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ICI Journals Master List

ISSN 0971-0876
RNI 50798/1990
University Grants Commission 20737/15554

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Indian JOURNAL *of* CLINICAL PRACTICE

A Multispecialty Journal

Volume 34, Number 9

February 2024, Pages 1-60

Single Copy Rs. 300/-

Peer Reviewed Journal

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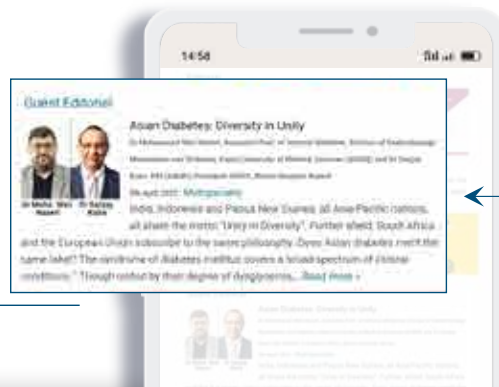
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Published, Printed and Edited by

Dr Veena Aggarwal, on behalf of
IJCP Publications Pvt. Ltd., and
Published at
3rd Floor, 39 Daryacha, Hauz Khas Village,
New Delhi - 110 016
E-mail: editorial@ijcp.com

Printed at

New Edge Communications Pvt. Ltd., New Delhi
E-mail: edgecommunication@gmail.com

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Medicine Update

CDC SOUNDS ALERT FOR MEASLES

The Centers for Disease Control and Prevention (CDC) has cautioned about measles making a comeback in the US following reports of 23 confirmed cases between December 1, 2023 and January 23, 2024. Majority of these cases were among children and adolescents who had not been vaccinated for measles. CDC has advised clinicians across the country to be on the lookout for patients with fever, rash and symptoms that are consistent with measles such as cough, runny nose or conjunctivitis, including those with a recent history of travel to measles affected parts of the world... (Source: CDC. Jan. 25, 2024).

ICMR INVITES SUGGESTIONS FOR REVISED NATIONAL ESSENTIAL DIAGNOSTICS LIST

The Indian Council of Medical Research (ICMR) has invited comments and suggestions in the revised National Essential Diagnostics List (NEDL), which has been placed in public domain till the end of February. The list includes the minimum number of tests that should be available at different levels of health care facilities. The first NEDL was released in 2019 making India the first country to do so.... (Source: PTI. Jan. 17, 2024).

FIRST TREATMENT FOR EOSINOPHILIC ESOPHAGITIS IN YOUNGER CHILDREN GETS FDA NOD

Dupilumab, a monoclonal antibody, has been FDA (Food and Drug Administration) approved for the treatment of eosinophilic esophagitis in children aged

1 to 11 years and weighing ≥ 15 kg. In 2022, dupilumab had been approved for use in older children aged ≥ 12 years and weighing ≥ 40 kg... (Source: Medscape. Jