and is inaccurate because of collection errors and improper timing. The research in the Indian adult population about the correlation of spot urine protein/osmolality ratio (UPOR) and spot urine protein/creatinine ratio (UPCR) as a predictor of 24-hour urinary protein excretion is lacking.

Objectives: To study the correlation of spot UPOR and spot UPCR as the prognosticator of 24-hour urinary protein excretion.

Materials and methods: The present cross-sectional observational study was undertaken on 50 patients >18 years of age and of either sex who presented with proteinuria (dipstick test or urine routine) and were advised 24-hour urine protein examination. A 24-hour urine was collected for protein analysis starting from any time of day. Random urine samples were collected and processed for protein, creatinine, and osmolality. The spot UPOR and UPCR were calculated. The sensitivity and specificity were determined. Pearson’s correlation was used to find the correlation.

Results: There was a statistically significant positive correlation of UPOR and UPCR (r = 0.418 and r = 0.512, respectively) with 24-hour urinary protein excretion. The sensitivity and specificity of UPOR to predict 24-hour urinary protein at cutoff point 1.32 was 82.3% and 81%, respectively. The sensitivity and specificity of UPCR to predict 24-hour urinary protein at cutoff point 1.09 was 87% and 86%, respectively.

Conclusion: For the medical determination of proteins in urine, spot UPOR and UPCR are suitable, cheap, and dependable methods that can substitute the measurement of 24-hour urine protein.

INTRODUCTION

Chronic kidney disease (CKD) was pointed out as a foremost cause of worldwide illness and deaths in the Global Burden of Disease Collaboration Study.¹ It was reported that worldwide illness due to CKD increased by 29.3%, whereas deaths due to CKD increased by 41.5% from 1990 to 2017.² In India, mortality due to renal failure increased by 38.0%.³ CKD is the sixth fastest-growing cause of death.

It is observed that in cardiovascular and renal diseases, proteins in urine remain a proven independent determinant and they can be utilized as a projector of end-organ injury.⁴ For managing many kidney diseases, the detection and precise quantity of excretion of proteins in urine are important diagnostic and prognostic tools.⁵ To evaluate the efficacy of treatment and the progression of renal disease, the precise quantity of excretion of proteins in urine is of significant value.⁶ The United States (US) National Kidney Foundation has suggested that for patients in danger of developing renal diseases, raised excretion of proteins in urine should be used as a screening tool.⁷ Therefore, accurate detection of the excretion of proteins in urine is an important part of renal function assessment.⁸

Available methods of estimating urine protein are qualitative by sulphosalicylic acid test or dipstick and quantitative by protein estimation in 24-hour urine. Sulphosalicylic acid test and dipstick are crude methods of estimating proteinuria and depend on the amount of urine produced at that time. Dipstick assessment is susceptible to interobserver variation.⁹ The perfect method for assessing proteinuria is the estimation of protein in urine within 24 hours. But, the drawback of 24-hour urine collection is that it is troublesome, takes a lot of time, and is inaccurate because of collection errors and improper timing.¹⁰ Instead of 24-hour urine collection, the US National Kidney Foundation kidney disease outcomes quality initiative recommendations of 2000 advocate the practice of spot UPCR for the measurement of proteinuria.¹¹ Usually alternative methods like, spot UPCR and spot UPOR are used. Both UPCR and UPOR measure the quantitative urinary protein excretion correctly. Using spot urine examination to measure proteinuria has some limitations. UPCR is severely influenced by the concentration of creatinine in the urine, that is, the total daily creatinine production, and also the excretion of protein in urine varies during the day (particularly subsequent to exercise and posture) and every day. Such studies are conducted in the United States of America and mostly in the pediatric population but the research on Indian adult people is limited. The present research was carried out to correlate UPOR and UPCR, as a prognosticator of 24-hour urinary protein excretion.

MATERIALS AND METHODS

This cross-sectional observational study was conducted from April to September 2022. The research was commenced after an acceptance from the Institutional Ethics Committee. All the patients gave written informed consent. A total of 50 patients >18 years of age of either gender who had proteinuria (dipstick test or urine routine) and were advised 24-hour urine protein examination were included. Patients with haematuria (blood +2 in urine routine), febrile illness, dehydration, and urinary tract infection were excluded from the study. All the patients admitted to the hospital who had proteinuria were included. The sociodemographic details, history recording, clinical examination along with relevant anthropometrical measurements, and relevant laboratory investigations were done. Collection of blood samples and urine samples for required investigations were taken.

For a 24-hour urine sample, a container containing toluene was provided to the
Correlation of UPOR and UPCR with 24-hour Urinary Protein Excretion

The collection of 24-hour urine protein was done starting at any time of day. The patient was told that before starting collection void the bladder, discard the urine, and then start the collection. The patient was instructed that after 24 hours of collection of urine in a container, take the container to the laboratory within 12 hours. Random urine samples were collected and processed for protein, creatinine, and osmolality. The urine protein was estimated by the biuret (Machine: Dimension® EXL™ 200 Integrated Chemistry System, Siemens, Georgia) method. Creatinine in the urine was assessed by modified Jaffe’s kinetic (Machine: Dimension® EXL™ 200 Integrated Chemistry System, Siemens, Georgia) method. Urine osmolality was calculated by formulae solute dissolved in it.

Formula—urine osmolality = 2 x urine sodium + [(urine glucose/18) + (urine urea nitrogen/2.8)]

Urine samples were calculated for UPCR—urine protein (mg/dL)/urine creatinine (mg/dL) and UPOR—urine protein (mg/L)/urine osmolality (mOsm/kg).

The primary objectives were the correlation between UPOR and UPCR with 24-hour urinary protein. The secondary objectives were the sensitivity and specificity of UPOR and UPCR to predict 24-hour urinary protein.

### Table 1: Demographic and clinical profile

<table>
<thead>
<tr>
<th>Variables</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group in years</td>
<td></td>
</tr>
<tr>
<td>20–30</td>
<td>01 (2.0)</td>
</tr>
<tr>
<td>31–40</td>
<td>06 (12.0)</td>
</tr>
<tr>
<td>41–50</td>
<td>19 (38.0)</td>
</tr>
<tr>
<td>51–60</td>
<td>16 (32.0)</td>
</tr>
<tr>
<td>61–70</td>
<td>08 (16.0)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>31 (62.0)</td>
</tr>
<tr>
<td>Women</td>
<td>19 (38.0)</td>
</tr>
<tr>
<td>Etiology of proteinuria</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15 (30.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>09 (18.0)</td>
</tr>
<tr>
<td>Diabetes mellitus +</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>03 (6.0)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>12 (24.0)</td>
</tr>
<tr>
<td>Postrenal transplant</td>
<td>03 (6.0)</td>
</tr>
<tr>
<td>SLE/other autoimmune</td>
<td></td>
</tr>
<tr>
<td>disorders</td>
<td>03 (6.0)</td>
</tr>
<tr>
<td>Others</td>
<td>02 (4.0)</td>
</tr>
<tr>
<td>Severity of proteinuria</td>
<td></td>
</tr>
<tr>
<td>0.1–1 gm/day</td>
<td>24 (48.0)</td>
</tr>
<tr>
<td>1–3 gm/day</td>
<td>17 (34.0)</td>
</tr>
<tr>
<td>&gt;3 gm/day</td>
<td>09 (18.0)</td>
</tr>
</tbody>
</table>

SLE, systemic lupus erythematosus

The correlation between UPOR and 24-hour protein excretion was \( r = 0.40 \) which was statistically significant (p-value < 0.001) (Fig. 1). The correlation between UPCR and 24-hour protein excretion was \( r = 0.512 \) which was statistically significant (p-value < 0.001) (Fig. 2).

Data collected were entered in Microsoft Excel 2016 and analyzed using Statistical Package for the Social Sciences version 22, IBM Corporation, USA. The qualitative variables are presented as n (% of cases). The continuous variables are presented as mean ± standard deviation and medians (interquartile range) for parametric or nonparametric data, respectively. The diagnostic efficacy indices such as sensitivity, specificity, positive predictive value, and negative predictive value were determined. The correlation was calculated by Pearson’s correlation method. Receiver operating characteristic (ROC) curve analysis was done to detect the cutoff value of UPOR and UPCR in predicting 24-hour urine proteinuria. A p-value < 0.05 was considered to be significant.

### RESULTS

The demographic and clinical profile of the study population is evident in Table 1. The mean age of the study population was 53.9 ± 13.1 years. The correlation between UPOR and 24-hour urinary protein excretion was \( r = 0.418 \) which was statistically significant (p-value < 0.001)

The ROC curve analysis of the protein/osmolality ratio to predict 24-hour urinary protein and protein/creatinine ratio to predict 24-hour urinary protein are depicted in Figures 3 and 4, respectively. At cutoff point 1.32 UPOR showed a sensitivity of 82.3% and specificity of 82.7%.
specificity of 81%, whereas at cutoff point 1.09 UPCR showed a sensitivity of 87.0% and specificity of 86.0% (Table 2).

**Discussion**

The present observational cross-sectional study was undertaken to correlate UPCR and UPOR as a predictor of 24-hour urinary protein excretion. In the present research, there was a statistically significant positive correlation of UPOR and UPCR ($r = 0.418$ and $r = 0.512$, respectively) with 24-hour urinary protein excretion ($p$-value $< 0.001$). Montero et al. observed a significant correlation between 24-hour proteinuria and the UPCR ($r = 0.91$, and $p$-value $< 0.001$), but the correlation was dissimilar with different levels of proteinuria. Wahbeh observed a robust positive correlation ($r = 0.7459$, and $p$-value $< 0.0001$) between spot UPCR and 24-hour urine protein excretion. Su et al. in a study on the correlation study between spot UPCR and 24-hour urine observed a significant correlation ($r = 0.95$, and $p$-value $< 0.0001$). The study further stated that the correlation was similar with different levels of proteinuria. Ahmed et al. reported that the correlation coefficient ($r$) between 24-hour proteinuria and spot UPCR ($r = 0.93$ (0.87–0.96, 95% confidence interval); $p$-value $< 0.001$). Rodby et al. reported that a random urine specimen UPCR correlated with the 24-hour urine protein collection ($r = 0.90$), and that the time of day the random urine specimen obtained has no effect on the ability to predict 24-hour urine protein from the random urine specimen UPCR. Antunes et al. reported the correlation of 24-hour urine protein (gm/24-hour) with UPCR was $r = 0.90$ and $p$-value $< 0.001$. Villafruela et al. reported that the correlation coefficient between UPCR and 24-hour urine protein was better in the groups with less severe proteinuria. It was reported that UPCR in single-voided urine samples correlated well with the computation of 24-hour urinary protein. Morales et al. reported high correlation coefficients ($r = 0.91$, 0.95, and 0.98) in patients with normal, reduced, and severely reduced renal function.

In the present research, the sensitivity and specificity of UPOR to predict 24-hour urinary protein at cutoff point 1.32 UPOR was 82.3 and 81%, respectively. The sensitivity and specificity of UPCR to predict 24-hour urinary protein at cutoff point 1.09 UPCR was 87 and 86%, respectively. Wahbeh reported that to determine 24-hour proteinuria, a sensitivity of 100 and specificity of 90% was observed if UPCR was >4.33. Morales et al. stated that the best UPCR cutoff values to detect abnormal or nephrotic proteinuria were, respectively, 0.3 and 2.6. Antunes et al. reported that taking the cutoff levels of 0.20 and 3.5 gm in ROC curve analysis for 24-hour urine protein showed that the UPCR ratio had excellent accuracy.

For managing patients with kidney disease, proper detection and quantification of proteinuria are of great importance. The 24-hour urine collection is unwieldy and it is not always done correctly; the easy, reliable unique method is a measurement of the UPCR. For the diagnosis, observation of therapeutic efficacy, prognostication of kidney ailments, and the determination of proteins in urine are beneficial. Evaluation of proteinuria by urine dipstick method is unreliable and is prone to interobserver variation. If the urine is alkaline or when there is an infection caused by bacteria, a false positive outcome may occur. The results of the dipstick test can be influenced by the hydration of the patient. If the urine is too concentrated or diluted, the results may be falsely high or low, respectively.

Shaw et al. stated that the errors of urine collection for 24-hour urine protein tests are approximately 30%. Measurement of UPCR in a spot urine sample is a simple, quicker, and more dependable method than a 24-hour urine protein test. The National Kidney Foundation Guidelines recommend that untimed (spot) urine samples should be used to determine and monitor proteinuria in children and adults and that timed urine collection (overnight or 24-hour) is generally not needed for these assessments.

**Limitations**

The sample size was small and the research was conducted in a tertiary care center which may make it difficult to extrapolate the results to a larger population. Secondly, a separate correlation with the individual etiology of proteinuria was not determined. Thirdly, an ideal method to measure osmolality is an osmometer which was not used in this study. The correlation was not calculated with different levels of 24-hour proteinuria. Multicentric studies with large sample sizes with help of a laboratory equipped with an osmometer should be conducted to validate the results reported in this manuscript.

![ROC curve](image1.png)

**ROC curve**

**ROC curve**

![ROC curve](image2.png)

**ROC curve**

**Table 2:** Diagnostic accuracy of urine protein/osmolality ratio and urine protein/creatinine ratio to predict 24-hour urinary protein

<table>
<thead>
<tr>
<th></th>
<th>Cutoff point</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine protein/osmolality ratio</td>
<td>1.32</td>
<td>82.3%</td>
<td>81%</td>
<td>77%</td>
<td>86%</td>
</tr>
<tr>
<td>Urine protein/creatinine ratio</td>
<td>1.09</td>
<td>87%</td>
<td>86%</td>
<td>75%</td>
<td>90%</td>
</tr>
</tbody>
</table>

NPV, negative predictive value; PPV, positive predictive value
CONCLUSION
There was a statistically significant positive correlation ($r = 0.418$) of UPOR with 24-hour urinary protein excretion. There was a statistically significant positive correlation ($r = 0.512$) of urine protein/creatinine ratio with 24-hour urinary protein excretion. The sensitivity and specificity of UPOR to predict 24-hour urinary protein at cutoff point 1.32 was 82.3 and 81%, respectively. The sensitivity and specificity of urine protein/creatinine ratio to predict 24-hour urinary protein at cutoff point 1.09 protein/creatinine ratio was 87 and 86%, respectively.

REFERENCES
Prevalence of Hypouricemia and Hyperuricemia and Looking Beyond Serum Uric Acid in Patients with Newly Onset Type 2 Diabetes Mellitus in Eastern Part of Uttar Pradesh: A Cross-sectional Study

Shailendra K Singh1, Rina Singh2, Santosh K Singh3
Received: 04 April 2021; Accepted: 22 February 2023

ABSTRACT

Introduction: The prevalence of hyperuricemia (HU) and hypouricemia (Hypo-U) is highly variable in different parts of India and there is a lack of data from the Eastern part of Uttar Pradesh. We designed this study in order to know the exact prevalence of HU and Hypo-U.

Materials and methods: This is a cross-sectional study conducted in Varanasi. Data were collected from newly onset diabetic patients over a period of 1 year.

Results: Among the 312 diabetic patients, 12.5 and 19.23% were found to have HU and Hypo-U, respectively. Hypouricemic diabetic patients are phenotypically different. They are characterized by the female sex, higher glycated hemoglobin A1c (GlyHbA1c), higher estimated glomerular filtration rate (eGFR), lower body mass index (BMI), and less insulin resistance.

Conclusion: The prevalence of HU and Hypo-U is high in newly-onset diabetic patients. Hypouricemic diabetic patients are phenotypically different. Hence routine screening of uric acid is essential for proper diagnosis and appropriate treatment of hypouricemic diabetic patients.

INTRODUCTION

Serum uric acid (SUA) is the final product of purine metabolism in humans.1 Its concentration in the body depends on purine breakdown and urate excretion. The prevalence of HU is increasing in the world, especially in developing countries.2 Reason for the rising prevalence of HU is rising obesity, hypertension, old age, high alcohol intake, and high intake of diet rich in purine. Raised SUA is associated with metabolic syndrome (MS), endothelial dysfunction, cardiovascular disease, dyslipidemia, gout, renal dysfunction, hypertension, heart failure, and atrial fibrillation.3–6 High serum uric is a feature of hyperinsulinemia and/or insulin resistance.7 Insulin is known to cause increased reabsorption of urate from the kidney.8 In patients with MS and impaired glucose tolerance, HU is more prevalent than in control.2,5 Various study shows that uric acid is an early biochemical marker of diabetes and an independent predictor of diabetes.9 But the relationship between uric acid metabolism and diabetes remains variable because the low level of uric acid is found in diabetes in recent studies as compared to control, and diabetes is related to a lower risk of development of gout in the United Kingdom and the Chinese population.10–14 Reasons for low SUA in diabetes are many; uricosuric effect of glucose, hyperfiltration (HF), low-calorie intake, and increase in extracellular fluid volume.10 But many studies also found a positive association3,5,6 between elevated SUA and diabetes, whereas other studies reported no correlation.17

In order to provide further insight into conflicting data on the uric acid level in type 2 diabetes patients, we conducted a cross-sectional study to know the exact magnitude of the problem in this part of India. There are data on the relationship between SUA and diabetes from different parts of India, but there is a lack of data from this part of India. Therefore, in this study, we aim to investigate the prevalence of HU and Hypo-U in newly onset type 2 diabetes patients from this part of India (Eastern Uttar Pradesh). Further, our aim is to see the various features associated with hypouricemic diabetic patients.

MATERIALS AND METHODS

To know the prevalence of HU and Hypo-U in newly diagnosed diabetes mellitus (DM) patients, we conducted a cross-sectional study at our endocrine clinic in Varanasi between February 2020 to February 2021 after obtaining clearance from the local ethical committee. Around 342 newly diagnosed (duration of <1 year) type 2 diabetic patients were enrolled in the study. A total of 30 patients were excluded from the study as they were either type 1 DM or suffering from chronic liver disease and/or chronic renal failure. Diagnosis of DM was done based on the American Diabetes Association 2014 criteria. Data regarding age, sex, height, weight, BMI, blood pressure (BP), A1c, and SUA were collected from patients on proforma. Weight was measured by a weighing machine with a precision of 0.1 kg. Height was measured by a stadiometer with a precision of 0.1 cm. For height measurement, patients were asked to remove footwear and stand with their heads kept in the Frankfort position. BMI was calculated by dividing the weight (in kg) by the square of height (in meters). BP was measured with the help of a digital BP machine.

Around 7 mL of venous blood was collected for fasting plasma glucose, GlyHbA1c, SUA, creatinine, and lipid profile. Blood glucose was estimated by the glucose oxidase-peroxidase method. SUA was estimated by the uricase/peroxidase method. Creatinine was measured by the creatinine enzymatic method. Lipid profile was done by the standard enzymatic method. Ultrasonography was done to rule out cirrhosis. MS was diagnosed by modified NCEP-ATP III criteria. eGFR was calculated by the chronic kidney disease epidemiological creatinine equation. HF was defined as eGFR above the age and gender-specific 95th centile for the subject with normal glucose tolerance, normotensive, and absence of proteinuria. We took Sun et al. 17

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Prevalence of HU and Hypo-U and Looking Beyond SUA in Patients

data for diagnosis of HF. HU was defined as ≥7 mg/dL of SUA in males and ≥6 mg/dL in females. Hypo-U was defined as SUA of <4 mg/dL. This was based on various studies defining the lowest quartile (Hypo-U) of SUA as around 3.87 mg/dL and our laboratory’s lowest SUA value was also 4.2 mg/dL.

Statistical Analysis
The collected data were entered into a Microsoft Office Excel spreadsheet and analyzed. Ratios and percentages were used for analysis. Excel function like mean, standard deviation (SD), and t-test were used. Student’s t-test and Chi-squared test were used to determine the statistical difference between variables. Results were considered significant if the p-value were <0.05. Pearson correlation coefficient and odds ratio were used to establish a relationship between various variables.

Results
A total of 312 newly onset type 2 diabetic patients were recruited in the study. Out of 312 subjects, 218 (69.87%) were male and 94 (30.13%) were female. The demographic and baseline characteristics of the study subjects are presented in Table 1. The mean ± SD age of all male and female patients was 47.03 ± 10.8, 47.03 ± 11.24, and 47.02 ± 9.78 years, respectively. The mean ± SD BMI of all male and female patients were 26.34 ± 4.38, 26.01 ± 3.99, and 27.11 ± 5.12 kg/m², respectively. The GlyHbA1c mean ± SD level was 9.84 ± 2.65, 10.016 ± 2.65, and 9.44 ± 2.63 % in all male and female patients, respectively. The prevalence of MS in all male and female patients were 83.01, 82.11, and 85.11%, respectively. Mean ± SD SUA in all male and female patients was 5.21 ± 1.42, 5.47 ± 1.43, and 4.61 ± 1.21 mg/dL, respectively. The prevalence of HF in all male and female patients was 52.88, 54.59, and 48.94%, respectively. Mean ± SD eGFR in all male and female subjects were 107.71 ± 16.87, 107.2 ± 17.89, and 108 ± 14.23 mL/minute, respectively. Except for SUA, all parameters were not statistically different between males and females. SUA was significantly higher in males as compared to females (p < 0.00001).

The prevalence of HU, normouricemia (NU), and Hypo-U were presented in Table 2. The prevalence of HU in all male and female patients was 12.5, 11.93, and 13.83%, respectively. Regarding the prevalence of NU in all, male and female patients were 68.27, 75.23, and 52.13%, respectively. Hypo-U was present in 19.23, 12.84, and 34.04% of all male and female subjects, respectively. The prevalence of Hypo-U was significantly more in females as compared to males (p < 0.0001) when compared to NU.

Patients were stratified into three groups based on eGFR. Those with eGFR of >97th centile were classified as group I (HF group), while those with eGFR between the 3rd to 97th centile were classified as group II (normofiltration group). Patients with eGFR of <3rd centile were classified as group III (hypofiltration group). SUA (mean) levels in these groups were presented in Table 3. SUA in group I of all, male and female subjects were 4.99, 5.22, and 4.38 mg/dL, respectively. In group II, SUA in all male and female patients were 5.34, 5.61, and 4.81 mg/dL, respectively. In group III, the SUA level in all male and female subjects were 7.15, 7.61, and 5.3 mg/dL, respectively. SUA level is significantly less in HF (group I) as compared to normofiltration (group II) in all patients. The number of patients in hypofiltration was very less, so we do not compare groups II and III.

The diabetic population was again stratified into two groups based on SUA of <4mg/dL (hypouricemic group) and ≥4mg/dL (nonhypouricemic; group II). Demographic and other baseline characteristics of these two groups are presented in Table 4. Mean ± SD age in groups I and II were 46.1 ± 10.44 and 47.25 ± 10.89 years, respectively.

Table 1: Baseline and demographic profile of study subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All</th>
<th>Male</th>
<th>Female</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>312 (100%)</td>
<td>218 (69.87%)</td>
<td>94 (30.13%)</td>
<td>&lt;0.99</td>
</tr>
<tr>
<td>Age</td>
<td>47.03 ± 10.08</td>
<td>47.03 ± 11.24</td>
<td>47.02 ± 9.77</td>
<td>&lt;0.065</td>
</tr>
<tr>
<td>BMI</td>
<td>26.34 ± 4.38</td>
<td>26.01 ± 3.99</td>
<td>27.11 ± 5.12</td>
<td>&lt;0.0756</td>
</tr>
<tr>
<td>GlyHbA1c</td>
<td>9.84 ± 2.65</td>
<td>10.016 ± 2.65</td>
<td>9.44 ± 2.63</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>SUA</td>
<td>5.209 ± 1.42</td>
<td>5.468 ± 1.43</td>
<td>4.607 ± 1.21</td>
<td>&lt;0.5178</td>
</tr>
<tr>
<td>MS (present)</td>
<td>83.01%</td>
<td>82.11%</td>
<td>85.11%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MS (absent)</td>
<td>16.99%</td>
<td>17.89%</td>
<td>14.89%</td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td>107.709 ± 16.87</td>
<td>107.2 ± 17.89</td>
<td>108.89 ± 14.23</td>
<td>&lt;0.374</td>
</tr>
<tr>
<td>HF</td>
<td>52.88%</td>
<td>54.59%</td>
<td>48.94%</td>
<td></td>
</tr>
<tr>
<td>NON-HF</td>
<td>47.22%</td>
<td>45.41%</td>
<td>51.06%</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Prevalence of HU and Hypo-U in study subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All</th>
<th>Male</th>
<th>Female</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HU</td>
<td>12.5%</td>
<td>11.93%</td>
<td>13.83%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Normouricemia</td>
<td>68.27%</td>
<td>75.23%</td>
<td>52.13%</td>
<td></td>
</tr>
<tr>
<td>Hypo-U</td>
<td>19.23%</td>
<td>12.84%</td>
<td>34.04%</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: SUA levels in different eGFR groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All</th>
<th>Male</th>
<th>Female</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF (group I)</td>
<td>4.99</td>
<td>5.22</td>
<td>4.34</td>
<td>&lt;0.018</td>
</tr>
<tr>
<td>Normofiltration (group II)</td>
<td>5.34</td>
<td>5.61</td>
<td>4.81</td>
<td></td>
</tr>
<tr>
<td>Hypofiltration (group III)</td>
<td>7.15</td>
<td>7.61</td>
<td>5.3</td>
<td></td>
</tr>
</tbody>
</table>

p-value < 0.0001 between Hypo-U and NU between male and female

p-value < 0.018 between groups I and II in all patients
Prevalence of HU and Hypo-U and Looking Beyond SUA in Patients

The mean ± SD BMI of groups I and II was 24.68 ± 5.45 and 26.74 ± 3.99 kg/m², respectively. The prevalence of MS in group I was 73.33%, while it was 85.32% in group II. SUA, mean ± SD in group I and group II was 3.39 ± 0.45 and 5.64 ± 1.22 mg/dL, respectively. Mean ± SD eGFR in groups I and II was 112.06 and 106.67 mL/minute, respectively. The prevalence of males in group I was statistically less than in group II. The prevalence of HF was 66.67% in group I, while it was 50% in group II, and the difference was statistically significant. Except for age, all parameter was statistically different between the two groups.

The predictor of Hypo-U is presented in Table 5. We found BMI (<25), GlyHbA1c (≥9), HF, and patients without MS are a predictor of Hypo-U in our study. The strongest predictor was BMI (<25) with an odd ratio of 3.28 with a 95% confidence interval (CI) of 1.796–5.761 followed by GlyHbA1c (≥9) with an odd ratio of 2.06 95% CI; 1.104–3.85). High prevalence rate (25%) of HU in diabetic patients was also reported by Ogbera et al. and the reasons for high prevalence could be due to older and more obese patients with long duration of diabetes and different ethnicity (African vs Indian). High prevalence of HU has also been reported in different countries—South Korea—5%, Spain—5–11%, Iran and Saudi Arabia—8%, China—6–25%, Sweden—10–16%, Italy—9–12%, Mexico—11%, Thailand—9–11%, Taiwan—10–52%, Turkey—12%, Brazil—13%, Nigeria and Russia—17%, Indonesia—18%, United States of America—21–23%, Seychelles—25%, and Japan—20–26%.

The recently low uric acid level has been reported in diabetic patients as compared to controls. Reasons for low SUA in diabetic patients can be due to high GFR, low-calorie intake, elevated extracellular volume, and osmotic diuresis causing uricosuria in diabetic patients. In our study, Hypo-U was prevalent in 19.23% of cases. Bindu-Pavani et al. also reported Hypo-U in type 2 diabetes patients from India, but they did not report the prevalence. This study, for the first time from India, reports the prevalence of Hypo-U in diabetes patients. Bo et al. from Italy reported the prevalence of Hypo-U (lower tertile) as 33.64%. High rate of Hypo-U in their study as compared to ours could be due to the low rate of hypertension in their study. In our study, low Hypo-U is associated with female patients with lower BMI, higher eGFR, poor control of blood glucose, and patients without MS. MS is an indicator of insulin resistance or hyperinsulinemia. This means that our hypouricemic patients are primarily insulin deficient and not primarily insulin resistant (MS). We propose that hypouricemic diabetic patients are a different phenotype from diabetic patients. Since these patients are primarily insulin deficient, they should be managed preferably by insulin secretagogue along with insulin sensitizers. SUA was less in females as compared to males in our study and it is reported by others also. The reason for lower SUA in females is due to high estrogen levels. Estrogen is known to have uricosuric properties. Other reasons for high SUA levels in males are different eating habits, exercise, and commute methods. SUA in MS patients is more than those without MS (data not shown). This is also reported by others. The prevalence of Hypo-U was less in patients with MS in our study. The reason for high SUA in MS is due to hyperinsulinemia. Insulin is known to cause increased reabsorption of uric acid from the kidney. Other reasons are high BMI, hypertension, hypertriglyceridemia, and impaired glucose tolerance in MS patients.

SUA was less in the HF group as compared to normofiltration group. This was also reported by other studies. HF is known to increase uric acid clearance from the kidney and that’s why Hypo-U is an indicator of high eGFR. So, when there is Hypo-U in diabetic patients, one should use drugs that reduce HF in order to prevent further kidney damage. There were a few limitations in our study. First, it was a single-center study, so referral bias might have played a role in including sicker patients. Second, the number of female patients was less than males. Third, there was

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hypouricemic group I</th>
<th>Nonhypouricemic group II</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>60 (19.23%)</td>
<td>252 (80.77%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>46.67%</td>
<td>75.4%</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>53.33%</td>
<td>24.6%</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>46.1 ± 10.44</td>
<td>47.25 ± 10.89</td>
<td>&lt;0.449</td>
</tr>
<tr>
<td>BMI</td>
<td>24.68 ± 5.45</td>
<td>26.74 ± 3.99</td>
<td>&lt;0.007</td>
</tr>
<tr>
<td>GlyHbA1c</td>
<td>10.928 ± 2.84</td>
<td>9.58 ± 2.54</td>
<td>&lt;0.00117</td>
</tr>
<tr>
<td>MS(present)</td>
<td>73.33%</td>
<td>85.23%</td>
<td>&lt;0.0263</td>
</tr>
<tr>
<td>MS(absent)</td>
<td>26.67%</td>
<td>14.68%</td>
<td></td>
</tr>
<tr>
<td>SUA</td>
<td>3.39 ± 0.45</td>
<td>5.64 ± 1.22</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>eGFR</td>
<td>112.06 ± 14.56</td>
<td>106 ± 17.24</td>
<td>&lt;0.0145</td>
</tr>
<tr>
<td>HF</td>
<td>66.67%</td>
<td>50%</td>
<td>&lt;0.020</td>
</tr>
<tr>
<td>NON-HF</td>
<td>33.33%</td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>

**DISCUSSION**

In the present cross-sectional study, we find the overall prevalence of HU as 12.5%. Normouricemia was present in 68.27%, while Hypo-U was present in 19.23% of patients. The prevalence of HU was lower in our study than those reported by Billa et al.15 In their study, the prevalence of HU in diabetic patients was 33.6%. The reason for the lower prevalence of HU in our study could be due to the lower age of patients and short duration of diabetes (<1 year) and different study populations (Pan India vs Eastern Uttar Pradesh). In obese patients, Remedios et al. also found a high prevalence of HU at 44.6%. The reason for the low prevalence in our study as compared to Remedios could be due to low BMI and a different cutoff value of HU and different study populations (obese vs diabetes). High prevalence rate (25%) of HU in diabetic patients was also reported by Ogbera et al. and the reasons for high prevalence could be due to older and more obese patients with long duration of diabetes and different ethnicity (African vs Indian). High prevalence of HU has also been reported in different countries—South Korea—5%, Spain—5–11%, Iran and Saudi Arabia—8%, China—6–25%, Sweden—10–16%, Italy—9–12%, Mexico—11%, Thailand—9–11%, Taiwan—10–52%, Turkey—12%, Brazil—13%, Nigeria and Russia—17%, Indonesia—18%, United States of America—21–23%, Seychelles—25%, and Japan—20–26%

The recently low uric acid level has been reported in diabetic patients as compared to controls. Reasons for low SUA in diabetic patients can be due to high GFR, low-calorie intake, elevated extracellular volume, and osmotic diuresis causing uricosuria in diabetic patients. In our study, Hypo-U was prevalent

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (&lt;25)</td>
<td>&lt;0.007</td>
</tr>
<tr>
<td>GluHbA1c (≥9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patient without MS</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>HF</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Age (&lt;45)</td>
<td>&lt;0.449</td>
</tr>
</tbody>
</table>
no healthy control to compare SUA levels between patients and healthy individuals. Fourth dietary habits and alcohol intake were not recorded in the study and all know that these affect SUA levels.

In conclusion, the overall prevalence of HU, Hypo-U, and NU in our study was 12.5, 19.23, and 68.27%, respectively. SUA level is more in males, MS patients, and patients with low eGFR. Hypouricemic diabetic patients are phenotypically different than nonhypouricemic patients. They are characterized by female sex, lower BMI (<25), less insulin resistance, higher GlyHbA1c level, and higher eGFR. In the era of precision medicine, this study is a small effort for treatment. Since the prevalence of HU and Hypo-U are highly prevalent in diabetes patients. They are characterized by female sex, lower BMI (<25), less insulin resistance, higher GlyHbA1c level, and higher eGFR. In the era of precision medicine, this study is a small effort for treatment. Since the prevalence of HU and Hypo-U are highly prevalent in diabetes patients, SUA should be tested routinely and treated accordingly. Hypouricemic diabetic patients are phenotypically different and so they should be treated differently.

References


Announcement

Association of Physicians of India (API) is planning to come out with Members directory this year. All the members are requested to send their updated contact details in the following format by e-mail at api.hdo@gmail.com or by WhatsApp message to phone number 9619561612 by 31st May 2023.

Name:
Life membership number:
Address:
Mobile number:
e-mail ID:

Dr Girish Mathur
President

Dr Agam Vora
Hon. General Secretary
Clinical Profile and Outcome of Snake Bite Patients from Tertiary Healthcare Center: In Sub-Himalayan Region: A Medical College-based Study

Ram Chander Negi1, Prem Machhan2, Monika Raj3, Vijay Kumar Barwal4*, Subhash Chander5, Suman Thakur6, Jatinder Mokta7

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Abstract

Objective: Snake bite is an emergency in tropical and subtropical countries. It is a neglected disease and is most commonly seen in rural setups, where people are ignorant about the venomous snake bites. It results in increased mortality and morbidity because precious time is wasted, either in consulting traditional healers or waiting for the development of signs and symptoms of envenomation. Then only the patient is shifted to a health center. Here we studied the clinical profile, management, and outcome of snake bite patients.

Materials and Methods: This study was done by retrieving the records of patients with snake bites admitted to the Department of Medicine, Indira Gandhi Medical College & Hospital, Shimla, from 13 January 2017 through December 2019. The recorded data was entered in a precoded performa, and analysis was done with respect to various variables.

Result: We evaluated the records of 190 patients. The incidence of the bite was higher among females, 62.1% (n = 118). The commonest age group involved was 21–50 years, 70.1% (n = 34). In 55.8% (n = 106), the site of the bite was the upper limb. The daytime bite was present in 54.7% (n = 106). The maximum incidence of snake bites was found during the rainy season, 81.5% (n = 155). 28.4% (n = 54) of patients presented within 6 hours of the bite. Coagulopathy [whole blood clotting test (WBCT) of >20 minutes] and neurotoxicity were seen in 77.9 and 7.9% of patients, respectively. Anti-snake venom (ASV) was given to 87.8% (n = 167) of patients. In 80% (n = 152) of the cases, hospital stay was up to 3 days. Mortality was seen in only two (1.05%) cases.

Conclusion: There is a need to create awareness among the community, particularly in rural areas, about snake bite envenomation and early transportation of victims to the nearest health center. Training of health professionals is also needed to manage cases of snake bites efficiently and judiciously, thereby reducing morbidity and morbidity.

Introduction

Snakebite is a major public health problem. It is a medical emergency most commonly seen in rural areas, where people are involved in outdoor activities, more so in tropical and subtropical countries. A total of >2.5 lakh snake bites are reported every year in India.1 We have the highest number of deaths due to snake bites in the world, and about 35,000–50,000 people die/per year, as per World Health Organization (WHO) report.2,3 The WHO included snake bites in its list of neglected tropical conditions in 2009. In Himachal Pradesh, around 90% of the population lives in rural areas.4 Their livelihood depends on agriculture, horticulture, and the rearing of livestock. So, their probability of getting a snake bite is high during summer and, most commonly, during the rainy season. Delay in reporting to the health center is due to many factors like lack of awareness, lack of knowledge, inaccessible transportation, and road facility due to difficult topography and terrain.

Materials and Methods

It is a retrospective descriptive observational study. We retrieved and analyzed all the cases of snake bites that were >18 years of age and admitted to the Department of Medicine from 13 January 2017 through December 2019. The data was retrieved from the record section of Indira Gandhi Medical College, 850 bedded hospital situated in the Capital of Himachal Pradesh. The recorded information was entered in a precoded performa. We included details with respect to demographic profile, clinical profile, management, and outcome of patients. Discrete data were summarized using numbers (n) and percentages (%) along with 95% confidence intervals (CI). Continuous data were summarized using mean (standard deviation).

Results

We evaluated and analyzed the records of 190 patients. Out of these, 118 were females with a mean age of 38.8 ± 14.1 years, and 72 were males with a mean age of 42.1 ± 14.1 years. The overall mean age was 40.8 ± 14.2 years. Snakebite was more common in young. 51% of patients were in the age group of 18–40 years. Occupation-wise, 99 (52.1%) were housewives, and 58 (30.6%) were farmers (Table 1). The site of bite in 106 (55.8%) was seen in the upper limb, and in 84 (44.2%), it was in the lower limb. The bite mark was present in 186 (97.9%) and absent in 4 (2.1%). Delay in reporting to the health center after >6 hours of snake bite was seen in 28.4% of patients (Table 2). The maximum incidence of snake bites, that is, 81.5%, was seen during the rainy season from June to September. There was no admission of snake bite cases during the months of December–February (Table 1). The majority of reported cases were from the districts of Shimla (63.7%), followed by Solan (13.7%) and Mandi (11.6%) (Table 3). Coagulopathy (WBCT of >20 minutes) was noted in 148 (77.9%) cases. The neurotoxicity was seen in 15 (7.9%) cases. Regarding the use of ASV, we found 50 (26.3%) patients required 5–10 vials (50–100 mL), 62 (32.6%) patients 10–20 vials (100–200 mL), and 39 (20.5%) patients 20–30 vials (200–300 mL) of ASV were given. A total of >30 vials (300 mL) of ASV were required only in 16 (8.4%) patients. Local complications like edema, cellulitis, and necrosis were seen in 32 (16.8%), while 11 (5.8%) patients developed acute kidney injury (AKI) (Table 4). The

average hospital stay of patients was <4 days, and mortality occurred in just two (1.1%) cases (Table 5). We also observed that >90% of the patients had used a tourniquet immediately after the snake bite. However, it is to be noted that no delayed toxicity was seen in any of the patients who reported for follow-up.

**Discussion**

The state of Himachal Pradesh is a hilly area situated in the northwestern Himalayas. Himachal is well known for its rich flora and fauna. Forests cover about 27.72% (15433 sq km) of the state’s area. The state has an ideal environment for the different species of reptiles. Probability of snake bite is more common in people who engage in outdoor activities in fields. Venomous snake inhabits the foothills and mountainous ranges of the state. Incidence of snake bite was more common in the age group of 18–40 years. Common incidence of snake bites in young patients was also reported by Raina et al. and Ali et al. Young people are more actively involved in outdoor activities, and their chance of bite by a snake is high as compared to other age groups. In the present study, 62.2% (118) were females. More incidence of snake bites in females was also reported by Kaushik et al. and Gupt et al., who reported a 54% incidence of snake bites in females in their study from Himachal Pradesh. In the hilly area of Himachal Pradesh, females are working more than males in irrigating the fields, cutting grass for animals, and harvesting crops. So, their chances of an encounter with snakes are high. Contrary to this, Raina et al. reported a high incidence in males as compared to females. This may be because of the difference in working culture and farming activities in the upper part of Himachal and in the lower part of Himachal, as Raina et al. did study in the lower part of Himachal, mostly in foothills with a hot and humid climate. We found that the common site of the bite was the upper limbs 62.1% (n = 106), mostly in hands and fingers, bitten during the cutting of grass in the forest, working in fields, and harvesting crops. Gupt et al. also reported a higher incidence of bite on the upper limb, mostly on the left upper limb. Kuiksh et al. and Sujeet et al. reported common sites of bite in lower limbs, 44.88 and 55%, respectively. A study by Mathur et al. also reported the incidence of the most common site of bite in lower limbs (50%). A similar incidence in lower limbs was reported by Saini et al. in their study of snake poisoning. The difference in the common site of the bite may be because of the difference in the timing of the bite and the working culture of the people of the catchment area. The studies which reported bites on lower limbs have reported nighttime more common than daytime, which correlates with more incidence of bites in lower limbs. But in hilly areas, people do not work at night time. Hence in the present study, the most common timing of bite was at daytime in 54.7% (n = 104), followed by nighttime in 18% (n = 36). In another study by Kuiksh et al., the most common timing of bite was observed during the daytime between 7 AM and 7 PM. The incidence of more bites during the daytime in the present study is correlated with the maximum chances of an accidental encounter with snakes during maximum outdoor activities of human beings.

The majority of snake bite incidence was seen during the summer and rainy seasons. In the present study, 81.5% (155) cases were admitted to the hospital with snake bites from June to September. Another study

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**Table 1: Sociodemographic profile of snake bite patients (N = 190)**

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Number (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Housewife</td>
<td>99 (52)</td>
<td>44.75–59.39</td>
</tr>
<tr>
<td>Farmer</td>
<td>58 (30.5)</td>
<td>24.07–37.61</td>
</tr>
<tr>
<td>Student</td>
<td>32 (16.8)</td>
<td>11.81–22.94</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.5)</td>
<td>0.01–2.90</td>
</tr>
</tbody>
</table>

**Table 2: Epidemiological profile of snake bite (N = 190)**

<table>
<thead>
<tr>
<th>Site of bite</th>
<th>Number (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper limb</td>
<td>106 (55.8)</td>
<td>48.42–62.97</td>
</tr>
<tr>
<td>Lower limb</td>
<td>84 (44.2)</td>
<td>37.03–51.58</td>
</tr>
</tbody>
</table>

**Delay in reporting**

| >6 hours | 54 (28.4) | 22.13–35.40 |
| 12–24 hours | 31 (16.3) | 11.36–22.35 |
| >24 hours | 42 (22.1) | 16.42–28.68 |

**Timing of bite**

| Morning (4–7 AM) | 20 (10.5) | 6.55–15.79 |
| Day (7 AM–5 PM)  | 104 (54.7) | 47.37–61.95 |
| Evening (5–8 PM) | 30 (15.8) | 10.91–21.77 |
| Night (8 PM–4 AM) | 36 (18.9) | 13.64–25.25 |
Clinical Profile and Outcome of Snake Bite Patients

Table 3: Region-wise distribution of snake bite cases (N = 190)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>District</th>
<th>Number of cases</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Lahaul and Spiti</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Kinnaur</td>
<td>4 (2.1)</td>
<td>0.58–5.30</td>
</tr>
<tr>
<td>3.</td>
<td>Kullu</td>
<td>3 (1.6)</td>
<td>0.33–4.54</td>
</tr>
<tr>
<td>4.</td>
<td>Shimla</td>
<td>121 (63.7)</td>
<td>56.41–70.52</td>
</tr>
<tr>
<td>5.</td>
<td>Solan</td>
<td>26 (13.7)</td>
<td>9.14–19.40</td>
</tr>
<tr>
<td>6.</td>
<td>Sirmour</td>
<td>2 (1.1)</td>
<td>0.13–3.75</td>
</tr>
<tr>
<td>7.</td>
<td>Mandi</td>
<td>22 (11.6)</td>
<td>7.40–17.00</td>
</tr>
<tr>
<td>8.</td>
<td>Bilaspur</td>
<td>10 (5.3)</td>
<td>2.55–9.47</td>
</tr>
<tr>
<td>9.</td>
<td>Kangra</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>Chamba</td>
<td>1 (0.5)</td>
<td>0.01–2.90</td>
</tr>
<tr>
<td>11.</td>
<td>Hamirpur</td>
<td>1 (0.5)</td>
<td>0.01–2.90</td>
</tr>
<tr>
<td>12.</td>
<td>Una</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Clinical presentation (N = 190)

<table>
<thead>
<tr>
<th>Signs and symptoms of envenomation</th>
<th>Number (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>164 (86.3)</td>
<td>80.60–90.86</td>
</tr>
<tr>
<td>Systemic</td>
<td>160 (84.2)</td>
<td>78.23–89.09</td>
</tr>
<tr>
<td>Hemotoxic</td>
<td>148 (77.9)</td>
<td>71.32–83.58</td>
</tr>
<tr>
<td>Neurotoxic</td>
<td>15 (7.9)</td>
<td>4.49–12.69</td>
</tr>
<tr>
<td>Both (hemotoxic and neurotoxic)</td>
<td>1 (0.5)</td>
<td>0.01–2.90</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complications</th>
<th>Number (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>32 (16.8)</td>
<td>11.81–22.94</td>
</tr>
<tr>
<td>AKI</td>
<td>11 (5.8)</td>
<td>2.93–10.12</td>
</tr>
</tbody>
</table>

Table 5: Management and outcome

<table>
<thead>
<tr>
<th>ASV</th>
<th>Number (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–100 mL (5–10 vials)</td>
<td>50 (26.3)</td>
<td>20.21–33.18</td>
</tr>
<tr>
<td>100–200 mL (10–20 vials)</td>
<td>62 (32.6)</td>
<td>26.02–39.79</td>
</tr>
<tr>
<td>200–300 mL (20–30 vials)</td>
<td>39 (20.5)</td>
<td>15.02–26.97</td>
</tr>
<tr>
<td>&gt;300 mL (30 vials)</td>
<td>16 (12.1)</td>
<td>4.89–13.32</td>
</tr>
<tr>
<td>ASV not given</td>
<td>23 (12.1)</td>
<td>7.83–17.61</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospital stays (days)</th>
<th>Number (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 3 days</td>
<td>152 (80)</td>
<td>73.60–85.44</td>
</tr>
<tr>
<td>Up to 5 days</td>
<td>19 (10)</td>
<td>6.13–15.18</td>
</tr>
<tr>
<td>Up to 7 days</td>
<td>9 (4.7)</td>
<td>2.19–8.80</td>
</tr>
<tr>
<td>&gt;7 days</td>
<td>10 (5.3)</td>
<td>2.55–9.47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ventilatory support given</th>
<th>Number (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>4 (2.1)</td>
<td>0.58–5.30</td>
</tr>
<tr>
<td></td>
<td>2 (1.05)</td>
<td>0.13–3.75</td>
</tr>
</tbody>
</table>

by Kaushik et al. observed 60.25% of the cases presented to the hospital from July to September.7 Mathur et al. also reported that 60.6% of cases occurred between June to November.11 Sharma et al. also reported a maximum incidence of snake bites at 58.33% during monsoon season. During this period, the habitat of reptiles may be flooded, and they wander in search of shelter and their prey which leads to encounters with human beings. No case of snake bite was observed during the months of December–February. We have observed 28.4% of cases reported to a health center within 6 hours of snake bite. Mathur et al. reported that 41% of the patients reached the health center within 6 hours of a snake bite.11 In another study by Sharma et al. from Jammu and Kashmir, 48.96% of the cases presented within 6 hours of a bite.12 Raina et al. from Himachal, in their study of snake bite profiles, reported 23% of cases presented to the hospital after 6 hours of snake bite.8 Delay in reporting to the health center may be due to unawareness about the seriousness of venomous snake bites, wasting time in consulting traditional healers, adopting a wait and watch phenomena for the development of signs and symptoms of envenomation and inaccessibility to transportation due to difficult topography and terrain. We also found that >90% of cases had used a tourniquet immediately after the snake bite. Despite the new guidelines which discourage its use, people get a sense of false security by using a tourniquet. Hence it causes a delay in seeking medical care, thereby increasing the morbidity as well as mortality of snake bite cases.

Many patients reported late and hence presented with local and systemic complications. Local complications like edema, cellulitis, necrosis, and bleeding from the site of the bite were seen in 16% (n = 32) of patients. Raina et al. reported 21.9% of cases with local complications.8 The bites by Himalayan pit vipers are known for predominant local signs in the form of pain, marked swelling, bruising, and bleeding. The green color is the most common color of snake recognized by victims. The green pit viper is quite common in Himachal Pradesh and is known to be hemotoxic.13 In the present study, AKI was seen in 5%, commonly observed in patients with coagulopathy and in those who received a large amount of ASV because of persisting coagulopathy (WBCT of <20 minutes). Sujeet et al. reported that 11% of cases presented with AKI.8 Another study from Himachal reported 14.1% of cases presented with AKI.7 In India, the incidence of acute renal failure is reported in 13–32% of cases, mostly following a viper bite.14 The venomous snake bite patients presented with either haemotoxicity or neurotoxicity. In the present study, 77.9% presented with coagulopathy, that is, whole blood clotting persisting for >20 minutes (WBCT of >20 minutes) at the time of admission. In other studies, reported by Himachal, Kaushik et al. and Raina et al., reported coagulopathy in 51.02 and 36%, respectively.25 Coagulopathy and platelet dysfunction are generally induced by viperid venoms. Coagulopathy, when present, is diagnostic of viper and pit viper bites in South Asia and is demonstrated by observing a 20-minute WBCT.15 The predominance of hematotic manifestation in the present study may be because of the widespread distribution of green pit viper in Shimla and in adjoining districts. In this region, elapids and krait are not common. We found that all patients with neurotoxicity (7.9%) presented with ptosis, ophthalmoplegia, descending paralysis, and respiratory depression. A study by Raina et al. reported that 28.5% of the patients presented with neurotoxicity. The higher percentage may be because it was conducted in the lower part of Himachal Pradesh, where elapids and krait are more commonly found.8 Neurapraxic patients generally presented in the morning with signs and symptoms, without any apparent mark of bite and pain. These types of presentation are seen in krait bite. The krait
The specific antidote available for the management of snake envenomation is ASV. In India, available polyvalent ASV covers only the “big four” species, that is, common cobra, common krait, russel viper, and saw scaled viper. The best option to avoid mortality and morbidity is the early administration of ASV. The best option to avoid mortality is the early administration of ASV. In the present study, 32.6% (n = 62) received 10–20 vials of ASV, and 20.5% (n = 32) received 20–30 vials, which corresponds with another study from Himachal Pradesh which used 1–40 vials (mean 23.41 ± 8.72 vials). Raina et al., in their study, observed that the mean dose of ASV used was 292 + 1.688 mL. Another study by Mathur et al. reported the use of 32.62 vials in hemotoxic and 10.0 vials in neurotoxic snake bite cases. Present study corresponds with the national snake bite management protocol 2008 (India), which has recommended a maximum dose of ASV for hemotoxic and neurotoxic bites as 30 vials (300 mL) and 20 vials (200 mL), respectively. In the present study, 12.1% (n = 23) did not receive ASV because no signs and symptoms of envenomation were observed. In such patients, probably, the bite was dry, or it was by a non-poisonous snake. There is a lot of uncertainty in the dose of ASV, and sometimes ASV may be avoided by treating physicians due to inexperience and fear of anaphylaxis. Sometimes ASV was administered irrationally, not indicated at all, resulting in a waste of resources and exposing patients to toxicity. Besides the WHO guidelines, there is a National Protocol on snake bite management formulated by the Ministry of Health and Family Welfare, Government of India. In the present study, 80% (n = 152) have a hospital stay of up to 3 days. In another study from Rajasthan, Hemant et al. reported a mean duration of hospital stay of 3.32 ± 0.78 days. Omogbai et al. reported a mean duration of stay in the hospital of 5.7 ± 51 days. In our study, overall mortality was 2 (1.1%) because of coagulopathy and acute renal failure. Other studies done by Patil et al. and Punde et al. have reported a mortality of 1.94 and 4.7%, respectively. Mortality in snake bites is commonly seen because of delays in reporting to the health center resulting in respiritory paralysis from neurotoxic venom and renal failure or bleeding in hemotoxic envenomation.

Preventive Measures
Snake bites can be prevented to a large extent if we follow simple preventive measures like; wearing long, loose pants and high, thick leather boots, remaining on the walking path, and staying out of snake-infested areas. Use a stick to poke in front while walking to scare away the snakes and carry a torch while moving out at night. Keep the surroundings of your house free from garbage and junk material. Avoid sleeping on the ground, dust bedding before sleeping, and use mosquito nets while sleeping at campsites. Don’t touch or handle a dead snake, as it may bite due to reflex action.

CONCLUSION
Snakebite is a common occupational hazard mostly seen in people involved in agriculture activities. From this study, it is inferred that delay in presentation between snake bite and administration of ASV leads to more complications, hospital stays and mortality. Ignorance, unawareness, difficult topography, and terrain are responsible for the delay in presentation. Lack of proper training and exposure in the management of venomous snake bites is a basic problem among physicians in managing poisonous snake bite cases. People should be educated about protection from snake bites and the advantage of prompt transportation of victims to the nearest health center.

REFERENCES
Abridged Prescribing Information

Active Ingredients: Metformin hydrochloride (as sustained release) and glimepiride tablets

Indication: For the management of patients with type 2 diabetes mellitus when diet, exercise and single agent (glimepiride or metformin alone) do not result in adequate glycemic control.

Dosage and Administration: The recommended dose is one tablet daily during breakfast or the first main meal. Each tablet contains a fixed dose of glimepiride and Metformin Hydrochloride. The highest recommended dose per day should be 8 mg of glimepiride and 2000 mg of metformin. Due to prolonged release formulation, the tablet must be swallowed whole and not crushed or chewed.

Adverse Reactions:
- For Glimepiride: hypoglycaemia may occur, which may sometimes be prolonged. Occasionally, gastrointestinal (GI) symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhoea may occur. Hepatitis, elevation of liver enzymes, cholestasis and jaundice may occur. Allergic reactions or pseudo allergic reactions may occur occasionally. For Metformin: GI symptoms such as nausea, vomiting, diarrhoea, abdominal pain, and loss of appetite are common during initiation of therapy and may resolve spontaneously in most cases.
- Metallic taste, mild erythema, decrease in Vit B12 absorption, very rarely lactic acidosis, Hemolytic anemia, Reduction of thioridazine levels in patients with hyperthyroidism.

Warnings and Precautions:
- For Glimepiride: patient should be advised to report promptly exceptional stress situations (e.g., trauma, surgery, febrile infections), blood glucose regulation may deteriorate, and a temporary change to insulin may be necessary to maintain good metabolic control. Metformin Hydrochloride may lead to lactic acidosis; in such cases metformin should be temporarily discontinued and contact with a healthcare professional is recommended. Sulfonylureas have an increased risk of hypoglycaemia. Long-term treatment with metformin may lead to peripheral neuropathy because of decrease in vitamin B12 serum levels. Monitoring of the vitamin B12 level is recommended.
- For Metformin: GI symptoms such as nausea, vomiting, diarrhoea, abdominal pain, and loss of appetite are common during initiation of therapy and may resolve spontaneously in most cases. Metallic taste, mild erythema, decrease in vitamin B12 absorption, very rarely lactic acidosis, Hemolytic anemia, Reduction of thioridazine levels in patients with hyperthyroidism.

Contraindications:
- Hypersensitivity to the active substance of glimepiride & Metformin or to any of the excipients listed.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis, diabetic pre-coma).
- Severe renal failure (GFR < 30 ml/min).
- In pregnant women.
- In lactating women.
- Acute conditions with the potential to alter renal function (dehydration, severe infection). In pregnant women. In lactating women. Acute conditions with the potential to alter renal function (dehydration, severe infection). In pregnant women. In lactating women. Acute conditions with the potential to alter renal function (dehydration, severe infection).
- Acute or chronic kidney disease which may cause tissue hypoxia (cardiac or respiratory failure, recent myocardial infarction, shock); hepatic insufficiency; acute alcohol intoxication; alcoholism.
- Use in a special population: Pregnant Women. Due to a lack of human data, drugs should not be used during pregnancy. Lactating Women. It should not be used during breastfeeding. Pediatric Patients: The safety and efficacy of drugs has not yet been established. Renal Impairment: A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of future progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

Additional information is available on request.

Last updated: March 13, 2023

* In case of any adverse events, kindly contact: pv@usv.in
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To Study the Effectiveness of Inhalation Technique Training in Patients with COPD and Asthma

Manoj Meena1, Piyush Arora2, M Srikanth Goud3, Lokender Kumar4

Accepted: 16 February 2023

ABSTRACT

Introduction: Asthma and chronic obstructive pulmonary disease (COPD) are characterized by chronic airway inflammation. Lack of knowledge about the correct inhalation techniques leads to poor control of both diseases. This study aimed to study the effectiveness of inhalation technique training in patients with COPD and asthma.

Materials and methods: A total of 132 patients fulfilling the inclusion criteria were trained with the correct technique of inhalation on day 0 and at the end of 1 and 6 months. Evaluation of technique training was done on these three occasions posttraining. The mean score of devices was obtained, and the mean inhalation technique score of various devices was compared.

Results: Out of 132 patients, 65.1% (86/132) patients were using a dry powdered inhaler (DPIs), 26.5% (35/132) patients used metered dose inhalers (MDIs), and 8.4% (11/132) patients used MDI with spacer. The mean scores of patients using MDI at baseline were 5.68 ± 0.83, and after 1 month, 6.68 ± 0.58 (p < 0.000). The inhalation technique mean score of MDI improved after 6 months, 7.02 ± 0.56 as compared to baseline (p < 0.008) mean score of the patients using DPIs improved after 1 month, 5.53 ± 0.58 as compared to baseline 4.37 ± 5.53 (p < 0.000). There was no statistical improvement in the device mean score of DPIs after 6 months, 5.62 ± 0.55 when compared with 1 month, 5.53 ± 0.58 (p < 0.117). Patients who used pressurized metered-dose inhalers (pMDI) with spacers improved their inhalation score after 1 month by 6.90 ± 0.94 as compared to the baseline score of 6.90 ± 0.94 (p < 0.001). The mean score decreased marginally after 6 months, 7.818 ± 0.60, as compared to the score at the end of 1 month of 8.27 ± 0.64 (p < 0.053).

Discussion: Patients showed improvement in the technique of inhalation after educational training, instructions, and a standard checklist.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is defined as a heterogeneous lung condition characterized by chronic respiratory symptoms of dyspnea, cough, sputum production, and exacerbations due to abnormalities of the airways (bronchitis and bronchiolitis) and/or alveoli (emphysema) that causes a persistent, often progressive, airflow obstruction.1 Severity of COPD in an individual is proportional to the exacerbations and comorbidities. Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation and a history of respiratory symptoms such as wheezing, shortness of breathe, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation.2 The core of the treatment for both these chronic entities lies in the right inhalation therapy with a proper technique that delivers the drug directly to the diseased site and provides the largest results with the slightest of adverse effects. On the contrary, there are some associated disadvantages with inhalation therapy as well, which results due to improper inhalation technique by the patients.3 The right inhalation technique is essential to deliver the required amount of inhaled drug to the Airways and improve the drug’s efficacy. However, the fallacious inhalation technique is very much common in patients with chronic airflow limitation3–5; hence right training is a must for all these patients to ensure maximal delivery of the inhaled drug.6–9 A substandard inhaler technique has been exhibited by many patients using both MDIs as well as DPIs. Various studies have revealed that to achieve a flawless inhalation technique, both written and verbal instructions along with stepwise inhalation training and further assessments of this technique are necessary to achieve good results. This applies to all inhaler devices, including the breathe-actuated ones.10 The primary aim of this study was to improve the inhaler technique by imparting education on the inhalation technique to the patients.

MATERIALS AND METHODS

The study was a follow-up observational study that included patients of COPD and bronchial asthma using any of the inhalation devices and attending outpatient clinics at the National Institute of Tuberculosis and Respiratory Diseases, Delhi, India.

The inclusion criteria for the study were:
• Diagnosed cases of COPD or bronchial asthma, who were using any inhalation device.
• Age 15–60 years.
• Signed consent form.

The exclusion criteria of the study were:
• Age <15 or >60 years.
• Patients having active infection of tuberculosis.
• Any associated comorbid condition which may hinder inhalation device use.
• Patients who are not willing to be a part of the study.

A total of 176 patients were taken up for the study, 40 patients did not turn up for further assessments, and they were excluded from the study, and 132 patients were analyzed. Patients fulfilling the inclusion criteria were given correct inhalation technique training on day 0 and at the end of 1 month. Evaluation of inhalation technique was done on three occasions—at baseline, at the end of 1 month, and 6 months posttraining. A score of 1 was given to each of the step performed correctly for different devices (maximum score for MDI—9, for DPI—7, and MDI with spacer—10).

The mean score of devices was obtained at baseline, at the end of 1 and 6 months and the impact of education was analyzed. The personal data included were age, sex, residence, diagnosis, education, matrimonial status, occupation, type, frequency of the inhalation device used, and previously who imparted inhalation technique.

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All inhalation technique training was given by the same investigator to exclude interobserver reliability. An Statistical Package for the Social Sciences version 20.0 was used to perform the statistical analysis. To analyze the various answers provided in the patient proforma Chi-squared test and Fisher’s exact test were applied. Paired t-test and analysis of variance test were done for comparison of mean scores of inhalation technique at baseline, at the end of 1 and 6 months. The included patients were then evaluated for the inhalation technique and steps as elaborated in the literature review by the European Respiratory Society. Table 1 shows the checklist for various devices.

**Results**

A total of 176 patients were enrolled in the study; 40 patients did not turn up for follow-up and were excluded. The remaining 132 patients were analyzed. Out of 132 patients, 65.1% (86/132) patients were using DPI, 26.5% (35/132) patients used MDI, and 8.4% (11/132) patients used MDI with spacer. The mean age observed patients used MDI, and 8.4% (11/132) patients were using DPI, 26.5% (35/132) of the total study population, and 34.9% (46/132) were females. DPI was the most used device among both males and females (68.6 and 58.6%, respectively). The COPD group used device among both males and females (46/132) were females. The mean percentage improvement of MDIs in our study was 63.1% at baseline, 74.2% at 1 month, and 78% at 6-month follow-up. The mean score of the inhalation technique of patients using DPIs in our study was 4.37 ± 0.70 at the baseline and 5.53 ± 0.79 after 1 month of education. The mean percentage improvement of DPIs in our study was 61.4% at baseline, 79% at 1 month, and 80.2% at 6-month follow-up. In this study, patients who used pMDI with spacers showed improvement in their inhalation score after 1 month, 8.27 ± 0.64 (82%) as compared to the baseline score of 6.90 ± 0.94 (69%) (p < 0.001)

**Discussion**

In the present study, we analyzed the effectiveness of education and training on patient inhalation technique in diagnosed cases of COPD and bronchial asthma, and results were analyzed at baseline, 1 and 6 months, respectively. Asthma and COPD are both preventable and treatable chronic respiratory diseases if the patient adheres to the treatment and uses a proper drug delivery technique. The maximal response elicited by any inhaled drug can be achieved only if the delivery technique is optimal. A poor inhalation technique with missed steps leads to subtherapeutic drug response, which subsequently leads to more adverse effects and, lastly, therapy discontinuation, thus adding to the mortality and morbidity caused by these chronic respiratory diseases. Both Global Initiative for Chronic Obstructive Lung Disease and Global Initiative for Asthma guidelines have highlighted the critical importance of inhaler technique and education on patients taking inhalation drug therapy. This needs a collaborative drive to educate healthcare professionals and patients and make them aware of how a proper inhalation technique can improve their level of disease control and lessen the side effects. In this study, asthma patients had a better baseline inhalation technique and critical errors were less in them as compared to COPD patients. A study done by Souza et al.8 also found that COPD patients committed more errors as compared to bronchial asthma patients. This inference was similar to our study. The study conducted by Melani et al.5 also concluded that bronchial asthma patients had a lower risk of critical errors than COPD patients. The available literature cited above reveals that the critical errors committed by patients in inhalation steps are different in COPD and asthma patients, and errors also vary with the type of device used.

The level of education plays a very pivotal role in how the patient starts inhalation therapy for the first time. A study done by Pothirat et al.13 found that low education level was an important factor related to incorrect technique, and in our study also, illiterate patients committed far more errors as compared to graduates. A study done by Coelho et al.7 also found that the risk of errors increased with a lower level of education.

Inhalation technique scores of the patients using MDI increased to 6.68 ± 0.58 (p < 0.001)
To Study the Effectiveness of Inhalation Technique Training

Table 1A: Characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients using MDI</th>
<th>Patients using DPI</th>
<th>Patients using MDI with a spacer</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>35 (26.5%)</td>
<td>86 (65.1%)</td>
<td>11 (8.4%)</td>
<td>132</td>
</tr>
<tr>
<td>Age (year) Mean</td>
<td>41.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>16–60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex Distribution (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (24.4%)</td>
<td>59 (68.6%)</td>
<td>6 (6.9%)</td>
<td>86 (65.1%)</td>
</tr>
<tr>
<td>Female</td>
<td>14 (30.4%)</td>
<td>27 (58.6%)</td>
<td>5 (10.8%)</td>
<td>46 (34.9%)</td>
</tr>
<tr>
<td>Diagnosed cases of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD and bronchial asthma</td>
<td>14 (18.2%)</td>
<td>61 (79.2%)</td>
<td>2 (2.6%)</td>
<td>77 (58.4%)</td>
</tr>
<tr>
<td>Inhabitance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>16 (21.3%)</td>
<td>55 (73.4%)</td>
<td>4 (5.4%)</td>
<td>57 (43.2%)</td>
</tr>
<tr>
<td>Urban</td>
<td>19 (33.4%)</td>
<td>31 (54.4%)</td>
<td>7 (12.2%)</td>
<td></td>
</tr>
<tr>
<td>Duration of Device use (year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>20 (34.5%)</td>
<td>28 (48.3%)</td>
<td>10 (17.2%)</td>
<td>58 (25.2%)</td>
</tr>
<tr>
<td>1–2</td>
<td>4 (13.4%)</td>
<td>26 (86.6%)</td>
<td>0 (%)</td>
<td>30 (25.2%)</td>
</tr>
<tr>
<td>2–5</td>
<td>3 (16.7%)</td>
<td>15 (83.3%)</td>
<td>0 (%)</td>
<td>18 (25.2%)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>8 (30.7%)</td>
<td>17 (65.3%)</td>
<td>1 (4%)</td>
<td>26 (25.2%)</td>
</tr>
<tr>
<td>Educator</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self</td>
<td>8 (61.5%)</td>
<td>2 (15.3%)</td>
<td>3 (23.2%)</td>
<td>13 (9.8%)</td>
</tr>
<tr>
<td>Chemist</td>
<td>15 (25.9%)</td>
<td>41 (70.7%)</td>
<td>2 (3.4%)</td>
<td>58 (44%)</td>
</tr>
<tr>
<td>Hospital staff</td>
<td>9 (17.6%)</td>
<td>40 (78.5%)</td>
<td>2 (3.9%)</td>
<td>51 (38.6%)</td>
</tr>
<tr>
<td>Doctor</td>
<td>3 (30%)</td>
<td>3 (30%)</td>
<td>4 (40%)</td>
<td>10 (7.6%)</td>
</tr>
</tbody>
</table>

Fig. 1: Mean Score of inhalation devices at baseline, 1 month and 6 months

Fig. 2: Inhalation technique scores in COPD and Asthma patients

Educational intervention in patients using MDIs from 15.4 to 46.2% after 3 months, and our study showed improvement at 1 month and 6 months post education, and it was 63.1% at baseline to 74.2% at 1 month and to 78% after 6 months. A study done by Rodrigues et al. was in cases of uncontrolled asthma, and no COPD patients were enrolled, which committed more critical errors in taking inhalation therapy.

In a study done by Basheti et al., mean scores for Diskus were 4.40 ± 2.60 vs 8.85 ± 0.41 and Turbohaler score, 4.96 ± 2.05 vs 8.63 ± 0.67, the results of which can be comparable with our study as both types of devices showed an increase in mean scores implying an improvement in inhalation technique after education. A study done by Rodrigues et al. showed improvement in technique prior to and after educational intervention in patients using DPIs from 21.3 to 76.6% after 3 months, and our study showed improvement from 61.4% at baseline to 79% at 1 month and to 82% after 6 months and this study was done only in patients with uncontrolled asthma, and age of patients was <14 years whereas our study was done in both COPD and bronchial asthma patients of age >18 years.

A study which was conducted by Pothirat et al. in COPD patients who used pMDI with spacers showed a decrease in the percentage of incorrect techniques from 70 to 60% after 1 month of education, which is comparable with our study. A study done by Dutt et al. found that the technique improved from 9 (34.61%) to 14 (53.84%) after 1 month of technical training in patients using pMDI with spacers, and our study showed improvement from 69% at baseline to 82% after 1 month which is almost similar to improvement seen in the above study. Figure 4 depicts the inhalation steps failed by patients using various inhalation devices.

In various European studies, the results revealed that 50–60% of cases of COPD and asthma have poor control of the disease. The probable reason for the imperfect level of control is due to faulty inhalation techniques leading to poor adherence to the prescribed inhalers and other treatments.

In the last 1 decade, the cases of respiratory diseases have been on the rise in India. The two leading diseases causing this surge are COPD and asthma. Nearly 63 million people nationwide suffer from COPD, which is nearly 32% of the global burden of COPD. To the best of our knowledge, based on an available literature search, no study has been done in India to evaluate the impact of education in improving inhalation techniques in patients with COPD and bronchial asthma.
To Study the Effectiveness of Inhalation Technique Training

Education of patients is the prime factor that leads to the proper use of inhalation devices and the effectiveness of inhalation therapy. Inhalation therapy is the cornerstone of any chronic respiratory disease. Awareness about the correct use of inhaler therapy may not only significantly improve the level of disease control but also allow dose tapering in the long run. This reduces the overall prescription cost as well. Our study was a prospective and observational study to analyze both the short and long-term effects of education on inhalation device use and handling.

This study is not without limitations. All patients using inhalers were included in the study ignoring the frequency and knowing their compliance to inhalation therapy. There was heterogeneity in the number of patients using each device. There was no control group in the study. Patients >60 years were not included. Lung functions were not done to see what was the impact of education on using inhalation devices. We did not assess the participant’s cognition, which has an influence on the inhaler technique.

**Conclusion**

Patients using any inhalational devices can commit errors irrespective of age, sex, educational level, and residence. Every patient should be instructed, re-instructed, and evaluated for the use of inhalation devices, but more importance is to be given to uncontrolled asthma, the elderly, and patients with low educational status. Periodic directions and between checkups of inhalation steps should be executed. Unceasing education of health care providers, treating doctors, paramedical staff, and pharmacists about the right inhalation technique should be ensured in hospitals and out-patient clinics.

**References**

To Study the Effectiveness of Inhalation Technique Training

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Prof. Dr. Mangesh Tiwaskar
Editor-in-Chief, JAPI
Efficacy and Safety of Injection Sepsivac® (Heat-killed Mycobacterium W) in Gram-negative Sepsis administered via an Intravenous Route

Rajat Agrawal*

Received: 07 March 2022; Accepted: 13 January 2023

ABSTRACT

Background: As an immunomodulator, the mycobacterium w (Mw) has improved outcomes for patients suffering from severe sepsis. The traditional route of administration for Mw is intradermal (ID), which is limited to administering 0.1 mL per injection (Inj). The intravenous (IV) route can be an alternative to ID.

Aims and objectives: To evaluate the safety and efficacy of Inj Sepsivac® IV in gram-negative sepsis.

Materials and methods: Present retrospective observational study was conducted in an intensive care unit (ICU) of tertiary care hospital. The study included 30 consecutive patients with presumed gram-negative sepsis within 48 hours of the first organ dysfunction. Patients received Inj Sepsivac® 0.3 mL diluted in 100 mL normal saline to be given as slow IV infusions over at least 15 minutes, every day for 3 consecutive days. Efficacy was assessed by recording the change in vital parameters, sequential organ failure assessment (SOFA) score, and laboratory investigations. Safety was evaluated by the occurrence of allergic reactions including anaphylaxis, the site of infection, and secondary infection. Each patient was followed up for 14 days from the day of enrolment.

Results: Mean age of patients with gram-negative sepsis was 62.67 ± 12.77 years with male preponderance (63.3%). Pneumonia (40.1%) and intraabdominal infections (26.7%) were the most common etiologies of sepsis. A significant improvement in all the vitals and mean SOFA scores was observed from day 2 onward. More than half of the patients required ventilator support (17 [56.7%]), and mortality was observed in 7 (25%) patients. None was reported to have a secondary infection. Laboratory parameters improved and oxygen requirement was reduced postday 4 till the end of treatment from baseline.

Conclusion: The IV route of administration was found to be efficacious and safe and allow ease of administration in treating gram-negative sepsis. Further large multicentric randomized trials are required to confirm our findings.

Journal of the Association of Physicians of India (2023): 10.5005/japi-11001-0221

INTRODUCTION

Sepsis is a potentially fatal disorder of the immune system that arises when the body’s defensive responses to infection cause harm to its tissues and organs.1 Recently, an estimated 48.9 million instances of sepsis were reported globally, with 11.0 million deaths attributed to sepsis, accounting for 19.7% of all deaths worldwide.2

As our understanding of the underlying pathology and immunological pathways advances, the definition of sepsis as a clinical illness is constantly evolving. For the first time, the current consensus definition (“sepsis-3”) highlights the critical role of the innate and adaptive immune systems in developing the clinical illness. Despite significant efforts over the last 3 decades of clinical and laboratory research, the treatment arsenal available to influence the course of disease remains limited. Even today, septic shock (28.3%), the most severe subset of sepsis, has a death rate of 18.1% as reported by an INDICAPS study involving 124 Indian ICUs.3 Despite advances in managing infectious disease, the inability to successfully treat sepsis remains an unsolved clinical problem. Sepsis remains an important and life-threatening problem and the most common cause of death in the ICU, with mortality between 20 and 50% for severe sepsis and 45–80% for septic shock.4 Each year, approximately 2,150,000 deaths are due to severe sepsis. Additionally, treating patients with severe sepsis is estimated to be more than $16.7 billion per year.5 The INDICAP study analyzed 4,038 patients data and reported a prevalence of severe sepsis of 28.3%, out of which 20.5% were ICU acquired.5

A significant difference in cytokine and biomarkers were reported in patients with gram-negative and positive sepsis. Patients with gram-negative sepsis have 6.567, 6.063, 11.46, 3.09, and 9.76 fold higher levels of tumor necrosis factor α (p < 0.01),6 Interleukins (IL) 4 (p < 0.01),6 IL-8 (p < 0.01),6 IL-6 (p = 0.001)7 and IL-10 (p < 0.01),7 respectively, compared to patients with gram-positive sepsis.

Mycobacterium w (Mw) is an immunomodulator. It is known to contain multiple antigens. Its administration is associated with the antigen-specific generation of cell-mediated immunity.8 Mw has been approved by the Drug Controller General of India for use in the treatment of gram-negative sepsis along with the standard of care treatment.9 The traditional route of administration for Mw is ID, which is limited to administering 0.1 mL per Inj Mw’s IV administration has not been explored in severe sepsis patients. Based on the efficacy and safety data of Mw, as observed in previous clinical studies, we hypothesize that using Mw as an adjuvant to standard treatment in sepsis via the IV route will be safe as well as effective in decreasing complications, hasten the organ function recovery, and reducing the mortality associated with sepsis.

MATERIALS AND METHODS

The present observational study was performed on 30 patients of >18 years of age, presumed to have gram-negative sepsis with one organ dysfunction and on single vasopressor support.

Those with a history of allergic reactions attributed to Inj Sepsivac® or any of its excipients, pregnant and lactating women, and those with generalized septic skin conditions were excluded.

Investigational Drugs

Injection Sepsivac® is an autoclaved suspension in physiological saline of Mw (heat-killed; 0.5 x 10^8) supplied by Cadila Pharmaceuticals Ltd.
Injection Procedure and Follow-ups
All the patients received Inj Sepsivac® 0.3 mL diluted in 100 mL normal saline to be given as slow IV infusions over at least 15 minutes, every day for 3 consecutive days in addition to the standard therapy for sepsis. The study drug was administered within 48 hours of the onset of first organ dysfunction on single vasopressor support. All patients were admitted to the hospital until the investigator deemed discharge from the hospital appropriate. Standard therapy for severe gram-negative sepsis was given to all the patients, and its duration depended on clinical and microbiological parameters.

Each patient was followed up for 14 days from the day of enrolment. Baseline, day 1, 2, 3, 4, 7, and 14 were the time points on which details on efficacy endpoints such as vital signs, SOFA score, and laboratory investigations (change in hemoglobin, packed cell volume (PCV) total leukocyte count (TLC), and peripheral capillary oxygen saturation (SpO2) and their changes were recorded. Patients were also followed up for the safety of intervention assessed by the occurrence of allergic reactions including anaphylaxis, site infection, and secondary infection, along with details on the requirement of ventilator and mortality till day 14.

All the data were analyzed using Statistical Analysis System software version 9.4 or higher. A descriptive analysis was performed to record the characteristic of the study population. Quantitative data were expressed as mean and standard deviation, whereas; categorical data were expressed as numbers and percentages. Means and differences in means at different time points compared to baseline were compared using the student t-test. A p-value of <0.05 was considered significant.

Results
The mean age of patients with gram-negative sepsis was 62.67 ± 12.77 years, ranging from 32 to 88 years. Male preponderance [19 (63.3%)] was observed (Table 1). The majority of the patients had pneumonia [12 (40.1%)] followed by intraabdominal infection [8 (26.7%)] and urinary tract infection [5 (16.7%)]. Other less common sites of infections were blood (n = 1), joint (n = 1), skin and soft tissue (n = 3).

All vital parameters showed significant change from day 2 onward. Respiratory rate, heart rate, temperature, and blood pressure had a significant change from day 2 onward from baseline posttreatment (Table 2).

The mean SOFA score was 13 at baseline (Fig. 1). At the end of day 1, the mean SOFA score did not significantly change from the

![Fig. 1: Trend in mean SOFA score among the study cases](image-url)

Table 1: Baseline characteristic of the study population

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; years</td>
<td>62.67 ± 12.77</td>
</tr>
<tr>
<td>Male/female; n (%)</td>
<td>19 (63.3)/11 (36.7)</td>
</tr>
<tr>
<td>Neutrophils; %</td>
<td>84.07 ± 8.54</td>
</tr>
<tr>
<td>Lymphocytes; %</td>
<td>12.57 ± 6.92</td>
</tr>
<tr>
<td>Eosinophils; %</td>
<td>0.50 ± 0.71</td>
</tr>
<tr>
<td>Monocytes; %</td>
<td>3.00 ± 1.00</td>
</tr>
<tr>
<td>Platelet count</td>
<td>146000.00 ± 72459.74</td>
</tr>
<tr>
<td>Serum total bilirubin; μmol/L</td>
<td>1.80 ± 1.71</td>
</tr>
<tr>
<td>Alkaline phosphatase; IU/L</td>
<td>290.50 ± 159.32</td>
</tr>
<tr>
<td>AST (SGOT); units/l</td>
<td>193.63 ± 263.11</td>
</tr>
<tr>
<td>ALT (SGPT); units/l</td>
<td>217.93 ± 251.36</td>
</tr>
<tr>
<td>Serum creatinine; mg/dl</td>
<td>2.13 ± 0.68</td>
</tr>
<tr>
<td>Blood urea; mg/dl</td>
<td>62.93 ± 26.89</td>
</tr>
<tr>
<td>C-reactive protein; mg/dl</td>
<td>42.96 ± 19.36</td>
</tr>
<tr>
<td>Hemoglobin; g/dL</td>
<td>9.20 ± 2.11</td>
</tr>
<tr>
<td>PCV; %</td>
<td>27.63 ± 3.83</td>
</tr>
<tr>
<td>TLC</td>
<td>18143.33 ± 8158.54</td>
</tr>
<tr>
<td>SPO₂; %</td>
<td>88.93 ± 4.95</td>
</tr>
<tr>
<td>ICU stay; days</td>
<td>0.96 ± 3.38</td>
</tr>
<tr>
<td>Hospital stay; days</td>
<td>14.48 ± 2.97</td>
</tr>
<tr>
<td>Vasopressors therapy; days</td>
<td>05.30 ± 2.85</td>
</tr>
<tr>
<td>Ventilator; days</td>
<td>06.10 ± 1.52</td>
</tr>
<tr>
<td>RR; bpm</td>
<td>26.14 ± 4.34</td>
</tr>
<tr>
<td>HR; bpm</td>
<td>107.60 ± 14.34</td>
</tr>
<tr>
<td>SBP; mmHg</td>
<td>087.72 ± 11.49</td>
</tr>
<tr>
<td>DBP; mmHg</td>
<td>52.39 ± 0.89</td>
</tr>
<tr>
<td>Temperature; 0°C</td>
<td>38.28 ± 0.88</td>
</tr>
<tr>
<td>SOFA score</td>
<td>13.45 ± 3.10</td>
</tr>
</tbody>
</table>

Table 2: Trend in vitals among patients

<table>
<thead>
<tr>
<th>Duration (days)</th>
<th>RR</th>
<th>HR</th>
<th>SBP</th>
<th>DBP</th>
<th>Temp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>26.14 ± 4.34 (29)</td>
<td>107.60 ± 14.34 (30)</td>
<td>087.72 ± 11.49 (29)</td>
<td>52.39 ± 08.95 (28)</td>
<td>38.28 ± 0.88 (28)</td>
</tr>
<tr>
<td>2</td>
<td>*24.71 ± 3.49 (28)</td>
<td>*101.70 ± 12.82 (30)</td>
<td>*091.48 ± 07.52 (29)</td>
<td>*55.64 ± 07.29 (28)</td>
<td>*37.86 ± 00.77 (28)</td>
</tr>
<tr>
<td>3</td>
<td>*22.62 ± 3.17 (29)</td>
<td>*095.87 ± 08.91 (30)</td>
<td>*098.31 ± 10.17 (29)</td>
<td>*63.32 ± 08.53 (28)</td>
<td>*37.08 ± 01.33 (25)</td>
</tr>
<tr>
<td>4</td>
<td>*20.86 ± 3.07 (29)</td>
<td>*091.13 ± 05.32 (30)</td>
<td>*101.59 ± 11.36 (29)</td>
<td>*65.64 ± 10.53 (28)</td>
<td>*37.23 ± 00.31 (28)</td>
</tr>
<tr>
<td>7</td>
<td>*19.89 ± 3.07 (27)</td>
<td>*087.96 ± 05.70 (28)</td>
<td>*109.69 ± 11.18 (26)</td>
<td>*71.28 ± 06.00 (25)</td>
<td>*37.19 ± 00.26 (25)</td>
</tr>
<tr>
<td>14</td>
<td>*19.53 ± 1.88 (15)</td>
<td>*084.13 ± 07.71 (16)</td>
<td>*116.63 ± 12.47 (16)</td>
<td>*77.60 ± 09.30 (15)</td>
<td>*37.14 ± 00.20 (14)</td>
</tr>
</tbody>
</table>

Data is expressed as mean ± standard deviation (number of patients). DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; student t-test was used, *significant; Temp, temperature.
Efficacy and Safety of Injection Sepsivac®

The use of Mw via IV route combined with standard care has shown significant improvement in all vital parameters and mean SOFA score from day 2 onward in patients with severe gram-negative. Similar improvement was observed for AST, ALT, blood urea, and C-reactive protein from day 4 onward. A significant improvement in TLC was observed from day 7 onward compared to the baseline (Table 5). None of the patients developed any major adverse event and Mw was well-tolerated in all patients.

Results obtained in the present study are comparable to previous research of Mw using the ID route. A randomized clinical trial by Sehgal et al. on 50 patients with severe sepsis reported a significant reduction in days on mechanical ventilation, ICU, and hospital length of stay, lower incidence of nosocomial infection, and delta SOFA score with the use of Mw along with standard care compared to standard care alone.

The overall mortality reported in this series was 25%. However, Mw was found to reduce the mortality associated with gram-negative sepsis in a previous multicentric randomized controlled trial.

Compared to ID treatment, IV administration of Mw immunomodulator results in a more favorable immune response.

**Discussion**

**Table 3:** Change in mean SOFA score at different time points

<table>
<thead>
<tr>
<th>Time points (days)</th>
<th>Mean change from baseline</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 (n = 29)</td>
<td>−0.21 ± 1.15</td>
<td>0.333</td>
</tr>
<tr>
<td>Day 2 (n = 29)</td>
<td>−1.24 ± 1.86*</td>
<td>0.001</td>
</tr>
<tr>
<td>Day 3 (n = 29)</td>
<td>−2.72 ± 2.46*</td>
<td>0.001</td>
</tr>
<tr>
<td>Day 4 (n = 29)</td>
<td>−4.17 ± 2.78*</td>
<td>0.001</td>
</tr>
<tr>
<td>Day 7 (n = 28)</td>
<td>−6.39 ± 3.12*</td>
<td>0.001</td>
</tr>
<tr>
<td>Day 14 (n = 15)</td>
<td>−8.33 ± 4.59*</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Table 4:** Trends in laboratory investigations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Day 4</th>
<th>Day 7</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils (%)</td>
<td>84.07 ± 8.54 (28)</td>
<td>*77.46 ± 7.68 (28)</td>
<td>75.76 ± 5.10 (21)</td>
<td>74.63 ± 6.74 (8)</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>0.50 ± 0.71 (2)</td>
<td>1.50 ± 0.71 (2)</td>
<td>1.00 (1)</td>
<td>–</td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>3.00 ± 1.00 (3)</td>
<td>2.67 ± 2.08 (3)</td>
<td>–</td>
<td>5.00 (1)</td>
</tr>
<tr>
<td>Basophils (%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Platelet count</td>
<td>146000.0 ± 72459.74 (30)</td>
<td>*199300.0 ± 20641.223 (30)</td>
<td>145692.48 ± 81269.0 (26)</td>
<td>*201357.14 ± 50396.29 (14)</td>
</tr>
<tr>
<td>Serum total bilirubin</td>
<td>1.80 ± 1.71 (30)</td>
<td>1.37 ± 0.63 (30)</td>
<td>1.35 ± 0.85 (20)</td>
<td>0.95 ± 0.15 (10)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>290.50 ± 159.32 (8)</td>
<td>121.00 ± 83.44 (2)</td>
<td>252.50 ± 180.31 (2)</td>
<td>98.00 (1)</td>
</tr>
<tr>
<td>AST</td>
<td>193.63 ± 263.11 (30)</td>
<td>*142.14 ± 116.97 (29)</td>
<td>*94.23 ± 102.74 (22)</td>
<td>*42.90 ± 44.89 (10)</td>
</tr>
<tr>
<td>ALT</td>
<td>217.93 ± 251.36 (30)</td>
<td>*162.10 ± 153.28 (29)</td>
<td>*96.09 ± 98.43 (22)</td>
<td>*46.70 ± 61.39 (10)</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>2.13 ± 0.68 (30)</td>
<td>2.20 ± 3.04 (30)</td>
<td>3.19 ± 5.97 (27)</td>
<td>2.10 ± 2.66 (13)</td>
</tr>
<tr>
<td>Blood urea</td>
<td>62.93 ± 26.89 (30)</td>
<td>*47.20 ± 26.76 (30)</td>
<td>*44.26 ± 32.83 (27)</td>
<td>*24.15 ± 13.94 (13)</td>
</tr>
<tr>
<td>C reactive protein</td>
<td>42.96 ± 19.36 (27)</td>
<td>*21.71 ± 12.65 (24)</td>
<td>*15.33 ± 9.39 (12)</td>
<td>*7.57 ± 2.30 (7)</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation (number of patients). ALT, alanine aminotransferase; AST, aspartate aminotransferase; *significant
in the lung parenchyma.\textsuperscript{11} Mw is also reported as being safe and effective when administered by IV as per data from other indications.\textsuperscript{12} The IV method of administration of Mw provides the following benefits—(1) ease of administration via a secure ongoing IV line and (2) capacity to administer the needed extra dose in a single Inj. ID administration requires additional training/skills not needed in the ICU setting for IV administration. The highest dose provided via the ID method is 0.3 mL/day compared to a dose as high as 5.0 mL/day by the IV route.\textsuperscript{12,13} Findings of the present study provide more strength to observations of the previous series. It also paves the way for evaluating Mw via the IV route in a larger study.

Bacterial endotoxin joins with toll-like receptor (TLR) 4 on the host leukocyte and other immune cells in gram-negative sepsis to activate pro-inflammatory and anti-inflammatory pathways simultaneously.\textsuperscript{14,16} While beneficial in the first few hours, the anti-inflammatory mechanism may be harmful, resulting in immunosuppression, which is counterproductive. The responses observed in the present study are because Mw is an immunomodulator. Its administration is associated with the antigen-specific generation of cell-mediated immunity, including generation of strong Type 1 T helper (Th1) response (TLR2 agonistic activity),\textsuperscript{10,17-19} suppression of cytokine production (poly TLR-4, 5, and 9 antagonist activity), macrophage activation, T cell proliferation, the release of cytokines IL-2, interferon-gamma and genetic expression modulation. Our study is the first study that has proved the safety and efficacy of Mw in septic shock including the geriatric patient population. However, it has its limitations like a small sample size, lack of randomization, and absence of a comparator arm (ID route). Further large multicentric randomized trials are required to confirm our findings.

**Conclusion**

The use of an immunomodulator Mw in Septic shock in addition to the standard of care was found to be well tolerated and efficacious. Its improved survival is evident from the improvement in clinical and biochemical parameters.

**Acknowledgment**

We would like to thank Dr Pratik Patel and Dr Ameet Soni (Medical Affairs Department, Cadila Pharmaceuticals Ltd.) for their assistance in writing the manuscript.

**References**


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**Table 5:** Showing changes in hemoglobin, packed cell volume, total leukocyte count, and peripheral capillary $\text{SpO}_2$ over time

<table>
<thead>
<tr>
<th>Duration (Days)</th>
<th>Hb</th>
<th>PCV</th>
<th>TLC</th>
<th>$\text{SpO}_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline #</td>
<td>9.20 ± 2.11 (30)</td>
<td>27.63 ± 3.83 (16)</td>
<td>18143.33 ± 80158.54 (30)</td>
<td>88.93 ± 4.95 (30)</td>
</tr>
<tr>
<td>4#</td>
<td>9.14 ± 1.65 (30)</td>
<td>25.85 ± 2.91 (13)</td>
<td>22370.00 ± 35947.86 (30)</td>
<td>92.00 ± 3.05 (30)</td>
</tr>
<tr>
<td>7#</td>
<td>9.33 ± 1.54 (28)</td>
<td>25.89 ± 3.02 (9)</td>
<td>09735.71 ± 04332.50 (28)</td>
<td>92.26 ± 2.45 (23)</td>
</tr>
<tr>
<td>14#</td>
<td>9.56 ± 0.80 (15)</td>
<td>26.67 ± 1.15 (3)</td>
<td>09420.00 ± 01770.47 (15)</td>
<td>93.38 ± 2.75 (13)</td>
</tr>
<tr>
<td>Mean difference (baseline-day 4)##</td>
<td>−0.06 ± 1.54 (0.832)</td>
<td>−1.92 ± 5.06 (0.196)</td>
<td>4226.67 ± 35502.63 (0.519)</td>
<td>*3.07 ± 4.53 (0.001)</td>
</tr>
<tr>
<td>Mean difference (baseline-day 7) ##</td>
<td>0.21 ± 1.53 (0.473)</td>
<td>−2.33 ± 5.39 (0.230)</td>
<td>*−8232.14 ± 5981.95 (0.001)</td>
<td>*3.74 ± 5.13 (0.002)</td>
</tr>
<tr>
<td>Mean difference (baseline-day 14)</td>
<td>0.79 ± 1.61 (0.078)</td>
<td>−4.33 ± 5.51 (0.306)</td>
<td>*−10680.00 ± 8276.32 (0.001)</td>
<td>*7.23 ± 6.50 (0.001)</td>
</tr>
</tbody>
</table>

*Data is expressed as mean ± standard deviation (number of patients); \textsuperscript{1} Data is expressed as mean difference ± standard deviation (p-value). Hb, hemoglobin; NC, not significant; PCV, packed cell volume; SPO$_2$, peripheral capillary oxygen saturation; *significant; TCL, total leukocyte count.
In hypertensive patients with CAD

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24 HOUR BP Control

1. Data on file

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In Post PCI

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MACE
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Nocturnal hypertension is more common in Asian population due to high salt intake & sensitivity

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Study of the Role of Cerebrospinal Fluid C-reactive Protein and Adenosine Deaminase to Differentiate Various Types of Meningitis

Ajeet Kumar Chaurasia1*, Poonam Gupta2, Manoj Kumar Mathur3, Viya Nagi4

Received: 22 September 2019; Accepted: 12 December 2022

ABSTRACT

Objective: (1) To study cerebrospinal fluid (CSF) adenosine deaminase (ADA) and CSF C-reactive protein (CRP) levels in the differentiation of viral, pyogenic, and tuberculous meningitis (TBM). (2) To estimate the borderline levels of CRP in CSF in viral, pyogenic, and TBM.

Methods: A prospective and cross-sectional study was conducted at the Department of Medicine, SRN Hospital, Prayagraj, Uttar Pradesh, India, between August 2016 and September 2018. In this study, a total of 100 patients with meningitis were included applying specific inclusion and exclusion criteria after proper ethical approval.

Results: Out of 100 patients, 61 were TBM, 31 were pyogenic meningitis, and eight were viral meningitis (VM). CSF CRP level was significantly increased in pyogenic meningitis (1.05 ± 0.36 mg/dL) compared to nonpyogenic meningitis [TBM (0.42 ± 0.13 mg/dL) and VM (0.37 ± 0.09 mg/dL)]. At the cut-off level of CRP in CSF > 0.6 mg/dL, its diagnostic sensitivity in pyogenic meningitis was 93.35% and specificity 94.20%. While CSF ADA levels were higher in the TBM group (13.32 ± 3.21 U/L) compared to other two groups [pyogenic meningitis (6.15 ± 1.27 U/L) and VM (4.86 ± 0.88 U/L)]. At a cut-off, CSF ADA level of >10 U/L, its diagnostic sensitivity for TBM was 91.67% and specificity 90%.

Conclusion: Cerebrospinal fluid (CSF) CRP levels were found to be raised in pyogenic meningitis, and CSF ADA was found to be elevated in TBM. While both ADA level and CRP level in CSF are found low in VM.

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INTRODUCTION

Infectious diseases are the leading cause of mortality and morbidity for millions of people worldwide, despite great progress in their prevention and treatment. Central nervous system (CNS) infection can lead to serious consequences and, in some cases, can lead to acute neurological conditions. Delays in differentiating viral, bacterial, and TBM can lead to delays in treatment, leading to significant increases in morbidity and mortality. Most available tests for the early diagnosis of meningitis are not sensitive, and other available useful tests may not be available for routine use. It is, therefore, crucial to find a reliable, simple, and cheaper tool for rapid diagnosis and differentiation of different types of meningitis.

A CSF examination is important in the diagnosis and differentiation of meningitis. The estimation of CSF ADA is useful for making the diagnosis of TBM, while CSF CRP is helpful in diagnosing pyogenic meningitis. In the case of VM, both CSF CRP and CSF ADA were found to be low.

CRP is an acute phase reactant from the “pentatrans” group, discovered in 1930 by Tillet et al. CRP is synthesized only in the liver, secreted just in 6 hours after acute inflammation in the fluid or serum of affected tissues in a larger amount. The elevated level of CRP in patients with meningitis in the CSF is because of passive diffusion through the inflamed meninges. Thus, an increase in serum CRP indicates an acute phase response, and an elevated CSF CRP indicates meningeal involvement. Given this measurement, the CSF CRP level looks to be a good choice for diagnosing pyogenic meningitis. Therefore, in this study, we estimated CSF CRP values to distinguish pyogenic meningitis from nonpyogenic meningitis and tried to develop a cut-off value of CSF CRP for the same.

Adenosine deaminase (ADA) is a polymorphic enzyme of the purine salvage pathway (Spencer et al.). It has two isoforms of ADA—ADA1 and ADA2. Of these two, ADA1 is found mostly in body cells like lymphocytes and macrophages. It is mainly involved in the intracellular activity. While ADA2 is mainly found in human serum and plasma. ADA is the marker of T lymphocyte activation and is released during the cell-mediated immune response. The ADA2 isozyme constitutes the major fraction of increased ADA levels in CSF of TBM patients, suggesting the monocyto-macrophage origin of ADA. CSF ADA level in TBM patients may be increased due to a damaged blood-brain barrier and/or due to the proliferation of lymphocytic macrophages, indicating a local immune response. Therefore, measuring ADA in CSF is a simple, fast, cheap, and specific test for establishing the diagnosis of TBM, especially when we need to distinguish tuberculous from nontuberculous etiology.

GOALS AND OBJECTIVES

- To study CSF ADA and CSF CRP levels in the differentiation of viral, pyogenic, and TBM.
- To estimate the borderline levels of CRP in CSF in pyogenic, viral, and TBM.

MATERIALS AND METHODS

A prospective and cross-sectional study was conducted at the Department of Medicine, Motilal Nehru Medical College, and Swaroop Rani Nehru Affiliated Hospital, Prayagraj, Uttar Pradesh, India between August 2016 to September 2018. Applying the below-mentioned inclusion and exclusion criteria, 100 patients with meningitis were enrolled.

Inclusion Criteria

- Meningitis patients of ≥18 years of age, both men and women.
- With clinical symptoms reminiscent of meningitis.
- Fever, headache, vomiting, and altered sensory perception.
- With meningeal irritation signs (nuchal stiffness and Kernig’s sign)

How to cite this article: Chaurasia AK, Gupta P, Mathur MK, et al. Study of the Role of Cerebrospinal Fluid C-reactive Protein and Adenosine Deaminase to Differentiate Various Types of Meningitis. J Assoc Physicians India 2023;71(5):67–69.
Study of the Role of CSF CRP and ADA

Exclusion Criteria

- Acute/chronic infections in non-CNS sites.
- Patients with hepatic encephalopathy.
- Patients already on immunosuppressive or steroid treatment.
- Patients with proven immunological disorders, e.g., systemic lupus erythematosus, rheumatoid arthritis.

Based on clinical symptoms and CSF reports, all selected patients were categorized into the following three groups.

Tuberculous meningitis (TBM)—included cases of TBM:

- Clinical signs—duration of fever for <1 week, tuberculosis in any other organ, and signs of meningeal irritation.
- Cerebrospinal fluid (CSF) analysis—appearance—clear/turbid, glucose—either <40% of plasma glucose or <40 mg/dL, protein >45 mg/dL (1.5 g/L), lymphocytosis—polymorphonuclear (PMN) leukocytosis (>100 cells/μL), positive gram stain and culture.

Pyogenic meningitis—included cases of pyogenic meningitis:

- Clinical signs—duration of fever <1 week and signs of meningeal irritation.
- Cerebrospinal fluid (CSF) analysis—appearance—clear/turbid, glucose—either <40% of plasma glucose or <40 mg/dL, protein >45 mg/dL, polymorphonuclear (PMN) leukocytosis (>100 cells/μL), positive gram stain and culture.

Viral meningitis (VM)—included cases of VM:

- Clinical features—shorter duration of fever along with the presence of signs of meningeal irritation.
- Cerebrospinal fluid (CSF) analysis—appearance—clear, glucose—normal, that is, > 60% of serum glucose, protein—normal or slightly elevated (20–80 mg/dL), pleocytosis—25–500 cells/μL (predominantly lymphocytes, but PMN soon).

Adenosine deaminase (ADA) activity in CSF was measured in all patients by the qualitative test. CRP leads to the agglutination of latex particles that is measured turbidimetrically.10,16 Any value proportionate to the concentration of CRP was considered significant.

Statistical Analysis

Statistical Package for the Social Sciences, Excel 2013 was used for the analysis of data. All statistical analyses were done by applying the student’s t-test. For comparing the two groups, pyogenic meningitis vs TBM or pyogenic meningitis vs VM or TBM vs VM, an unpaired t-test was used. While the analysis of variance test was used to compare all three groups. A p-value <0.05 was considered significant.

Result

Out of 100 patients, 61 patients had TBM, 31 patients had pyogenic meningitis, and eight patients had VM. At a CSF CRP cut-off of 0.6 mg/dL, 29 patients with pyogenic meningitis and 4 patients with nonpyogenic meningitis (TBM and viral) had CRP levels of >0.6 mg/dL, whereas two patients with pyogenic meningitis and 65 patients without pyogenic meningitis had CRP levels in CSF of <0.6 mg/dL (Table 1).

The mean CSF CRP value was 1.05 ± 0.36 mg/dL in pyogenic meningitis cases, 0.42 ± 0.13 mg/dL in TBM, while 0.37 ± 0.09 mg/dL in VM patients. This difference was statistically significant (p < 0.001) in pyogenic meningitis compared to TBM and VM.

Table 2 depicts the CSF CRP levels in meningitis cases.

When applying a CSF, ADA cut-off level of 10 U/L, 55 patients with TBM and 4 patients without TBM had CRP ADA > 10 U/L, while 6 patients of TBM and 35 patients without TBM had CSF ADA of <10 U/L (Table 3).

The mean CSF ADA in TBM, pyogenic meningitis, and VM was 13.62 ± 2.88 U/L, 6.15 ± 1.27 U/L, and 4.86 ± 0.88 U/L respectively, which is statistically significant (p < 0.001).

The sensitivity of CSF CRP for making the diagnosis of pyogenic meningitis is 93.55%, while specificity is 94.20%, positive predictive value (PPV) is 97.01%, while negative predictive value (NPV) is 93%. The PPV of CSF ADA is 93.22%, while NPV was 97.88%.

Discussion

In this study, mean CSF CRP levels were 1.05 ± 0.36 mg/dL in pyogenic meningitis, 0.42 ± 0.13 mg/dL in TBM, and 0.37 ± 0.09 mg/dL in VM. This study shows that CRP level in CSF was significantly increased in patients of pyogenic (bacterial) meningitis as compared to nonpyogenic (viral and tuberculous) meningitis (p < 0.001). However, the difference between mean CSF CRP levels in VMs and TBM was statistically insignificant (p-value 0.2932). The elevated level of CRP in patients with meningitis in the CSF might be because of passive diffusion through the inflamed meninges or by de novo synthesis in the CNS. At a CSF CRP cut-off level of >0.6 mg/dL, its diagnostic sensitivity for pyogenic meningitis was found to be 93.55%, specificity was 94.20%, PPV was 87.88%, and NPV was 97.01%. The results of our current study are similar to the findings of studies conducted in India by Hemavani et al.17 and Vaishnavi et al.18 who observed that the CSF CRP level was higher in pyogenic meningitis cases as compared to TBM patients significantly. So the measure of CSF CRP could be used for the diagnosis of pyogenic meningitis. In one of the studies, Gerdes et al. concluded that negative CRP levels, either in serum or CSF, can be used to rule out bacterial meningitis strongly.19,20 Belagavi et al. observed that with CSF CRP levels greater than or equal to 0.6 mg/dL, the specificity & sensitivity of CRP was 100 and 83.3%, respectively, with an accuracy of 98% and NPV 97.88%, suggesting that bacterial meningitis can be ruled out at the CRP level of <0.6 mg/L.

The CSF ADA level is elevated in TBM and is used to differentiate TBM from bacterial and VM.21,22 In this study, mean CSF ADA levels was 13.32 ± 3.21 U/L in TBM, 6.15 ± 1.27 U/L in pyogenic meningitis, and VM was 13.62 ± 2.88 U/L, 5.88 ± 1.27 U/L respectively, which is statistically significant (p < 0.001).

Table 1: Cerebrospinal fluid (CSF) CRP in pyogenic and non-pyogenic meningitis

<table>
<thead>
<tr>
<th>CRP Type</th>
<th>Meningitis (n=31)</th>
<th>Non-Meningitis (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>Negative</td>
<td>2</td>
<td>65</td>
</tr>
</tbody>
</table>

Table 2: Cerebrospinal fluid (CSF) ADA positivity in the TBM group and non-TBM group

<table>
<thead>
<tr>
<th>ADA Type</th>
<th>TBM (n=61)</th>
<th>Non-TBM (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>55</td>
<td>4</td>
</tr>
<tr>
<td>Negative</td>
<td>6</td>
<td>35</td>
</tr>
</tbody>
</table>

Table 3: Cerebrospinal fluid (CSF) ADA positivity in the TBM group and non-TBM group

<table>
<thead>
<tr>
<th>ADA Type</th>
<th>TBM (n=61)</th>
<th>Non-TBM (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>55</td>
<td>4</td>
</tr>
<tr>
<td>Negative</td>
<td>6</td>
<td>35</td>
</tr>
</tbody>
</table>
Study of the Role of CSF CRP and ADA

and 4.86 ± 0.88 U/L in pyogenic meningitis and VM, respectively. On comparing the ADA levels in three groups, it was found that the CSF ADA levels were significantly higher in the TBM group as compared to the other two groups (p < 0.0001). Using a CSF ADA cut-off level >10 U/L, its diagnostic sensitivity for TBM was 91.67%, specificity 90%, NPV was 87.81%, and PPV 93.22%. These values are consistent with other studies conducted by Mishra et al.23 to compare CSF CRP and CSF ADA levels in partially treated pyogenic meningitis and TBM in children. In their study, the sensitivity of ADA was 62.5%, and the specificity of ADA was 88.9%, while the sensitivity and specificity of CRP were 75 and 100%. In their study, Choi et al.24 found that the mean CSF ADA in patients with TBM was 12.7±7.5 U/L, and when compared to CSF ADA in viral and pyogenic meningitis, it was significantly higher. Sensitivity was 83% and specificity 95% using a cut-off of 7 U/L for CSF ADA. Chotmongkol et al.25 proposed a cut-off value of 15.5 U/L for CSF ADA to differentiate non-TBM from TBM, having a specificity of 93% and a sensitivity of 75%. Other studies report a lower efficiency and show an overlap between bacterial and TBM.26 Mean CSF ADA value in TBM patients was 9.61 ± 4.10 U/L in the study by Gambhir et al.,23 and it was significantly high as compared to VM. This difference was not statistically significant as compared to pyogenic meningitis.

An elevated CSF CRP level in meningitis is highly suggestive of pyogenic meningitis, whereas an elevated CSF ADA level is highly suggestive of TBM. But any of these tests performed separately would cause confusion in distinguishing the three meningitis, as certain studies show overlapping of ADA levels between bacterial and TBM, such as Malan et al.15 Gambhir et al.23 Distinguishing pyogenic meningitis and TBM by ADA alone in CSF is difficult. So it may be suggested to perform CSF CRP and CSF ADA both at the same time, which can increase the specificity of the test.

**Conclusion**

The measure of CRP and ADA both in CSF may help in differentiating viral, bacterial, and TBM. While CSF CRP is raised in pyogenic meningitis, CSF ADA has been found to be elevated in TBM. Both CSF ADA and CSF CRP have been found to be lower in VM. Testing of both ADA and CRP in CSF is simple and rapid to perform, and it may help reduce the diagnostic dilemma and ensure the rapid etiological diagnosis of different forms of meningitis.

**References**

Clinico-laboratory Profile and Outcomes of Megaloblastic Anemia presenting as Severe Pyrexial Illness mimicking Tropical Infection

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ABSTRACT

Background: Anemia-causing fever has been described in patients with megaloblastic anemia. Although the exact mechanism of this is unknown, high-grade fever is relatively less reported.

Materials and methods: This prospective observational study included all new cases of megaloblastic anemia presenting with febrile illness (>101°F) during a 3-year period. Patients with existing anemia, comorbidities, and other causes of macrocytosis were excluded. A detailed evaluation for megaloblastic anemia and workup for excluding tropical infections was done. The patients were treated with parenteral vitamin B₁₂, folic acid, and other hematinics.

Results: Around 24 cases of megaloblastic anemia presenting with high-grade fever were included, with 14 (58.3%) males, mean duration of fever 7.7 days (4–18 days), and 09 (37.5%) having temperature >103°F. The mean hemoglobin (Hb) was 8.15 g/dL (3.7–11.1 g/dL), the mean corpuscular volume (MCV) was 111 ± 7.8 fL, 18 (75%) had unconjugated hyperbilirubinemia, the mean lactate dehydrogenase (LDH) was 814 ± 24 IU/L, and 21 (87.5%) had low B₁₂ or folate levels. Most showed good therapeutic response to B₁₂ or folic acid with defervescence in 1–5 days (mean 2.6 days) and improvement in lab parameters in 1 week. The study population was divided into those with temperature >103°F and temperature <103°F it was seen that there was a significant association (p < 0.05) with leucocyte count of ≤3000/cumm, and MCV ≥110 fL in patients with temperature ≥103°F.

Conclusion: Megaloblastic anemia should be considered in the differentials of a patient presenting with a febrile illness with no clinical localization and a negative initial fever workup. Early identification and prompt therapy of this easily treatable disorder are very essential.

BACKGROUND

Megaloblastic anemia is a common illness known to have protean manifestations involving various organ systems. There are case reports of megaloblastic anemia presenting as catastrophic acute anemia, and severe pyrexial illness mimicking infections, such as malaria, leptospirosis, dengue, rickettsia, or other bacterial infections. Low-grade fever is known to occur in megaloblastic anemia but a high-grade pyrexial illness mimicking a tropical infection is anecdotal and not known. We studied all cases of megaloblastic anemia who initially presented with acute pyrexial illness mimicking a tropical illness, and assessed the clinicopathological profile and outcomes in them.

MATERIALS AND METHODS

Study Design and Population

This was a prospective observational study conducted in a tertiary care hospital in Western India over a period of 3 years. All cases of acute high-grade febrile illness who were detected to have new onset megaloblastic anemia were included in the study.

Inclusion Criteria

The diagnosis of megaloblastic anemia was defined as anemia (Hb < 11 g/dL in females and <12 g/dL in males) with any one of the following:

- Mean corpuscular volume (MCV) > 110 fL
- Peripheral blood smear (PBS) showing hyper segmented neutrophils, macroovalocytes, or other typical features of megaloblastic anemia.
- Bone marrow picture suggestive of megaloblastic anemia.
- Low serum vitamin B₁₂ or folic acid levels.
- Moderate to high-grade fever (core body temperature >101°F) for at least 3 days.
- Patients ≥ 18 years.

EXCLUSION CRITERIA

- Patients who had proven infections, malignancies, or other abnormalities as an underlying cause of fever.
- Patients with preexisting anemia, megaloblastic anemia, or hematological disorders like aplastic anemia or myelodysplastic syndrome.
- Patients with other causes of macrocytosis such as hypothyroidism, drugs, chronic liver disease, and others.

Study Procedure

All cases presenting with high-grade pyrexial illness detected to have megaloblastic anemia, and qualifying the inclusion and exclusion criteria were included in the study. Requisite consent was obtained from all patients. Appropriate clearance was taken from the Institutional Ethics Committee. The clinical and laboratory profile of the cases was studied. Serum vitamin B₁₂, folate levels, and bone marrow examination was done.

Detailed evaluation was done in the study population which included complete blood count (leucocyte count, platelet count (Plt), and red blood cells (RBC) indices) with PBS (including reticulocyte count, anemia typing, and features of hemolysis) and immunochromatographic card test for vivax/falciparum malaria, latex agglutination for enteric fever (Widal test), serum immunoglobulin M (IgM)/ immunoglobulin (IgG) for Leptospira, serum IgM/IgG/NS1 for dengue, TORCH titers, IgM/IgG for rickettsia, blood and urine culture, microscopy and staining tests of
Megaloblastic Anemia presenting as Severe Pyrexial Illness

The study population was treated for megaloblastic anemia with an injection of vitamin B12 1000 µg given intravenous/intramuscular every alternate day, oral folic acid 5 mg once daily, and oral B complex once daily. A packed RBC (PRBC) transfusion was given if indicated. Orally or parenteral iron therapy was also added if concomitant iron deficiency was detected. The subsequent therapeutic response was noted in terms of number of days to become afebrile, reticulocyte response, and improvement in other parameters.

Statistical Analysis
Statistical analysis of the data was carried out using appropriate statistical packages (Statistical Package for the Social Sciences version 19). Data was reported as mean ± standard deviation (SD). For purpose of comparison, frequency, percentage, and paired t-tests were used. A p-value of < 0.05 was considered statistically significant. Changes in different parameters between the two fever groups were done using the t-test for paired observations.

Results
Demographic and Clinical Characteristics
A total of 30 cases were presented to this center with high-grade fever and evidence of megaloblastic anemia during the study period. Six cases had evidence of infection or other causes of macrocytosis and hence were excluded. The remaining 24 cases were included in this study as given in Flowchart 1.

The average age of patients was 33.9 years (range 17–69 years), 14 (58.3%) being males and 16 (66.70%) patients were Hindus. A total of 10 (41.6%) patients consumed a strict vegetarian diet. All patients presented with an acute febrile illness ranging from 4 to 18 days (mean duration 7.7 days), with 09 (37.5%) having temperature ≥103°F, and 14 patients (58%) having chills or rigors with fever. All patients had features of anemia like dyspnea, fatigue, or palpitations, as given in Table 1. Clinical evaluation revealed icterus in 12 patients (50%), splenomegaly and/or hepatomegaly in 11 (45.8%), and features of peripheral neuropathy in 4 (16.7%), as shown in Table 1. Hyperpigmentation of the tongue, knuckles (Fig. 1), or elbows was a striking finding seen in 11 (45.8%) patients.

Laboratory Findings and Evaluation
Investigations revealed a mean Hb of 8.15 g/dL (range 3.7–11.1 g/dL), leucopenia, and thrombocytopenia in 19 (79.1%) patients. MCV was increased in all patients with the mean (±SD) being 111 ± 7.8 fl (maximum 128 fl), as given in Table 2. The peripheral smear was characterized by macrocytosis in 19 (79%), hyper-segmented neutrophils in 20 (83.3%), and other features such as macroovalocytes, Howell Jolly bodies, poikilocytosis, or basophilic stippling. The biochemistry tests revealed unconjugated hyperbilirubinemia in 18 (75%) cases, prerenal azotemia, and hypoalbuminemia in 5 (20.8%) cases each. LDH was an important marker being raised in most patients with the mean LDH being 814 ± 24 IU/L. Estimation of serum B12 and folate levels revealed low B12 levels in 9 (37.5%), low serum folic acid levels in 6 (25%), and combined deficiency in 6 (25%), while three patients (12.5%) had normal levels of both. Bone marrow examination showed cellular reactive bone marrow with megaloblastoid changes in all patients.

The infectious disease workup, autoimmune workup, radiological evaluation, and cultures were negative in all patients. Eight (33.4%) of the patients were pure vegetarian (milk only) and etiology could not be ascertained in four (16.5%) patients. Five (20.5%) patients showed gastritis on an upper gastrointestinal endoscopy, as shown in Figure 2. About a quarter of all patients had been given anti-infective agents before the diagnosis of megaloblastic anemia intravenous antibiotics in five (20.8%) and antimalarials in one (4.1%) patient.

Response to Therapy
The patients were treated with parenteral vitamin B12 and oral folate as per the protocol. PRBC support was given to five patients (20.8%) who had features of congestive heart failure or severe anemia (average of 1.6 PRBC units transfused). The response to therapy was closely monitored. The patients showed a satisfactory improvement with defervescence of fever and a sense of well-being occurring within 1–5 days (mean 2.6 days) after initiating therapy. The investigations after one week showed a mean improvement of Hb of 1.42 g/dL after 1 week, a fall in mean MCV by 3 fL, a fall in mean LDH by 180 IU/L, and an appropriate reticulocyte response. A serial follow-up showed gradual normalizing of total leucocyte count (TLC), platelet count, and bilirubin levels. There was no mortality in this study.

Flowchart 1: Consort diagram of the study
Megaloblastic Anemia presenting as Severe Pyrexial Illness

**Discussion**

Megaloblastic anemia was first described by Addison in 1849 and since then this disease has fascinated physicians due to myriad presentations.\(^{13,14}\) Megaloblastic anemia generally presents as insidious onset gradually progressive symptomatic anemia with hepatosplenomegaly, neurological features, gastrointestinal manifestations, hyperpigmentation, pancytopenia, unconjugated hyperbilirubinemia, and other features of ineffective erythropoiesis.\(^{15,16}\) The presentation may vary from asymptomatic chronic illness to an acute rapidly progressing disease.\(^{13}\)

Acute rapidly progressing megaloblastic anemia is rare and has been described in association with inhalational nitrous oxide exposure, high dose trimethoprim, in dialysis patients, alcoholics, and debilitated patients on parenteral nutrition.\(^{17-19}\) Agents such as nitrous oxide or trimethoprim cause destruction or severe suppression of methylcobalamin leading to acute megaloblastic anemia.

Fever is known to occur in megaloblastic anemia but it is usually mild with only minimal elevation of temperature (100ºF).\(^{20}\) Studies have shown that fever occurs in about 40% of patients with megaloblastic anemia, caused by a deficiency of either vitamin B\(_{12}\), folic...
Megaloblastic anemia presenting as Severe Pyrexial Illness

Etiology of megaloblastic anemia presenting with fever

Fig. 2: Etiology of megaloblastic anemia presenting with fever

Table 3: Comparison of hematological and biochemical parameters in megaloblastic anemia with temperature ≥103ºF and <103ºF (by Chi-squared test, two-tailed p-value given, p-value < 0.05 considered statistically significant)

<table>
<thead>
<tr>
<th>Serial no</th>
<th>Parameter</th>
<th>Temperature ≥103ºF</th>
<th>Temperature &lt;103ºF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N = 9 n (%)N</td>
<td>N = 15 n (%)N</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Hb (g/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hb ≤ 8</td>
<td>04 (44.4%)</td>
<td>05 (33.4%)</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>Hb &gt; 8</td>
<td>05 (55.6%)</td>
<td>10 (66.6%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>TLC (/cumm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TLC ≤ 3000</td>
<td>07 (77.8%)</td>
<td>04 (26.6%)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>TLC &gt; 3000</td>
<td>02 (22.2%)</td>
<td>11 (73.4%)</td>
<td></td>
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<tr>
<td>3</td>
<td>Plt (/cumm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plt ≤ 80,000</td>
<td>06 (66.7%)</td>
<td>06 (40%)</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>Plt &gt; 80,000</td>
<td>03 (33.3%)</td>
<td>09 (60%)</td>
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</tr>
<tr>
<td>4</td>
<td>MCV (fL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MCV ≥110</td>
<td>08 (88.9%)</td>
<td>04 (26.4%)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>MCV &lt;110</td>
<td>01 (11.1%)</td>
<td>11 (73.4%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>LDH (IU/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LDH ≥ 700</td>
<td>05 (55.6%)</td>
<td>07 (46.7%)</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>LDH &lt; 700</td>
<td>04 (44.4%)</td>
<td>08 (53.3%)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Serum bilirubin (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilirubin ≥2</td>
<td>06 (66.7%)</td>
<td>06 (40%)</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>Bilirubin &lt;2</td>
<td>03 (33.3%)</td>
<td>09 (60%)</td>
<td></td>
</tr>
</tbody>
</table>

Bold values are statistically significant (p < 0.05)

Acid, or both.\(^9\) In a study by Tahlan et al.,\(^21\) the incidence of low-grade fever in nutritional megaloblastic anemia varied from 28 to 60%. Persistent low-grade fever has been described in 70% of the females with B\(_12\) and/or folate deficiency in a study from North India.\(^22\) The exact cause of pyrexia in megaloblastic anemia is not known. It may be due to a defect in oxygenation to the temperature regulatory centers in the brain due to severe anemia, causing hypoxia to these centers, resulting in their stimulation and causing fever.\(^23\) However, this hypothesis fails to explain the absence of fever in other etiologies with anemia as the principal manifestation. It is also proposed that megaloblastic anemia leads to hyperplasia of the bone marrow and thus increased activity within the bone marrow leads to systemic pyrexia.\(^3, 10, 23\) However, the exact cause of fever in megaloblastic anemia is not established.

Megaloblastic anemia presenting as an acute severe illness with high-grade fever is very rare but has also been reported in the literature.\(^3, 11\) The cause of such a rapid and acute presentation is not understood. It could be due to an acute worsening of an underlying compensated disease, precipitated by a trigger such as an infection, comorbid illness, stress, drugs, and surgery. But in our cases, there was no clinical or laboratory evidence of any of these conditions. Therefore, it is postulated that it could be due to a severe manifestation of the mechanisms causing fever, as discussed above.

Megaloblastic anemia presenting in this fashion can mimic various illnesses especially tropical infections like malaria, leptospirosis, dengue, rickettsial infections; hematological malignancies, hemolytic anemia, or autoimmune conditions.\(^10\) Moreover, high fever with leucopenia, can also be due to febrile neutropenia in some cases. This leads to extensive workup and a battery of investigations for the above-mentioned conditions which are costly, and cause patient inconvenience. Moreover, the patients are often empirically given antimicrobial agents like broad-spectrum antibiotics, antimalarials, and antivirals which may be unnecessary. The timely diagnosis of megaloblastic anemia prevents the unnecessary battery of investigations to exclude the abovementioned conditions, prevents unnecessary fear of conditions like malignancy, can restrict the unnecessary use of antimicrobial agents, and helps in the timely initiation of B\(_12\)/folate therapy in this easily treatable condition.

A high index of suspicion and early identification of megaloblastic anemia becomes imperative in such a situation especially if there is a history of a purely vegetarian diet, gastrointestinal symptoms, neurological abnormalities, or pigmentation of knuckles or tongue.\(^15\) A macroryctic picture, typical PBS findings of hyper-segmented neutrophils and macroovalocytes with leucopenia/thrombocytopenia, MCV ≥ 110 fL, biochemical abnormalities such as raised LDH levels or unconjugated hyperbilirubinemia are strong pointers to the diagnosis of megaloblastic anemia.\(^13, 15\) The diagnosis is clinched by a therapeutic response of resolution of pyrexia and improvement in patient condition following parenteral B\(_12\) and folate supplementation.

The limitations of this study are that there is a rare possibility of this high-grade fever being caused by an unknown self-limiting infection like a mild viral illness or other conditions, which could not be detected by the tests done by us. Secondly, it can be argued that the response to therapy was due to the antimicrobial agents used, in the patients in whom it was used. But as some of these patients persisted to have fever despite antibiotic use till B\(_12\)/folate replacement was started, and a group of patients who were not given antibiotics also responded well showed that the defervescence is likely due to the use of hematinsics, and not antimicrobials.

It is therefore recommended that megaloblastic anemia be considered as a differential diagnosis of tropical illness with high-grade fever, and clinical indicators as described above and routine investigations like a complete haemogram with PBS, LDH,
Megaloblastic Anemia presenting as Severe Pyrexial Illness

and bilirubin be done in all these cases. In case of doubt, a confirmatory evaluation like bone marrow evaluation or serum levels of vitamin B12 or folic acid can be done, and appropriate treatment should be initiated concurrently in all these cases to look for the therapeutic response and avoid unnecessary evaluation and antimicrobial agents.

CONCLUSION

Megaloblastic anemia has protean manifestations and can present with high-grade fever mimicking an infectious etiology. The exact mechanism of this severe presentation is not clear and further research is recommended in terms of larger trials and studies to establish the mechanism of the same. Our study demonstrates that in the Indian context, megaloblastic anemia should be considered in the differentials of a patient presenting with a febrile illness with no clinical localization, a negative initial fever workup, and a hematological profile classical of megaloblastic anemia. Early identification and prompt therapy of this easily treatable disorder are very essential to prevent unnecessary investigations for various tropical disorders and unnecessary usage of antimicrobial agents.

REFERENCES


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**A Review on Vitamin D Deficiency and Related Disorders: What is the Right Serum Vitamin D Level?**

Ganapathi Bantwal*

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**Abstract**

To maintain a healthy skeleton, vitamin D is crucial for phosphate as well as calcium uptake. It is of great significance for maintaining the various adaptive and innate immune response components. To reduce the development of various immune-related disorders, such as diabetes, hypertension, cardiovascular diseases, rheumatoid arthritis, and coronavirus disease 2019 (COVID-19), numerous studies evaluating the optimal threshold levels for serum 25-hydroxyvitamin D (25(OH)D). It is documented in various evidence to increase the serum 25(OH)D intake from the current mindset of 30–50 ng/mL to attain the best overall vitamin D benefits. These values are in line with the results of various research showing that increased vitamin D intake is linked to a decreased risk of cancer and cardiovascular diseases. Therefore, it becomes vital to understand the “right” vitamin D levels to avoid deficiency along with its related disorders. In contrast to 30 ng/mL, this review emphasizes the significance of increasing vitamin D levels to 50 ng/mL to obtain several physiological benefits. An individual needs at least 60000 IU for 12 weeks to maintain serum vitamin D levels above 30 ng/mL. The article will interest physicians who desire to profit fully from vitamin D’s influence on clinical practice.

**Introduction**

A crucial fat-soluble vitamin, vitamin D, is vital for maintaining calcium homeostasis. Its functions are multifold and help in sustaining bone health. The dietary source for vitamin D includes milk, red meat, egg yolk, and oily fish. It exists in two bioequivalent inert forms—ergocalciferol and cholecalciferol (D$_3$). They are further converted to 25(OH)D (in the liver), a significant form of vitamin D that circulates. To maintain the physiological effects on the skeleton and extraskelatal tissues, adequate serum 25(OH)D levels are required. The total serum 25(OH)D level gives the best estimate of vitamin D supply in the body. Serum 25(OH)D levels are reported to be best between 30 and 80 ng/mL. Nevertheless, there may be disagreements regarding the definitions of insufficiency (30 ng/mL) and deficiency (20 ng/mL), with >30 ng/mL being seen as sufficient and 40–60 ng/mL being the ideal range or physiological range offering physiological benefits. Table 1 indicates the diagnostic cutoff level for serum 25(OH)D. The lack of vitamin D can raise the chance of developing rickets, osteoporosis, and other conditions like diabetes, cancer, tuberculosis, and heart problems.

Globally, vitamin D insufficiency is most pronounced in countries lacking food fortification programs. Also, in India, the problem is widespread, with high occurrence in young adults, pregnant and lactating women, and women above 50 years. The deficiency is widely spread over the Indian subcontinent, with a prevalence rate of 50–94%. Effects on the bones and musculoskeletal system are the most frequent consequences of vitamin D insufficiency. A recent study, however, indicates that vitamin D might also have an impact on other elements of health, such as asthma and respiratory infections. Nutritional rickets has become a source of concern for pediatricians worldwide. It is caused due to inadequate calcium intake in children. Also, dark-skin people with limited ultraviolet B exposure have a high chance of developing rickets. Adults with severe vitamin D deficiency may develop osteomalacia. Adults’ vitamin D levels should be closely monitored due to their significant impact on morbidities and high out-of-pocket expenditures. Babies born to pregnant women who are vitamin D deficient are more prone to have hypocalcemia and congenital bone disease.

Martineau et al. suggested that vitamin D insufficiency can potentially negatively impact respiratory outcomes. An estimated 1.7 million deaths are caused per year due to tuberculosis. Globally, 300 million people experience difficulties such as asthma, with over 2,50,000 causalities. Therefore, reducing the prevalence of disease can significantly reduce overall global mortality. Vitamin D is assumed to aid in the prevention of *Mycobacterium tuberculosis* infection.

A study demonstrated that a drop in vitamin D supplementation could increase the incidence of hypertension by 16%. This is because it is often conjectured that its deficiency raises blood pressure by stimulating the renin-angiotensin system. Vitamin D acts as a protective agent by accelerating apoptosis and preventing angiogenesis. Thus, vitamin D deficiency can be correlated with lung, breast, or colon cancer. Looking at the huge range of consequences, it becomes important to take measures to reduce the burden of its deficiency.

As already discussed, different limits have been defined for deficiency. This is because different aspects, such as genetics, age, calcium intake, obesity, and ethnicity, are taken into consideration. Though 30 ng/mL is the standard set for vitamin D sufficiency, changing world scenario suggests that 30 ng/mL might not be sufficient, and a switch should be made to a minimum of 50 ng/mL to maintain an optimum 25(OH)D levels. Studies show that 25(OH)D levels 30–50 ng/mL are linked with a reduced risk of non skeletal diseases. It is suggested that in order to achieve parathyroid hormone suppression, 25(OH)D levels larger than 30 ng/mL are required. Despite extensive literature available on global vitamin D deficiency, physicians are not comfortable recommending larger doses of serum 25(OH)D levels. This can be due to the scarcity of reports on vitamin D toxicity and the fear associated with it. To obtain ideal 25(OH)D levels (40–60 ng/mL) with high-dose vitamin D supplementation, most adults (particularly the elderly, obese, and those with dark skin) will need substantially higher dosages (Table 2). A study suggested that patients receiving 25(OH)D levels greater than 30 ng/mL did not develop hypercalcemia. Thus, it becomes important...
to change the perception regarding sufficient serum 25(OH)D level from 30 to 50 ng/mL. This review article aims at establishing a 50 ng/mL serum 25(OH)D level as the goal for physicians to see physiological benefits in patients instead of the current mindset of using 30 ng/mL for vitamin D sufficiency and using 60000 IU as the loading dosage regimen to maintain the optimum serum levels. The effect of vitamin D on the immune system and its connection to numerous immunological-related disorders are also highlighted in this article.

**Optimal Serum 25(OH)D Levels in Various Chronic Health Conditions**

Numerous immune-related disorders can be treated and prevented with the help of vitamin D. This section will elaborate on its role in various chronic health conditions such as bone health, infections, diabetes, hypertension, etc. A study proposed serum 25(OH)D levels between 36 and 48 ng/mL are advantageous in cancer prevention.

**Bone Health and Vitamin D**

Vitamin D consumption and calcium absorption are positively correlated. According to a study by Gallagher et al., serum 25(OH)D levels increase from 20 to 66 ng/mL, leading to a 6% increase in calcium absorption. Vitamin D is significant for keeping bones healthy, and its deficiency may lead to bone demineralization with an increased risk of fractures. This is because, with decreased calcium absorption, it is released from the bones leading to osteomalacia and osteoporosis. It has been observed that 40–50 ng/mL serum 25(OH)D level improved muscle strength, reduced muscle fatigue, and increased bodily function in postmenopausal women. Peak 25(OH)D levels of 50 ng/mL are linked to optimal neuromuscular function. Various studies have pointed out the reduced occurrence of fracture when supplemented with vitamin D. Trivedi et al. observed a decreased first fracture rate in comparison to the placebo group when administered with 100000 IU D3. Four monthly supplements of 1,000,000 oral vitamin D helped in preventing fractures in both genders (<65 years). Additionally, there was a 22 and 33% decrease in the overall fracture incidence and fractures in significant osteoporotic locations, respectively. Hillstroms et al. investigated how postmenopausal women’s structure and function were affected by elevated vitamin D and calcium levels. A total of 26 postmenopausal women (with serum levels between 20 and 30 ng/mL) were enrolled in the study. They received serum concentrations between 40 and 50 ng/mL and serum calcium concentrations greater than 9.2 mg/dL. Results, including muscle strength and fatigue, postural balance, and the amount of time needed to complete functional tasks, were investigated. The results showed that vastus lateralis increased as serum levels rose, and the time needed to climb stairs decreased. Thus, the preliminary results indicated that enhancing vitamin D levels may augment muscle structure and functional task performance. Therefore, a clinical trial with a bigger sample size and control group is necessary. Another such study by Lolascon et al. discovered that postmenopausal women with serum levels >30 ng/mL had improved physical performance, greater handgrip strength, and knee extension strength in comparison to the group with serum levels lesser than 30 ng/mL. Thus, a positive association can be found between bone health and serum levels.

**Defense against Infections**

As mentioned, vitamin D may enhance the overall immune response because of its ability to improve the functions of macrophages and dendritic cells. Deficiency can lead to respiratory and viral infections. With the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic spreading at an alarming rate, it becomes vital to understand the relationship between the virus and vitamin D. Supporting the immune system is one of vitamin D’s many crucial roles. It aids in lowering coagulation problems in COVID-19 patients and can lower the inflammation spread by reducing cytokine production. Cytokine release syndrome responsible for multiple organ failures in COVID-19 patients can be attenuated by vitamin D supplementation and patients with severe COVID infections. The ideal vitamin D level is 125 nmol/L or 50 ng/mL 25(OH)D, which could prevent fatalities and lessen the effects on patients with comorbid conditions.

Various studies also depicted that people having high vitamin D levels are unlikely to experience fatal outcomes of COVID-19. Thus, a lower threshold of 50 ng/mL of vitamin D could be recommended to reduce the impact in comorbid patients. A similar study pointed out that patients provided with 55 ng/mL of vitamin D displayed the least infections. Therefore, the data strongly suggest that the COVID-19 mortality risk is inversely correlated with vitamin D status and that at 50 ng/mL across latitudes, different races, ethnicities, sexes, and ages, a death rate close to zero may theoretically be obtained. Hence, the insufficiencies are huge and can provide a cheap alternative for preventing COVID-19 infection. This result was long established by Zhang et al., which demonstrated that serum levels higher than 30 ng/mL were sufficient to inhibit interleukin 6 and tumor necrosis factor a production by lipopolysaccharide and cytokine production in human monocytes. Directors of an Iranian hospital observed that patients with vitamin D levels above 40 ng/mL were released from the facility before 4 days had passed without hypercoagulation or cytokine storm. Lakkereddy et al. demonstrated the use of pulse D therapy helps to lower the COVID-19 inflammatory cytokines. Vitamin D levels were found to be increased from 16 ± 6 ng/mL to 89 ± 32 ng/mL, and a highly significant decrease (p < 0.01) in assessed inflammatory markers was observed without any side effects. Thus, this method can be used safely to enhance the current COVID-19 treatment protocols. Hence, increasing the vitamin D supplementation to 50 ng/mL will not only help in strengthening the immune system but also help in increasing the success of vaccination.

**Vitamin D and Cardiometabolic Disorders**

Type 1 diabetes prevention is another potential benefit of vitamin D. Furthermore, children with increased vitamin D ingestion have a reduced
A Review on Vitamin D Deficiency and Related Disorders

chance of developing type 1 diabetes. A meta-analysis demonstrated that circulating 25(OH)D levels were negatively and significantly correlated with the risk of type 2 diabetes. Every 10 nmol/L increase in vitamin D levels was related to a 4% decreased incidence of type 2 diabetes, according to linear trend analysis (p < 0.0001). According to a study, individuals with higher vitamin D (greater than 25 ng/mL) have a 43% lower chance of acquiring type 2 diabetes than individuals with less than 14 ng/mL. Vitamin D also reduces insulin resistance. Interest in vitamin D’s involvement in cardiovascular health has grown significantly in recent years. The observational evidence suggests that the optimal range of serum 25(OH)D levels (20–50 ng/mL) may influence a reduction in cardiovascular disease events at both low (<50 nmol/L) and high (>50 ng/mL) levels of 25(OH)D.

According to a cohort study, individuals receiving <50 mmol/L vitamin D had increased chances of high blood pressure and hypertension after 6 years. Around 1 billion people have hypertension, and the number is expected to reach 29% by 2025. Studies have suggested it might be connected with low vitamin D levels. According to a meta-analysis, a negative correlation exists between 25(OH)D levels and incident hypertension, decreasing by 7% for every 25 nmol/L increase in 25(OH)D levels. As 25(OH)D declined, the risk of hypertension rose significantly below 75 nmol/L but remained substantial over the range of 75–130 nmol/L. Different studies suggest diverse opinions on vitamin D in hypertension. Therefore, additional randomized controlled trials (RCTs) are necessary to determine the optimum dose and dosing interval to validate its actual impact on hypertension.

Additionally, it has been demonstrated that a deficiency of vitamin D increases the risk of dyslipidemia. Dyslipidemia can be linked to increased plasma cholesterol or a low level of high-density lipoprotein cholesterol (HDL-C). This is further linked with a high chance of developing atherosclerosis. According to the study by Wang et al., this association is more prominently visible in males than females. A meta-analysis by Dibaba highlighted the beneficial effects of vitamin D on serum total cholesterol, triglycerides, and low-density lipoprotein-cholesterol. However, HDL-C showed no discernible impact. It is also evidenced that hypercholesterolemia patients with vitamin D insufficiency may benefit from increased vitamin D levels.

### Dosing and Duration of Vitamin D Supplements

This section will highlight the guideline recommendations and appropriate serum 25(OH)D target levels to be attained for general and at-risk populations. A loading dose is required to achieve the desired effect sooner, and a maintenance dose is required to maintain the effective drug concentrations throughout the dosage regimen. Also, bioavailability should be adjusted while calculating the loading and maintenance dose. The maintenance dose is essential for sustaining adequate vitamin D levels over an extended period and preventing the onset of a deficit. However, it has been noted that after individuals reach the desired vitamin D level, they are unable to keep it up since they are not getting enough vitamin D maintenance.

### Table 3: Different studies highlighting dosage regimens to comprehend the role of vitamin D in overall health

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rastogi et al., 2022</td>
<td>Patients received either 60000 IU of cholecalciferol daily for 7 days or a placebo (control group). 40 SARS-CoV-2 positive patients, with 16 and 24 individuals in the intervention and control groups, respectively.</td>
<td>A total of 10 patients achieved vitamin D levels greater than 50 ng/mL by day 7 and another two by day 14. 20.8% of participants (control arm) and 62.5% of participants (intervention group) both developed SARS-CoV-2 RNA negative status (p &lt; 0.018).</td>
</tr>
<tr>
<td>Sandhu et al., 2015</td>
<td>A 12-week, open-label research on vitamin D and type 2 diabetes insufficiency involved 50 participants. 60000 IU of vitamin D per week (for 12 weeks) was administered orally.</td>
<td>HbA1c reduced significantly (p &lt; 0.05), and FBG levels significantly decreased. A highly significant increase in vitamin D levels (p &lt; 0.001) and a considerable (p &lt; 0.05) rise in calcium levels were both noted.</td>
</tr>
<tr>
<td>Salehpour et al., 2011</td>
<td>A double-blind, randomized, placebo-controlled study in two groups. (n = 77 participants). Cholecalciferol (1000 IU/day), 25 gm/day, was given to group I (n = 42 women). Group II (placebo, n = 43 women) (1000 IU/day).</td>
<td>Group I: Increased level of serum 25(OH)D than group II. Vitamin D treatment reduced the level of serum iPTh. When compared to the placebo group, group I’s body mass significantly decreased (p &lt; 0.001). 25(OH)D levels and body fat mass were found to have an inverse relationship.</td>
</tr>
<tr>
<td>Harris et al., 2011</td>
<td>A double-blind, randomized clinical trial comprised two groups: one that received vitamin D and the other that received a placebo. (16 weeks, n = 57 women). The placebo group received an identical placebo containing silica, while the vitamin D group received oral vitamin D3.</td>
<td>In the placebo and vitamin groups, the serum concentrations rose significantly. Only the group receiving vitamin D indicated a reduction in FMD (1.8 ± 1.3%).</td>
</tr>
<tr>
<td>Chaudhary et al., 2016</td>
<td>102 patients were randomly assigned to groups I and II (intervention and control groups, respectively). For 8 weeks, group I received cholecalciferol at 60000 IU/week and calcium at 500 mg/day; group II received calcium at 500 mg/day.</td>
<td>100 AIDT patients’ results were analyzed. Patients with the lowest 25(OH)D quartile were found to have the highest TPO-Ab titers. At the end of 3 months, group I showed a significant decrease in TPO-Ab.</td>
</tr>
<tr>
<td>Bhatt et al., 2020</td>
<td>121 females with vitamin D deficiency and prediabetes were randomly assigned to the intervention (n = 61) and placebo (n = 60) groups.</td>
<td>A significant difference between the intervention group and the placebo group in terms of FBG, 2-h blood glucose HbA1c. Following intervention, the intervention group’s subscapular and suprailliac skinfolds were considerably lower than those of the control group.</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; BMI, body mass index; iPTh, intact parathyroid hormone; FMD, flow-mediated dilation; AITD, autoimmune thyroid disease; TPO-Ab, thyroid peroxidase antibody
dosage. The maintenance dose is essential to preserve the benefits of vitamin D.

Guideline Recommendations on Dosing and Duration of Vitamin D Supplements

Endocrine Society recommends people should have blood levels of at least 30 ng/mL 25(OH)D levels to maintain the appropriate bone condition and strength. Therefore, to prevent vitamin D deficiency, the Endocrine Society suggests 1500–2000 IU/day for all adults to maintain overall health. In the case of obese individuals, the level should be 2–3 times more than the prescribed values. However, the Institute of Medicine (IOM) advised 600 IU/day (15 gm/day), which supports 97.5% of the population, using a more restricted approach. The IOM used average group serum 25(OH)D levels as 600 IU/day (physiological range 40–60 ng/mL); however, it cannot suffice for people living in colder areas or individuals with darker skin living in temperate latitudes. In contrast to IOM, the Endocrine Society suggests 4000 IU/day and 10000 IU/day for children and adults, respectively. To maintain sufficient blood levels, 50000 IU must be taken every week for 8 weeks.41

The American Academy of Pediatrics suggests 400 IU/day for children and supplementation of a minimum of 700–800 IU/day for grown-ups to avoid severe health conditions such as osteomalacia or increased incidence of fracture. Treatment for vitamin D deficiency involves taking 50000 IU/week for 8 weeks and at least 800–1000 IU/day as a maintenance dose from food and supplements.42

Clinical Evidence: How Much Vitamin D Supplementation Is Enough?

A study analyzed nine RCTs, and it was observed that vitamin D at a high dose of 1000/day could lower the risk of cancer. Mixed-effect dose-response analysis revealed that a 10 nmol/L increase in 25(OH)D concentration could lower the risk of colorectal cancer by 6%.43 People having a body mass index (BMI) greater than 30 kg/m² require for at least 4–5 half-lives to attain the steady-state level. In some cases, ≥1 dose than the maintenance dose can be given at the beginning with a loading dose. In a study, patients received vitamin D (60000 IU) orally for 12 weeks, after which the glycemic status was compared to the starting points.45 It was observed that fasting blood glucose (FBG) levels (p < 0.001) and glyceded hemoglobin reduced significantly (p < 0.05). Thus, vitamin D therapy can help in the improvement of glycemic control and subsequently help in delaying the advancement and problems associated with type 2 diabetes mellitus. Another such study found that African American people receiving 60000 IU of oral vitamin D each month (for 4 months) helped to improve vascular endothelial functioning.46 Table 3 helps in comprehending the role that vitamin D plays in overall health.

Rastogi et al. showed that a single high dose of 60000 IU did not exhibit any instances of hypercalcemia, indicating the safety of short-term high doses of vitamin D supplementation.47 In a study, a weak inverse relationship was found between thyroid peroxidase antibody (TPO-Ab) and 25(OH)D levels. As a result, vitamin D insufficiency is related to autoimmune thyroid disorders, and vitamin D supplementation may have a large influence since it can lower TPO-Ab titers.48

Therefore, daily supplementation of 4000–10,000 IU is required for ideal vitamin D blood levels in the 40–60 ng/mL range. In addition, it can be safely used when combined with vitamin K2 (200 µg/mL).49 However, the medical community does not utilize vitamin D to its full potential, and regrettably, outdated warnings regarding the dangers of vitamin D overdoses are still frequently propagated.50

As highlighted, the health benefits of vitamin D can be experienced at 25(OH)D blood levels greater than 30 ng/mL. Therefore, a big initial dose of 600000 IU administered intramuscularly monthly, or an oral dose of 200000 IU monthly, or 50000 IU weekly for 8 weeks, should be the optimal regimen to maintain 25(OH)D blood levels in healthy persons.41 As recommended by the Endocrine Society, Khwaja et al. administered 50000 IU bimonthly to maintain 25(OH)D serum levels above 30 ng/mL.52 A study conducted in North India points out that a starting dose of 120000–180000 IU of vitamin D is needed to raise 25(OH)D above the deficiency level. However, the improved serum values started declining after 2 months, and hence maintenance dose of 60000 IU was required to achieve the optimum level. It was also observed that maintenance dose at a shorter interval was effective in maintaining the required levels.53 Healthcare practitioners can greatly profit from this finding by using the recommended dosage to treat and maintain the proper 25(OH)D blood concentration.

Conclusion

The maintenance of the metabolism of calcium, phosphate, and bone is greatly aided by vitamin D. According to historical evidence; our ancestors had vitamin D levels between 10 and 50 ng/mL.54 Serum 25(OH)D levels in native Maasai herdsmen and Hadza tribesmen ranged from 40 to 60 ng/mL. They are thought to have a minimal chance of developing certain cancers, cardiovascular conditions, and autoimmune illnesses. Therefore, a person needs 4000–6000 IU of vitamin D daily to keep their blood 25(OH)D levels at a constant 40–60 ng/mL range.55 It is evident that vitamin D is crucial for boosting the immune system. Researchers can further explore its effect on the immune system to fully utilize its potential. The bottom line is that one should take a loading dosage regimen of 60000 IU for 12 weeks followed by maintenance therapy of 60000 IU monthly or bimonthly to achieve serum vitamin D levels of 50 ng/mL rather than the traditional sufficiency level of 30 ng/mL to enjoy the physiological benefits of the vitamin.

Author Contribution

The author has contributed to the concept, design, review, and finalization of the manuscript.

Acknowledgment

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References


**Naftifine: A Topical Allylamine for Superficial Dermatophytosis**

Abhijit A Trailokya¹,², Amar B Shirsat², R Madhu³, Bela Shah⁴

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**Abstract**

Dermatophytosis is a very common public health problem with high prevalence. Dermatophytes are a highly specialized set of filamentous fungi, which are adapted to keratinized tissues of humans and animals. Dermatophytosis is the most common fungal infection worldwide, affecting approximately 20–25% of the world’s population. The etiological agents of dermatophytosis, called dermatophytes, change with geography and socioeconomic status. *Trichophyton rubrum* is the prime species for skin and nail infections followed by *T. mentagrophytes/ T. interdigitale* complex. There is a shift from *T. rubrum* to *T. mentagrophytes* in India for superficial fungal infections. In order to deal with fungal infections, treatment strategies involve the use of systemic antifungals and/or topical antifungal agents. Naftifine is a synthetic allylamine antifungal that was first reported in 1974 and in 1985 became the first commercially available allylamine. The highly lipophilic nature of naftifine allows efficient penetration and reasonably high concentrations in the stratum corneum (SC) and hair follicles. Naftifine is fungicidal as well as fungistatic. The higher efficacy rates of allylamines over imidazoles for the treatment of fungal infections, even for months after cessation of treatment, is thought to be due to their fungicidal effect, as well as to potentially greater keratin binding and slower release from the SC. The effectiveness of naftifine is also demonstrated against various bacteria belonging to both gram-negative and gram-positive classes. The antifungal activity of naftifine has been reported in various preclinical studies where it has been shown to target the prostaglandin pathway. Naftifine 1 and 2% gel and cream is approved by The United States Food and Drug Administration (USFDA), recently naftifine has been approved in India by the Indian regulatory authority Drug Controller General of India (DCGI) for the treatment of dermatophytosis. Naftifine 2% also appears to be a promising treatment, requiring fewer applications than the 1% formulation. Naftifine appears to be effective in a single dose and has a shorter treatment duration than azoles. Naftifine demonstrated its efficacy and safety in various clinical studies of tinea infections. Naftifine offers a very useful and promising option for treating dermatophytosis.

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**Dermatophytosis**

Superficial fungal infections are usually caused by dermatophytes, nondermatophytes, and commensal yeasts. Dermatophytosis is a superficial fungal infection caused by dermatophytes affecting the skin, hair and/or nails.¹ They have also been named tinea infections. Dermatophytes are filamentous fungi that cause infection by invading keratinized tissues such as skin, hair, and nails. There are nine genera of dermatophytes. The important ones for causing infections in humans include *Trichophyton* (which affect the skin, hair, and nail), Epidermophyton (which affect the skin), and *Microsporum* (which affect the skin and hair).² In India, the prevalence of dermatophytosis ranges between 36.6 to 78.4%.⁶ Prevalence rates ranging from 6.09 to 27.6% have been reported in studies conducted in southern India, while prevalence rates as high as 61.5% have been recorded in northern India.³ The etiological agents of dermatophytosis, termed dermatophytes, change with geography and socioeconomic status. The predominant species causing skin and nail infections is *T. rubrum* and then another species that follows is *T. mentagrophytes/T. interdigitale* complex. There is a shift from *T. rubrum* to *T. mentagrophytes* in India for superficial fungal infections.⁴ Dermatophytes colonize the keratinized tissue of the stratum corneum (SC). In susceptible individuals there occurs the deposition of viable arthropores or hyphae on the surface of the skin leading to infection. The arthroconidia and the hyphae germinate radially under suitable environmental conditions at the local site. As a result, there occurs the hydrolysis of the disulfide bonds and also there occurs secretion of pathogenic enzymes like proteases, fungalysins, and hydrolases, which facilitates the biodegradation of keratin.⁵ When the diagnosis is uncertain or the response to treatment needs to be assessed, a 10–20% potassium hydroxide (KOH) wet mount is recommended whenever possible as a simple and sensitive test. Identification of the dermatophyte species by culture may be done on modified Sabouraud’s dextrose agar media with antibiotics and cycloheximide. The species identification can be done by the various morphologies of the microconidia and macroconidia, and also of the other vegetative structures. Also, the appearance of the fungal colony on the culture media helps in the identification of the species. For the identification of drug susceptibility patterns, antifungal susceptibility testing can be done. This is not feasible at all times and is available in research institutes and some specific laboratories only.⁶

**Management**

The management of dermatophytosis depends on general measures and medical management. In order to deal with fungal infections, treatment strategies involve the use of systemic antifungals and/or topical antifungal agents. All forms of corticosteroids should be avoided as they can lead to abnormal appearance, diagnostic difficulties, and treatment failure. Prior to the discovery of newer antifungal agents, dyes like gentian violet, magenta paint, and brilliant green were the historically used effective antimitotic agents. Whitefield’s ointment was one of the earliest available compounds used topically which constituted of benzoic acid and salicylic acid. But over the last 2–3 decades there has been the development of various newer antifungal agents. The major group of antifungal agents which are in use routinely at present are the azoles, the polyenes, the morpholines, the allylamines, and the pyrrolidines. Naftifine is approved by The United States Food and Drug Administration (USFDA), recently naftifine has been approved in India by the Indian regulatory authority Drug Controller General of India (DCGI) for the treatment of dermatophytosis.

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**Conflict of Interest:** Dr Abhijit A Trailokya, Dr Amar B Shirsat are associated with Indoco Remedies, Mumbai, Maharashtra, India.
the allylamines, and the group of unrelated compounds. According to the Indian Expert Consensus on the Management of Dermatophytosis, India developed by Rajagopalan et al., the systemic and topical antifungals, are to be used empirically in the treatment of the naive tinea pedis and also the recalcitrant tinea pedis. Topical antifungals alone are to be used empirically in the treatment of naive tinea cruris and corporis (localized lesion) cases. The combination of topical and systemic antifungals is to be used in the treatment of patients who have extensive lesions and patients who fall under the category of recalcitrant tinea. In difficult-to-treat cases, the combination of topical and systemic antifungals can improve the treatment outcomes.

For the prevention of the emergence of resistance and also for wider coverage, experts recommend the use of drugs from different classes as a combination therapy.

**Topical Antifungal Therapy**

Topical antifungal therapy is the cornerstone of glabrous tinea management, particularly in the setting of local infections, pregnancy, children, and certain comorbidities that preclude the use of systemic antifungal agents.

In the current context, topical antifungals can be beneficial adjuncts to systemic antifungals because they can have additive effects and reach higher local concentrations. The topical antifungal agent which is ideal for the treatment of dermatophytosis should have the following characteristics. It should have broad-spectrum activity; it should be efficacious at low concentrations, it should be fungicidal and have a dosing regimen, which is more convenient that is once a day application, should be lipophilic in nature and have strong keratin binding properties, should have high clinical cure rates and better mycological cure rates, should show a good retention and reservoir property in the SC, with the lower risk of side effects, relapses, and fungal resistance, and should be economical.

Ergosterol is a crucial component of the fungal cell wall. The antifungal agents majorly interfere with the ergosterol synthesis and thus inhibit fungal growth and replication. The most commonly used medications are topicalazole antifungals, which include clotrimazole, miconazole, ketoconazole, luliconazole, etc. These are active against all the common skin fungi. Terbinafine, naftifine, and ciclopirox olamine are amongst the other potent antifungal agents which are used topically in the treatment of dermatophytosis. A Cochrane review of topical treatments for tinea cruris and corporis (126 studies with 18,086 participants) data suggested that topical terbinafine and naftifine were effective.

**Allylamine**

A chemical research program was conducted for the synthesis of new central nervous system drugs, during which the antifungal agent of the allylamine class was discovered by chance. This product which had a novel chemical structure was yielded due to an unexpected chemical reaction. This compound had excellent antifungal activity as observed and was named naftifine based on the in vitro biologic screening assays. The experimental studies in animal models of infection and in clinical trials in humans confirmed the antifungal property of naftifine.

Terbinafine and naftifine belong to the allylamine group of antifungal agents, which are comparatively a newer class of antifungal agents. The topical allylamine, naftifine was found to be highly active against a wide range of important fungi. In 1974, naftifine was discovered at Sandoz Research Institute in Vienna, Austria. Naftifine was found to be a very effective and safe agent against various pathogenic fungi and was the first derivative of the allylamines group.

**Allylamine vs Azole**

<table>
<thead>
<tr>
<th>Allylamines</th>
<th>Azoles</th>
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<tr>
<td>Allylamines inhibit the squalene epoxidase enzyme, leading to the accumulation of squalene. Thus allylamines act in the early stages of ergosterol synthesis. The fungicidal activity of allylamines results from the accumulation of squalene which is very toxic to the fungal cell wall. They are very effective against <em>Trichophyton</em> spp. but only fungistatic action only on <em>Candida albicans</em> (C. albicans) and <em>Malassezia furfur</em> (M. furfur).</td>
<td>Azoles inhibit the 14α-lanosterol demethylase enzyme, leading to the accumulation of lanosterol. The fungistatic action of imidazoles is due to lanosterol which is less toxic than squalene. The azole group of antifungals is potent against <em>C. albicans</em> and <em>Trichophyton</em> spp.</td>
</tr>
</tbody>
</table>

**Terbinafine Resistance**

Antifungal resistance is one of the most important hindrances and emerging issues in the treatment of dermatophytosis. Antifungal resistance has been in large proportion to the commonly used antifungal agent i.e., terbinafine as per the data and reports that are available across the globe. Missense mutations in the squalene epoxidase gene have been found in *T. rubrum* and *T. mentagrophytes* in Switzerland and India. Pathogens exhibit resistance to terbinafine, requiring higher doses due to increased Minimum inhibitory concentration (MIC). This is called clinical resistance, which means that higher-than-safe doses are needed to suppress the pathogens mentioned above.
**Naftifine**

Naftifine was discovered at Sandoz Research Institute in Vienna, Austria. Naftifine was found to be a very effective and safe agent against various pathogenic fungi and was the first derivative of the allylamines group. Naftifine is the first allylamine approved for usage in humans. But it is only available in the topical form and not in oral form. The highly lipophilic nature of the molecule allows efficient penetration and high concentrations in the SC and hair follicles. Naftifine is both fungicidal and fungistatic. Through inhibition of squalene epoxidase, naftifine results in decreased ergosterol synthesis and increased accumulation of the sterol precursor squalene with subsequent disruption of fungal cell membranes.

**Mechanism of Action**

The topical allylamine, naftifine has a fungicidal property and is effective against dermatophytes, aspergillus species and candida species. Naftifine has also been shown to have an antibacterial effect and is found to be effective against gram-positive and gram-negative bacteria. Naftifine has been shown to target the prostaglandin pathway, and thus have an anti-inflammatory activity.

The lipophilic property of naftifine ensures an effective penetration into the epidermis and also hair follicles. The allylamines are powerful inhibitors of the pathway for the biosynthesis of ergosterol, a vital component of the fungal cell membrane. Inhibition of ergosterol synthesis by inhibition of squalene epoxidase leads to the arrest of fungal cell growth, which may explain the funginal inhibitory (fungistic) effect of naftifine. Inhibition of squalene epoxidase leads to accumulation of squalene in membranes, particularly the endoplasmic reticulum. This caused a dramatic increase in squalene before the ergosterol deficiency. Squalene alters the properties of fungal cell membranes, so naftifine has a fungicidal action.

**In Vitro Action Spectrum of naftifine against Filamentous and Dimorphic Fungi**

<table>
<thead>
<tr>
<th>Fungus</th>
<th>Naftifine [range of MIC values (µg/mL)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatophytes</td>
<td></td>
</tr>
<tr>
<td>Epidermophyton</td>
<td>&lt;0.06–0.5</td>
</tr>
<tr>
<td>floccosum</td>
<td></td>
</tr>
<tr>
<td>Microsporum species</td>
<td>&lt;0.06–2.0</td>
</tr>
<tr>
<td>Trichophyton species</td>
<td>0.05–1.0</td>
</tr>
<tr>
<td>Dimorphic fungi</td>
<td></td>
</tr>
<tr>
<td>Blastomycetes</td>
<td>≥0.05–0.4</td>
</tr>
<tr>
<td>dermatitidis</td>
<td></td>
</tr>
<tr>
<td>Histoplasma</td>
<td>≤0.05–0.2</td>
</tr>
<tr>
<td>capsulatum</td>
<td></td>
</tr>
<tr>
<td>Sporothrix schenckii</td>
<td>≤0.06–8.0</td>
</tr>
</tbody>
</table>

**Pharmacokinetics**

After the topical administration, the systemic absorption of naftifine is very minimal (2–6%). There has been no reporting of any major systemic side effects. Topical naftifine is categorized under pregnancy category B. There is no data available as to whether topical naftifine is secreted in human milk.

**Clinical Usage and Approval Status of Naftifine**

The in vitro activity against the broad range of dermatophytes, yeasts, and saprophytes explains the spectrum of naftifine. In animal studies, naftifine has shown strong in vivo activity. In Europe and the United States of America, various clinical trials have demonstrated the therapeutic efficacy of naftifine against several dermatomycoses.

Naftifine 1% and 2% gel and cream—approved by USFDA, recently naftifine has been approved in India by the Indian regulatory authority DCGI. Naftifine is approved only for topical usage. It should not be used for ophthalmic, oral, or intravaginal applications.

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**In Vitro Action Spectrum of naftifine on Pathogenic Yeasts**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Naftifine [range of MIC values (µg/mL)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans (yeasts)</td>
<td>1.6±128</td>
</tr>
<tr>
<td>C. albicans (mycelium)</td>
<td>0.2–3.1</td>
</tr>
<tr>
<td>C. guilliermondii</td>
<td>25</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>≥200</td>
</tr>
<tr>
<td>C. krusei</td>
<td>50–200</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>1.0–100</td>
</tr>
<tr>
<td>C. pseudotropicalis</td>
<td>16–200</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>50–128</td>
</tr>
<tr>
<td>Candida species</td>
<td>1.0–128</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>4.0–64</td>
</tr>
<tr>
<td>Malassezia furfur</td>
<td>0.8–300</td>
</tr>
</tbody>
</table>

Advantage of 2% naftifine—naftifine 2% appears to be an effective treatment requiring fewer applications (once daily) than the 1% formulation (twice daily)—possibly improving adherence. Naftifine appears effective in a single application and for a shorter treatment duration compared to azoles.
Naftifine: A Topical Allylamine for Superficial Dermatophytosis

**Naftifine—Therapeutic Clinical Efficacy Data**
Topical naftifine hydrochloride has been shown to have greater efficacy than other topical agents. It also has been shown to cause faster symptom resolution with a lower incidence of side effects.

**Important Clinical Trials on 2% Naftifine**

### Tinea Corporis (Efficacy and Safety of 2% Naftifine)

<table>
<thead>
<tr>
<th>Trail design/disease condition/no. of patients/treatment received</th>
<th>Efficacy and safety endpoints</th>
<th>Result</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinea corporis&lt;sup&gt;21&lt;/sup&gt; Randomized, double-blind, and vehicle-controlled trial</td>
<td>Assessment of treatment effects</td>
<td>At week 2 (end of therapy) for naftifine cream 2% vs vehicle</td>
<td>Naftifine 2% cream is effective and better tolerated in children with tinea corporis</td>
</tr>
<tr>
<td>Tinea corporis Baseline Randomization Naftifine cream 2% (n = 116) Vehicle (n = 115)</td>
<td>Baseline Week 2 (end of therapy) Week 3—clinical symptom severity Mycologic determination (KOH mount and cultures) Efficacy assessment [n = 181 (naftifine n = 88; vehicle n = 93)]—in patients with a culture and KOH mount positive report at baseline with the availability of week 3 assessment report Safety assessment [n = 231 (naftifine n = 116; vehicle n = 115)]</td>
<td>Significantly greater improvements in mycological cure (p &lt; 0.0001) Treatment effectiveness (p = 0.003) Response rates were highest 1 week after the stoppage of therapy—complete cure p = 0.003 Mycological cure p &lt; 0.001 Treatment effectiveness p &lt; 0.001 There was minimal AE</td>
<td>More improvement was seen in all the efficacy parameters including clinical signs and symptoms (erythema, induration, and pruritus), 1-week after the stoppage of therapy</td>
</tr>
<tr>
<td>Tinea corporis&lt;sup&gt;22&lt;/sup&gt; A multicentric, randomized, double-blind, and vehicle-controlled trial Symptomatic and dermatophyte culture positive tinea corporis A total of 184 pediatric (≥2 to &lt;18 years of age) subjects were randomized to receive naftifine hydrochloride cream (n = 91) or vehicle (n = 93) Patients applied naftifine Cream or vehicle to the affected area once a day for 2 weeks including a half-inch margin of the healthy skin surrounding the lesion</td>
<td>Efficacy endpoints were Complete cure Effective treatment Mycological cure Primary efficacy endpoints were assessed on day 21 Signs and symptoms (erythema, induration, and pruritus) KOH mount Fungal culture</td>
<td>Complete Cure was seen in 42 (46%) vs 26 (28%) in the naftifine Hydrochloride Cream 2% vs vehicle respectively. Effective treatment was seen in 53 (58%) vs 32 (34%) in the naftifine hydrochloride cream 2% vs vehicle, respectively Mycological cure was seen in 57 (63%) vs 36 (39%) in the naftifine hydrochloride cream 2% vs vehicle, respectively</td>
<td>Naftifine 2% cream is effective and better tolerated in patients with tinea corporis</td>
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</table>

### Tinea Cruris (Efficacy and Safety of 2% Naftifine)

<table>
<thead>
<tr>
<th>Trail design/disease condition/no. of patients/treatment received</th>
<th>Efficacy and safety endpoints</th>
<th>Result</th>
<th>Conclusion</th>
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</thead>
<tbody>
<tr>
<td>Tinea cruris&lt;sup&gt;23&lt;/sup&gt; Randomized, double-blind, and vehicle-controlled study T. cruris Baseline randomization of 334 patients was done naftifine 2% (n = 166) Vehicle (n = 168)</td>
<td>Parameters assessed at week 2 (end of treatment) Week 4 Efficacy parameters (naftifine n = 75; vehicle n = 71) at—complete cure Treatment effectiveness Clinical and mycological cure Clinical success Safety parameters AE Laboratory parameters Clinical status</td>
<td>Week 4—naftifine vs vehicle Complete cure 25 vs 3% Mycological cure 72 vs 16% (one-sided, p &lt; 0.001). Treatment Effectiveness 60% vs. 10% (one-sided, p &lt; 0.001). Clinical cure rate 33% vs 10% Clinical success rate 84 vs 46% (both p &lt; 0.001, two-sided) Treatment-related AE (naftifine n = 7; vehicle n = 4) Most common AE were contact dermatitis (naftifine n = 2), pruritus (vehicle n = 2), and application site reaction (naftifine n = 1 and vehicle n = 1)</td>
<td>Naftifine 2% cream is efficacious and safe in patients with tinea cruris</td>
</tr>
</tbody>
</table>

Contd...
### Tinea Pedis (Efficacy and Safety of 2% Naftifine)

<table>
<thead>
<tr>
<th>Trail design/disease condition/no. of patients/treatment received</th>
<th>Efficacy and safety endpoints</th>
<th>Result</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A total of 709 patients received — NAFT-2 (2 weeks) (n = 235)</td>
<td>Efficacy endpoints were</td>
<td></td>
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<tr>
<td>Vehicle (2 weeks) (n = 118)</td>
<td>Complete cure</td>
<td></td>
<td></td>
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<tr>
<td>NAFT-1 (4 weeks) (n = 237)</td>
<td>Effective treatment</td>
<td></td>
<td></td>
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<tr>
<td>Vehicle (4 weeks) (n = 119)</td>
<td>Mycological cure</td>
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<td></td>
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<td></td>
<td>Primary efficacy endpoint</td>
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<tr>
<td></td>
<td>(week 4)</td>
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<tr>
<td></td>
<td>Signs and symptoms of tinea</td>
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<tr>
<td></td>
<td>cruris</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>KOH mount and fungal</td>
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<td></td>
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<tr>
<td></td>
<td>culture</td>
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<td></td>
<td>Efficacy assessment (n = 425) done in subjects with positive baseline dermatophyte culture</td>
<td></td>
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<td></td>
<td>Clinical symptom severity scoring (erythema, scaling, and pruritus)</td>
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<td>Safety assessment (n = 707)—assessed by AE laboratory parameters</td>
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<td>Week 6</td>
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<tr>
<td></td>
<td>NAFT-2 vs vehicle</td>
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<td></td>
<td>Complete cure rate—18 vs 7% (one-sided, p &lt; 0.01)</td>
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<tr>
<td></td>
<td>Mycological cure rate—67 vs 21% (p &lt; 0.001)</td>
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<tr>
<td></td>
<td>Treatment effectiveness—57 vs 20% (p &lt; 0.001)</td>
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<tr>
<td></td>
<td>Clinical cure rate—22 vs 11% (p = 0.04)</td>
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<tr>
<td></td>
<td>Clinical success rate—78 vs 49% (p &lt; 0.001)</td>
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<tr>
<td></td>
<td>NAFT-1 versus Vehicle</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Efficacy responses were significantly higher than the vehicle</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>NAFT-2 and NAFT-1 had increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mycological cure and clinical response rates from weeks 2 to 6.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment-related AEs NAFT-2 (5%) vs vehicle (7%)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>NAFT-1 (4%) vs vehicle (8%)</td>
<td></td>
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<tr>
<td></td>
<td>Pruritus and skin irritation at the application site were the most common AEs for all groups</td>
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<tr>
<td></td>
<td>NAFT-2 is superior and better tolerated than a vehicle in patients with tinea pedis</td>
<td></td>
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<tr>
<td></td>
<td>NAFT-2 is equi-efficacious to 4 weeks of NAFT-1 treatment.</td>
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<tr>
<td></td>
<td>There is a continuous increase in the antifungal activity of naftifine for 1 month postcompletion of therapy</td>
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<td></td>
</tr>
</tbody>
</table>

### Safety Profile of Naftifine

Adverse events are mild to moderate in severity and do not lead to discontinuation of therapy. The adverse effects include stinging or burning, erythema, dryness, itching, and local irritation, which occur typically in <5% of patients. Naftifine has not been known to show any irritancy, sensitization, photosensitization, or phototoxicity as per the data from dermatotoxicology studies in humans. Naftifine use is rarely associated with...
Naftifine: A Topical Allylamine for Superficial Dermatophytosis

Use in Special Population

**Pregnancy**

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>No data is available in relation to drug-associated major birth defects risk and miscarriage with the usage of naftifine hydrochloride cream in pregnant women.</td>
</tr>
</tbody>
</table>

**Lactation**

<table>
<thead>
<tr>
<th>Details</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no information available about the presence of naftifine hydrochloride in breast milk, the effects of this medicine on a nursing infant, or the effect of this medicine on milk production.</td>
<td></td>
</tr>
</tbody>
</table>

**Place of Naftifine in Therapy**

Naftifine is a topical allylamine that is effective against dermatophytes and has a fungicidal property. This activity appears to derive from a complex mechanism of action, the central element of which involves squalene epoxidase inhibition—an action distinguishing the allylamines from other antifungal agents. In clinical indications associated with dermatophyte infection, naftifine has proved highly effective. Daily application for 2–4 weeks in controlled trials produced therapeutic success (clinical and mycological cure) in 60–96% of patients with tinea cruris or tinea corporis, and generally in over 80% of patients. The cure rate among patients with tinea pedis tended to be slightly lower at 50–80% of patients. There is some evidence that naftifine may have a more rapid onset of action than other antifungal agents, although this—and a claimed antinflammatory activity—require further investigation. Several efficacy studies of naftifine have consistently reported increased residual fungicidal activity and sustained improvement in mycological and clinical cure rates after treatment discontinuation, with the highest efficacy response rates observed within 6–8 weeks after treatment. A similar trend has been observed in recent clinical trials involving higher concentrations of naftifine (naftifine 2%), using shorter treatment regimens (2 weeks) in the treatment of tinea pedis and/or tinea cruris.

Naftifine 2% also appeared to be an effective treatment, requiring fewer applications than the 1% formulation which improved compliance. Naftifine 2% appears to be effective as a once a day application and has a shorter treatment duration compared to azoles.

**Acknowledgment**

We would like to acknowledge Dr Manjiri Jagtap MBBS, DDV, FCPS, and DNB for helping us in reviewing the manuscript.

**References**

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14. Adapted from Stephen E. Wolverton. Comprehensive Dermatologic Drug Therapy. FOURTH EDITION. Chapter 42.
POINT OF VIEW

“Status Quo”: A Necessity for Clinical Medicine due to Corporatization: Clinician’s Perspective in a Developing Country

Arjun M Balakrishna1*, Atul Goel2
Received: 20 January 2019; Accepted: 15 February 2023

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In the present era of evidence-based medicine, skepticism towards a generation of evidence though intriguing is a prerequisite during clinical practice. In 2015, Richard Horton, Editor-in-Chief of The Lancet, stated, “The case against science is straightforward: much of the scientific literature, perhaps half, may simply be untrue, afflicted by studies with small sample sizes, tiny effects, invalid exploratory analyses, and flagrant conflicts of interest, together with an obsession for pursuing fashionable trends of dubious importance, science has taken a turn towards darkness.”

The present article seeks to explore possible reasons that account for the corporatization of clinical medicine, as also the occult ways in which the pharmaceutical industry controls every aspect of daily clinical practice and academic research.

Status Quo

Let us all for a moment imagine that tomorrow morning somebody reports a permanent cure for diabetes mellitus. What would follow is somewhat unimaginable. The insulin market, which is worth >$30 billion in the United States of America alone, would crumble into dust overnight. Antidiabetic medications, sugar-free products, chains of laboratories, and clinics that thrive on comprehensive diabetes management would all go “Lehman Brother’s way” in less than a fortnight. Millions of dieticians and diabetologists in the world would have nowhere to go, and the massive pharmaceutical industry (that has managed to survive almost all economic crises) melt-down would be enough to collapse the world economy into a hole, from where it would find itself difficult to recuperate.

Is it worth the loss? Are we even really looking for a disease-free world? Or have we peacefully settled for a world where we neither want to cure nor prevent disease? Do we just want to maintain it as it is or status quo? A wide range of chronic diseases, some as simple as hay fever and complex ones like cancer are being maintained “status quo” to meet the economic demands of the pharmaceutical industry.

The recent champions in the race of status quo are the exorbitantly priced biological products that are being used extensively in every corner of rheumatology, making it one of the most lucrative branches of clinical medicine for young graduates to pursue upon. In a way, they are for physicians what drug-eluting stents were for interventional cardiologists and prostheses are for orthopedic surgeons.

The misdemeanor has also set its foot into other aspects of clinical practice, like revising the diagnostic criteria too frequently just to fit in as many people under the banner of a chronic disease. More than half of the Indian adult population turned hypertensive overnight in 2017 when the American Heart Association revised their diagnostic criteria to classify a blood pressure of >120/80 mm Hg as elevated. The same is true for the diagnosis of diabetes mellitus, wherein the upper limit of fasting blood sugar was consistently brought down to increasingly categorize more and more individuals as diabetics. The conflict with the acceptable level of glycated hemoglobin (Hba1c) was highlighted when the Annals of internal medicine in 2018 quoted that “an Hba1C level between 7 and 8% was more acceptable and perhaps beneficial as opposed to that of <6.5% that had been used for decades.” The fact that hypoglycemia is more life-threatening than hyperglycemia is also well-known from the days of the United Kingdom prospective diabetes study.

Academic Research


If we live in a polio-free world today, we owe it all to Jonas Salk. This is the level of selflessness that had made medicine the noblest profession of them all, but unfortunately, with the invasion of commercialization, graduates of modern medicine are being explicitly taught to maintain a “status quo.”

Corporatization of medical research is a gradual process that was started due to purported benefits like financial support for universities, improved faculty access to research and development, enhanced technological innovation, and scientific progress. However, the metamorphosis of pharmaceuticals from just being an ally of clinical medicine into a giant monster that reigns over the medical code of ethics has brought in a set of unfortunate perils like conflicts of interest, research bias, and ghostwriting.

Research topics by students as well as scholars are being selected based on corporate demand; all research is being directed and repeatedly redirected towards the maintenance of a “status quo” but progressively profitable margins.

The concept of vaccination was discovered by Edward Jenner in 1791. Subsequently, the malarial parasite was discovered in 1880 by Alphonse Laveran. It is not just simply unfortunate that there is no effective vaccine for malaria yet, even though it infects >200 million people annually in the developing world. Is it not surprising and regrettable that tuberculosis, which claims >1,00,000 lives every year in India, has only one effective vaccine for over a century! However, on the other hand, we are almost on the verge of a vaccine for obesity which can be prevented simply by lifestyle modifications. Yes, that nobody wants to research diseases that affect the underprivileged of the third
world is a hard truth. Where, then, do we fit in the philanthropy of Warren Buffet or Bill Gates?

Medical students and research scholars are being motivated to adjust their curiosities to match the interests of available sponsors and strengthen their chances of obtaining a grant. Corporate partnerships enhance research secrecy through nondisclosure and intellectual property agreements, thereby gaining control over academic data with the help of “academic capitalists” within the university.6

Conflicting of Interest

A national daily newspaper recently published an advertisement of a pharmaceutical giant being endorsed by an Indian Bollywood actor.7 Medical science has reached a dreadful state wherein medicines are not just being prescribed; they are being endorsed like commodities.

To quote Hippocrates, the father of medicine, “The greatest medicine of all is teaching people how not to need it.” But unfortunately, we have come very far on a fallacious path from where there seems no return unless strict necessary actions are taken right at the level of entry to medical schools. Monetary benefits, promotions based on research publications, obtaining grants, and admissions into reputed universities, are some of the reasons why clinicians and research scholars succumb to the pressures of corporate demand and resort to practices like ghostwriting and biased research (Flowchart 1).

According to Campbell, most physicians (94%) reported some type of relationship with the pharmaceutical industry, and most of these relationships involved receiving food in the workplace (83%) or receiving drug samples (78%). Canadian companies alone spend $4.8 billion every year on doctors.10 No such survey has been conducted in India to date, but I’m sure the problem may be as serious, if not more. We may be on the cusp of complete corporatization of the healthcare industry, including medical education.

In 2012, a group of 100 researchers tried to replicate the results of the most widely cited cancer research papers; Shockingly, only six were validated.11 Ghost articles are written especially after dangerous side effects are reported with newer drugs. How can one forget a common drug like metoclopramide introduced in the early 1980s or proton pump inhibitors in 2001.11 Premarin and zyprexa are recent drug examples which could be quoted here. Lexin Wang stated that no >15% of newer drugs offer any significant advantage over the ones that already exist, but still, newer drugs that are costlier than the previous ones enter the market every day with a lot of data supporting their supremacy over the existing ones of the same class.12

The deceit does not end at just prescribing drugs but has also intruded into other modalities of treatment like interventions and unnecessary surgical procedures. In March 2018, the Journal of American Heart Association published a study inferring that the in-patient 30-day mortality in patients of acute coronary syndrome who were treated medically without any intervention was significantly lower, especially when interventional cardiologists were away for cardiology conferences.13 The leading author even stated that many medical interventions deliver no mortality benefit, and the fact that mortality actually falls for heart attack patients during these conference dates raises important questions about how care might differ during these periods. It is data like this which makes us wonder if we are just chasing a mirage in pursuit of a fictitious perfection under the label of “evidence-based medicine” and also the hidden agendas behind the generation of such evidence.

Need for a Quantum Leap

There has been a phenomenal pharmaceutical revolution during the past 2 centuries; however, the need of the hour is a break through at a personal level. A breakthrough to curb malpractices like ghostwriting, research bias, academic capitalism, and receiving monetary benefits from pharmaceuticals. We, as clinicians, have to independently take an oath and join our hands together to protect the dignity of clinical medicine rather leaving our services at the disposal of pharmaceutical companies. Due to technological advances, information is available at the fingertips of every patient, which further creates dubiousness in the minds of patients towards the medical profession. The goal of academic research should be to advance public knowledge and not to produce marketable products. Knowledge sharing should be encouraged amongst the researchers, and research secrecy has to be condemned.

An unsympathetic “status quo” of clinical medicine due to such nugatory benefits would not mean just the extermination of clinical medicine but humanity as a whole. We cry about the increasing litigations in the field of medicine, but there would be nowhere for us to hide if we do not take corrective action today and move scientific activity back from pharmaceuticals to medical schools.

References

Unusual Case of Secondary Pneumothorax in a Patient of Allergic Bronchopulmonary Aspergillosis (ABPA)

Hitender Kumar1, Surender Kumar2, Shivali Sandal3

Received: 06 December 2018; Accepted: 28 December 2022

Abstract

Pulmonary aspergillosis is a well-recognized fungal lung disease caused by the Aspergillus species (especially Aspergillus fumigatus). Allergic bronchopulmonary aspergillosis (ABPA) is milder form of pulmonary aspergillosis compared to other more invasive forms. However, if left untreated, ABPA can cause significant lung damage. We present the case of a 33-year-old man who came with complaints of shortness of breath, chest discomfort, and productive cough. The patient underwent High Resolution Computed Tomography (HRCT) scan of the chest which, suggested the diagnosis of ABPA with secondary tension pneumothorax.

Keywords: Allergic bronchopulmonary aspergillosis, Pneumothorax, Secondary spontaneous pneumothorax

Introduction

Spontaneous pneumothorax is characterized by the presence of air in the pleural space. It can be divided into two types—primary and secondary. Primary spontaneous pneumothorax occurs in the absence of known lung disease, while secondary spontaneous pneumothorax occurs due to underlying lung diseases such as acute severe asthma, cystic fibrosis, tuberculosis (TB), necrotizing pneumonia, malignancy, interstitial lung diseases, etc.1

Allergic bronchopulmonary aspergillosis (ABPA) is a lung disease that occurs due to an overreaction of the immune system to Aspergillus antigen, which triggers an inflammatory response that can cause damage to the airways. ABPA is often seen in patients with asthma and cystic fibrosis. An inflammatory response can cause symptoms such as shortness of breath, coughing with expectoration, and wheezing.2,3

Pleural involvement in ABPA is less common. Pleural involvement may occur in the form of pleural thickening, ipsilateral pleural effusion, and lung collapse.4 ABPA complicating as secondary spontaneous pneumothorax which is unusual and a few cases have been reported in the literature to date.5

Case Description

A 33-year-old male patient who worked as a farmer visited the radiology department for a high-resolution computed tomography (HRCT) scan of the thorax. He reported a history of difficulty in breathing for the last 2 days and a cough with expectoration for 7 days. Over the past 2 years, he has been experiencing symptoms of atopy and recurrent upper and lower respiratory tract infections. He did not smoke or drink alcohol. There was no record of previous TB in his medical history.

The patient’s vital parameters were assessed during the physical examination, revealing an oral temperature of 99.3°F, blood pressure of 122/78 mm Hg, pulse rate of 104 beats/minute, and respiratory rate of 24 breaths/minute. During chest auscultation, the left hemithorax exhibited diffuse wheezing, while the right hemithorax had absent breath sounds. Upon percussion, a hyper-resonant note was observed in the right hemithorax.

The HRCT scan of the chest showed central bronchiectasis in both lungs, with bronchoceles formation due to impacted mucoid secretions. A large pneumothorax was observed on the right side, with a visible connection between dilated bronchioles and the pleura (known as broncho-pleural communication or fistula), causing the right lung to collapse. Additionally, a small amount of pleural fluid was visible (Figs 1 and 2).

Follow-up laboratory investigations showed a hemoglobin level of 12 gm/dL, a total leukocyte count of 7100/mm² with 25% eosinophils on the differential count, an erythrocyte sedimentation rate of 40 mm in 1 hour, and a fasting blood sugar level of 78 mg/dL. The coagulation profile was normal. Renal function tests, liver function tests, and electrolytes were within normal limits. The follow-up immunological survey showed a total serum immunoglobulin E (IgE) level of 2750 IU/mL, with increased levels of serum IgE and IgG against A. fumigatus. Sputum microscopy and Ziehl–Neelsen staining for acid-fast bacilli were negative.

Based on the patient’s clinical, pathological, and radiological characteristics, the diagnosis of secondary spontaneous pneumothorax complicated by ABPA was suggested. The patient underwent intercostal drainage under a water seal to treat the pneumothorax. Additionally, oxygen inhalation, nebulization, antibiotics, antifungal medication, and oral steroids were administered. The patient improved on follow-up.

Discussion

In 1952, Hinson et al. were the first to describe ABPA among individuals suffering from asthma.6 Since then, further research has been conducted on ABPA to better understand its pathogenesis, clinical presentation, and management. ABPA has been associated with bronchial asthma, cystic fibrosis, and tobacco use.7 ABPA is characterized by recurrent bronchial infections, asthma exacerbations, and bronchiectasis.8

The diagnosis of ABPA is typically made based on a combination of clinical symptoms, laboratory findings, and imaging studies. A high-resolution computed tomography (HRCT) scan of the chest is the imaging modality of choice for diagnosing ABPA.9 The imaging findings in ABPA are characterized by bronchiectasis, mucoid impaction, and bronchial wall thickening.10

Conclusion

Our case report highlights the importance of considering ABPA in the differential diagnosis of recurrent respiratory tract infections, particularly in patients with a history of asthma or cystic fibrosis. Early recognition and appropriate management of ABPA can prevent significant lung damage and improve patient outcomes.

Fig. 1: Shows an axial image obtained from the HRCT chest, revealing bilateral central bronchiectasis with bronchoceles formation (indicated by white arrows). The image also demonstrates a large pneumothorax on the right side, with dilated peripheral bronchiole showing direct communication with the pleural air, suggestive of bronchopulmonary communication (indicated by a red arrow).

Fig. 2: Shows a coronal image obtained from the HRCT chest, revealing bilateral central bronchiectasis.

References


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Unusual Case of Secondary Pneumothorax in a Patient of ABPA

The clinical presentation of ABPA typically involves nonspecific respiratory and systemic symptoms such as shortness of breath, pleuritic chest pain, cough with expectoration, wheezing, fatigue, weight loss, low-grade fever, etc. Elevated total serum IgE levels, typically exceeding 1000 ng/mL, are commonly observed through laboratory testing in individuals with ABPA. Additionally, laboratory examination may also reveal peripheral blood eosinophilia in these patients.

Patterson et al. in 1982 described five clinical stages of ABPA. The stages are acute, remission, exacerbation, corticosteroid-dependent asthma and fibrotic. Pleural complications that can arise from ABPA include pleural effusion, pleural thickening, and pneumothorax. These complications are more commonly observed during the fibrotic stage of the disease.

The International Society for Human and Animal Mycology (ISHAM) working group has classified ABPA into four major categories based on radiological findings, which indicate disease progression from mild to severe. These categories are as follows—(1) serologic ABPA (ABPA-S), (2) ABPA with bronchiectasis (ABPA-B), (3) ABPA with high-attenuation mucus (ABPA-HAM), and (4) ABPA with chronic pleuropulmonary fibrosis (ABPA-CPF).

Radiologically, ABPA can be classified into different categories based on disease severity. HRCT can reveal several characteristic features of ABPA, including central bronchiectasis, mucus plugging, centrilobular nodular infiltrates, and in advanced stages, extensive fibrosis, and cavitation.

Modified ISHAM working group 2013 criteria for diagnosis of ABPA are as follows:

- Predisposing asthma or cystic fibrosis.
- Obligatory criteria—(1) IgE > 1000 IU/mL and (2) positive immediate skin test or increased IgE antibody to Aspergillus.
- Supportive criteria (two or more should be present)—(1) eosinophilia > 500 cells/μL, (2) precipitins or increased IgG antibody to Aspergillus, and (3) fixed or fleeting radiographic opacities.

Pleural involvement in ABPA is uncommon and usually presents as pleural effusions, pleural thickening and pleural calcifications. Secondary spontaneous pneumothorax is a rare complication or clinical presentation of ABPA. Secondary spontaneous pneumothorax with ABPA is a relatively uncommon condition.

In the literature, spontaneous pneumothorax cases in patients with ABPA have been reported by several authors (Ricketti et al., 1984, Judson et al., 1993, Das et al., 2014, Vishnukanth et al., 2017). These cases were successfully treated with primary intercostal chest tube drainage to evacuate the pneumothorax.

There is a high prevalence of ABPA as well as pulmonary TB (PTB) in India. In areas with a high prevalence of PTB, patients with ABPA having atypical radiological presentations are often misdiagnosed with PTB. In some Indian studies, ABPA was misdiagnosed as TB in as high as 17–50% of cases.

Conclusion

In the evaluation of chronic lung diseases that present with pneumothorax, it is essential to include ABPA in the differential diagnosis. However, the incidence of ABPA is often underestimated in India because of the high prevalence of PTB. To diagnose ABPA accurately and identify its complications, HRCT of the thorax is a reliable and precise imaging modality that provides both high sensitivity and specificity.

References

A Diagnostic Journey

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ABSTRACT

We describe the case of a patient who came with features suggestive of diabetic ketoacidosis. On further evaluation of DKA, we found that it was caused by acute pancreatitis. This acute pancreatitis was found to be caused by hypercalcemia, which was in turn due to primary hyperparathyroidism. Imaging studies done for hyperparathyroidism revealed a thyroid nodule which later turned out to be malignant. This patient was also incidentally found to have hypertrophic obstructive cardiomyopathy.

Introduction

We describe the case of a patient whose disease required a diagnostic journey. The patient was a 55-year-old housewife from Mumbai, Maharashtra, India, with no history of any prior comorbidities but for a double J (DJ) stent placement for an obstructive right ureteric calculus done a week prior to admission on 13th June 2022. After her successful treatment for the calculus, she was discharged home only to get readmitted to another hospital on 20th June 2022 with complaints of abdominal pain and vomiting. An ultrasound (USG) abdomen was done, which was suggestive of acute pancreatitis, following which she was brought to the emergency room of Hinduja Hospital on 22nd June 2022 for further management.

Case Description

Clinical Features and Examination

On arrival to the emergency room, the patient was conscious, cooperative, and well oriented to time, place, and person. Her pulse was 100/minute, regular. The blood pressure was 110/80 mm Hg in the right arm in a recumbent position. Respiratory rate was 20/minute and oxygen saturation was 96% on room air. Her blood glucose level was checked and it was 546 mg/dL.

General examination showed no pallor, icterus, clubbing, cyanosis, or edema. No lymph nodes were palpable in the neck. No nodules in the thyroid gland were palpable.

Abdominal examination revealed tenderness present diffusely over the entire abdomen, more marked in the epigastric region.

Examination of the cardiovascular system revealed audible first and second heart sounds. A systolic murmur was audible in the neo-aortic area. The character of the murmur could not be assessed due to tachycardia.

Examination of the respiratory and nervous systems did not reveal anything of significance.

Immediate Investigations and Management

A complete blood count, renal function test, and electrolytes were sent along with amylase, lipase, and hemoglobin A1C (Hba1c) level. Stat urine ketone dipstick was done, which showed 2+ (moderate) ketonuria.

Arterial blood gas analysis was also done, which showed a pH of 7.32 with a bicarbonate of 18 and a partial pressure of carbon dioxide of 30. The anion gap was only 12.

The patient was started on intravenous crystalloids. A bolus of 500 mL 0.9% normal saline was given, followed by crystalloids at 100 mL/hour overnight. She was also given intravenous potassium correction. Insulin therapy was started with a bolus of 0.1 units/kg, followed by infusion of 0.1 units/kg/hour. She responded to insulin well, and her blood sugars reduced to 200 mg/dL over the next several hours. Once the ketoacidosis had resolved and the patient started taking food orally, she was switched over to subcutaneous insulin after a brief overlap period.

The complete blood counts showed a total white blood cell count of 22,000 with 90% neutrophils. HbA1c was 6.5%, indicating a relatively recent worsening of her blood sugars. The amylase and lipase, which were sent, turned out to be 400 and 260, respectively, supporting the diagnosis of pancreatitis.

It was determined that the diabetic ketoacidosis was likely to have been caused by acute pancreatitis. Since common causes of acute pancreatitis are gallstones, alcohol, hypertriglyceridemia, and hypercalcemia, relevant investigations were sent.

The calcium levels turned out to be 13.6 with albumin of 2.0, resulting in a corrected calcium level of 15.2! Thus, it was determined that acute pancreatitis was most probably caused by hypercalcemia. Hypercalcemia also explains the lower than expected anion gap in diabetic ketoacidosis.

Common causes of hypercalcemia include parathormone (PTH) independent causes like iatrogenic hypercalcemia due to hypervitaminosis D, lytic lesions of the bone including multiple myeloma, and PTH dependent causes including hyperplasia or adenoma. Thus, we evaluated the patient for the same.

There was no history of recent vitamin D use. Serum 25 hydroxy vitamin D levels were normal. Serum protein electrophoresis was found to be normal. Serum phosphate levels were sent, which were low at 2.3, while PTH levels sent were found to be very high at 2065 pg/dL against the normal range of 10–55 pg/dL! Thus, the hypercalcemia was likely due to a primary parathyroid disease.

In order to evaluate the parathyroid disease, USG of the neck was done, which showed a well-defined heterogeneously hypoechoic nodular lesion with few cystic spaces within, showing rich vascularity on Doppler suggestive of left parathyroid adenoma.

However, this USG also incidentally revealed a well-defined hypoechocytic taller than wider nodule in the right thyroid lobe measuring 1.6 × 1.3 cm, which was reported as thyroid imaging reporting and data system–4 (Fig. 1).

A sestamibi parathyroid scan was then done, which confirmed increased uptake in...
A Diagnostic Journey

Acute pancreatitis was caused by hypercalcemia. Hypercalcemia was caused by a parathyroid adenoma. The hypercalcemia also caused renal calculi, for which DJ stenting was required. She also had a papillary carcinoma of the thyroid detected incidentally on evaluation of the parathyroid gland, for which a total thyroidectomy was done. In addition to that, the patient was also incidentally found to have hypertrophic obstructive cardiomyopathy.

When an abnormality is detected on investigation, it is important to search for the cause of this abnormality. Such an approach may reveal difficult to diagnose diseases and may help improve patient morbidity and mortality in the long term.

**Management**

The patient was observed in the general wards for further management initially. Intravenous hydration was continued in view of hypercalcemia. She was also started on a furosemide infusion. However, on the 2nd day of admission, the patient developed drowsiness and was shifted to the intensive care unit (ICU). In the ICU, she was given an injection furosemide and intranasal calcitonin, after which she improved over time. She was also given a single dose of 5 mg of zoledronate.

A referral was given to the oncosurgeon for surgical management.

Surgery was performed on 2nd of July 2022. Excision of the left inferior parathyroid adenoma was done, and the sample was sent for frozen section examination. On table, the right lobe of the thyroid was noted to have a 2 × 1.5 cm hard nodule adherent to the thyroid bed. Right hemithyroidectomy was done, and the sample was sent for the frozen section.

**Discussion and Comments**

This patient came to the hospital with pain in the abdomen and was found to have diabetic ketoacidosis. It was found that diabetic ketoacidosis was caused by acute pancreatitis. Acute pancreatitis was caused by hypercalcemia. Hypercalcemia was caused by a parathyroid adenoma. The hypercalcemia also caused renal calculi, for which DJ stenting was required. She also had a papillary carcinoma of the thyroid detected incidentally on evaluation of the parathyroid gland, for which a total thyroidectomy was done. In addition to that, the patient was also incidentally found to have hypertrophic obstructive cardiomyopathy. When an abnormality is detected on investigation, it is important to search for the cause of this abnormality. Such an approach may reveal difficult to diagnose diseases and may help improve patient morbidity and mortality in the long term.

**References**

A 65-year-old male presented with right-sided chest swelling in the upper parasternal area for 6 months. The swelling was increasing in size gradually. There were no complaints of dyspnea, cough, or hoarseness of voice. On examination, there was a pulsatile lump in the right infraclavicular area (Fig. 1). Cardiovascular system examination was normal. Chest X-ray revealed a widening of the mediastinum. Transthoracic echocardiography was done, followed by transesophageal echocardiography (TEE). It showed evidence of an aneurysm of ascending aorta (Fig. 2). There was a history of untreated syphilis in the patient. A positive Venereal Disease Research Laboratory (VDRL) test and Treponema pallidum hemagglutination (TPHA) assay were found, suggesting that the patient had tertiary syphilis. After penicillin G therapy, the patient underwent successful surgical repair. Pathological findings also confirmed syphilitic aortitis.

Historically, 5–10% of all cardiovascular fatalities were attributable to cardiovascular syphilis; however, today, syphilis is only occasionally discovered at the autopsy table. Latent periods range from 5 to 40 years, with 10–25 years being normal. Syphilitic aortitis, syphilitic aortic aneurysm, syphilitic aortic valvulitis with aortic regurgitation, and syphilitic coronary ostial stenosis are the four subtypes of syphilitic heart disease.

The number of reported instances of human immunodeficiency virus infection has increased recently, according to epidemiologic reports. The identification is challenging due to the rarity of this aetiology, primarily because syphilis testing is not commonly done. When compared to treponema-specific tests in late syphilis like the TPHA, micro hemagglutination test, and fluorescent treponemal antibody absorption test, nontreponemal tests like the VDRL test and rapid plasma reagin test are less accurate (71–73%) vs. (94–96%). Syphilitic serological testing is advised in cases of aortic aneurysm, especially in younger patients. Aortic aneurysms can only be repaired surgically, which entails resection of the dilated segment of the aorta and replacing it with a synthetic vascular graft. Surgery should be performed concurrently if substantial coronary disease or aortic regurgitation is present.

References

Fig 1: Swelling on the right side of the chest

Fig 2: Transesophageal echocardiography (TEE) showing aneurysm of ascending aorta

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A 24-year-old female presented to the Department of Pulmonary Medicine, Government Medical College and Hospital, Chandigarh, India, with shortness of breath, cough with expectoration, and scanty hemoptysis for 12 weeks. There was no previous history of any respiratory disease. Chest radiograph done outside showed a mass-like opacity leading to left lower paratracheal and hilar enlargement (Fig. 1). Contrast enhanced computed tomography (CECT) of the chest revealed a mass-like lesion with minimal heterogeneous enhancement in the left upper lobe abutting the mediastinal pleura adjacent to the arch of the aorta and its branches with surrounding ground glass opacities (Figs 2 to 4). Central and segmental varicose and cystic bronchiectasis changes involving central bronchi, mainly in the upper and middle lobes and superior segment of lower lobes were also seen along with scattered surrounding nodular and ground glass opacities in the involved segment (Figs 3 and 4). The patient was referred to us with a suspicion of malignancy/tuberculosis.

A general physical examination revealed tachypnoea and tachycardia. On respiratory system examination, bilateral rhonchi were present. Hemogram revealed peripheral blood eosinophilia. Mantoux test, sputum for acid fast bacilli, and malignant cytology were negative. Spirometry showed an obstructive ventilatory defect with positive bronchodilator reversibility suggestive of bronchial asthma. Considering the possibility of allergic bronchopulmonary aspergillosis (ABPA), the patient underwent an Aspergillus skin test, which showed immediate cutaneous hyperreactivity. Total immunoglobulin E (IgE), specific IgE, and specific immunoglobulin G levels for Aspergillus fumigatus were raised (9232 IU/mL, 7.91 kUA/L, and 67 mgA/L, respectively). CECT chest findings were reviewed, and it was also noticed that some of the bronchiectasis showed mucus plugging with hyperdense components and peribronchial thickening. The mass-like opacity due to bronchocele/mucoid impaction was strongly considered. Further invasive investigations

**Fig. 1:** Chest radiograph (posteroanterior view) showing left lower paratracheal and hilar enlargement (white arrow)

**Fig. 2:** Contrast enhanced chest tomography showing a mass-like lesion in the left upper lobe abutting the mediastinal pleura (white arrow)

**Fig. 3:** Contrast enhanced chest tomography showing a mass-like lesion in the left upper lobe abutting the mediastinal pleura (white arrow) with surrounding ground glass opacities and cystic bronchiectasis changes in bilateral upper lobes (black arrows)

**Fig. 4:** Contrast enhanced chest tomography coronal section showing mass-like lesion in the left upper lobe (white arrow) and bronchiectasis in the right lung with surrounding ground glass opacities (black arrow)
Dilemma in a Patient with Paratracheal Enlargement: Tuberculosis, Malignancy or Else?

Reaching the diagnosis of bronchial asthma with ABPA asperdiagnostic criteria, the patient was started on inhalational bronchodilators and corticosteroids, oral corticosteroids, and itraconazole.

The patient improved clinically, and only after 6 weeks, there was a complete clearing of the opacity on chest radiography (Fig. 5).

The radiological picture of ABPA sometimes is a diagnostic challenge. ABPA is commonly misdiagnosed as tuberculosis, and patients are even advised antitubercular treatment for the same. However, radiological presentation as a paratracheal/hilar opacity/mass-like lesion mimicking tubercular lymphadenopathy/malignancy is rarely seen. If the clinician is unaware of such a presentation, the patients may be subjected to unnecessary investigations, remaining undiagnosed, and subsequently mistreated for long periods of time, leading to further complications. In young patients, especially with bronchial asthma, ABPA should be kept in the differential diagnosis, and the patient should be investigated thoroughly and accordingly. Rapid resolution of the mass like radiographic opacities, following treatment in itself, confirms the correct diagnosis and signals timely management in the right direction.

**References**

Carl Linnaeus (1707–1778), was a botanist, physician, and zoologist. He was born in Råshult, Sweden. Today he is known as the father of modern taxonomy and is also considered the pioneer of modern ecology. Linnaeus became interested in plants and moved to Uppsala University in the 1730s and became an extremely popular teacher in botany.

In 1732, he traveled 4000 miles through Northern Scandinavia (Lapland) discovering hundreds of new species of plants and carefully observing animals as well; he followed this in England and Europe in 1733. Linnaeus went to the Netherlands and obtained his medical degree from Holland in 1735. While he was in the Netherlands, he published his Systema Naturae (The System of Nature), in 1735.

Linnaeus was appointed professor of medicine and natural history at Uppsala. In 1741 and was allowed to extend his collection and investigations of plants. He continued to collect and classify animals and plants. Linnaeus's lasting service to taxonomy was his binomial system nomenclature (generic name and species name) in 1749, which remains unchallenged to date. He presented a formal classification of the three kingdoms of nature: plants, animals, and minerals. Each kingdom was subdivided into genus, family, order, class, and later phyla.

Linnaeus's classification system grew and grew, and soon his contemporaries were sending specimens for him to name, record, and classify. The initial folio volume was only 11 pages which later extended to 2,500 pages.

Linnaeus had become convinced of the idea that all organisms reproduce sexually. As a result, he expected each plant to possess male and female sexual organs (stamens and pistils). “Sexual system,” as Linnaeus called it, became extremely popular due to its practicality and for its explicit passages of erotic connotations. He also was the first, to use the symbol we use today for male and female.

The Linnaean system helped pave the way toward notions of evolution, an idea he had vehemently rejected as he was rigidly orthodox.

He was ennobled to Carl Von Linnaeus in 1757 and the London-based Linnean Society was founded by Smith in 1798.
Porencephaly may Present even in Elderly

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Sir,

Porencephaly is a rare disorder with a cyst or cavity formation in the cerebral hemispheres of the brain. No reliable data are available to date regarding its prevalence. It is commonly detected in early childhood. It can be detected prenatally by sonography. However, porencephaly may also be detected first time, even in elderly patients, either during the investigation of seizure disorders or may be detected incidentally.

A 60-year-old male was admitted to the emergency medical ward with a focal seizure with secondary generalization. His seizure was controlled with lorazepam and a loading dose of phenytoin (800 mg), and the patient was subsequently maintained on phenytoin with a daily dose of 300 mg/day. He had no history of neurological insults since childhood except one similar attack of seizure 2 years back. He was a manual laborer and had no formal education in school. His physical and mental development was normal. He was nonalcoholic, nondiabetic, and nonhypertensive. Family history did not reveal any neurological disorders. During the examination, the patient was alert, conscious, and cooperative. His speech and visions were normal. No neurodeficits were detected except asymmetric plantar responses. His computerized tomography (CT) scan of the brain revealed cystic encephalomalacia lined with the gliotic white matter in a left parietal region extending from the inner surface of the skull to the left lateral ventricle, and his left lateral ventricle was comparatively dilated (Figs 1A to C). The patient had porencephaly likely of prenatal origin, as he had no major neurological insults since infancy.

Porencephaly is associated with a zone of encephalomalacia with the formation of a cerebrospinal fluid (CSF) filled cavity or cyst, which is lined by gliotic white matter. It can be located in any lobe and communicates with either subarachnoid space or ventricles, or both. Richard L Heschl coined the term ‘porencephaly’ in 1859 (Greek origin: “poros” meaning opening or passage) to describe a full thickness defect in the cerebral hemisphere forming a channel between subarachnoid space and lateral ventricle. Porencephaly develops prenatally during the second half of pregnancy or postnatally. It is either a developmental defect or may be acquired due to brain injury from infarction, hemorrhage, infection, or trauma. Different risk factors associated with porencephaly include thrombophilia like, protein C or protein S deficiency, factor V Leiden mutations, von Willebrand disease, neonatal alloimmune thrombocytopenia, maternal use of warfarin and other drugs like cocaine, congenital infections, the trauma of fetus during amniocentesis, antenatal abdominal trauma of mother, etc. Familial cases of porencephaly are associated with genetic mutations encoding α-1 and α-2 chains of type IV collagen (COL4A1 and 2). COL4A1 mutation can also cause kidney, eyes, and cardiac or skeletal muscle defects, and both COL4A1 and COL4A2 mutations can cause a stroke. So, the affected infants of porencephaly and at-risk family members need neurologic, ophthalmologic, renal, and cardiac screening.

Porencephaly may remain asymptomatic throughout life or may have mild symptoms. Severe cases have hemiplegia, quadriplegia, speech abnormalities, hearing and visual disturbances, seizures disorders, mental retardation, and other neurodeficits. While symptomatic cases are easily detected in early childhood, asymptomatic cases may remain undetected throughout life. Porencephaly may be detected in adults or the elderly with the onset of seizures or may be detected incidentally or during post-mortem examination.

Differential diagnosis of porencephaly includes schizencephaly, hydranencephaly, multicystic encephalopathy, arachnoid cyst, ependymal cyst, focal encephalomalacia, mega cisterna magna (MCM), Dandy-Walker syndrome (DWS), etc. Schizencephaly is a CSF-filled cavity extending from the ventricle to the brain surface and is lined by gray matter (heterotopic), while porencephaly is lined by white matter (gliotic). Schizencephaly is usually unilateral but may be bilateral also. It is either “open-lipped” or “closed-lipped.” In severe cases of bilateral open-lipped schizencephaly, both lateral ventricles communicate widely with extra-axial space. Other malformations which may be associated with schizencephaly include corpus callosum dysgenesis, absent septum pellucidum, septo-optic dysplasia, polymicrogyria, and microcephaly. For porencephaly, brain insult is in the mid or later part of gestation or postnatal, while for schizencephaly, insult is earlier. A relatively mature brain helps to develop glial scarring around the cyst in porencephaly. In hydranencephaly (bubble brain), brain hemispheres are replaced by fluid-filled sacs covered with thin membranes representing leptomeninges. It may be considered porencephaly in its extreme form. Rarely hydranencephaly is seen in Fowler syndrome, also known as proliferative vasculopathy and hydranencephaly—hydrocephaly syndrome,

Figs 1A to C: Computerized tomography (CT) scan brain showing cystic encephalomalacia in the left parietal region extending from the inner surface of the skull to the left lateral ventricle
and is caused by mutations in Feline leukemia virus subgroup C cellular receptor family, member 2. Multicystic encephalopathy is associated with numerous loculated lacy pseudocysts within the white matter and cortex due to an extensive brain insult (e.g., hypoxic ischemic encephalopathy) in the perinatal period. Hydranencephaly, Proliferative vasculopathy and hydranencephaly–hydrocephaly syndrome, and multicystic encephalopathy patients rarely survive beyond infancy.

Encephalomalacia can also occur in adults due to brain infarction, hemorrhage, etc. Focal encephalomalacia may not communicate with a CSF space. An arachnoid cyst is a CSF containing an intra-arachnoid cyst (due to splitting) without ventricular communication. Arachnoid cysts are extra-axial and may have a mass effect. They are commonly supratentorial and usually seen in the middle cranial fossa and Sylvian fissure. Other places of arachnoid cysts include the cerebellopontine angle, cisterna magna, quadrigeminal cisterns, suprasellar regions, cerebral convexities, and spinal cord. Ependymal cysts are usually seen deep in the parenchyma and in intraventricular, periventricular, and subarachnoid spaces, and they are lined by ependymal cells. MCM and DWS are cystic lesions in the posterior cranial fossa. MCM is characterized by intact cerebellar vermis and absence of hydrocephalus, while DWS is associated with dysgenesis or agenesis of the cerebellar vermis, hydrocephalus, and agenesis of the corpus callosum.

Management of porencephaly includes antiepileptics, treatment of underlying disorders, physiotherapy, and rehabilitation therapy. Prognosis is dependent on the size, extent, and anatomical distribution of the lesion, underlying aetiologies, and associated abnormalities. Awareness regarding porencephaly, its presentation, and differential diagnosis will help in better management of the disorder.

References
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ARCV: Angiotensin Receptor Neprilysin Inhibitor. MRA: Mineralocorticoid receptor antagonist. SGLT2i: Sodium-glucose cotransporter 2 inhibitors. ESC: European Society of Cardiology. ACC: American College of Cardiology. HFSA: Heart Failure Society of America. HFrEF: Heart Failure with reduced Ejection Fraction

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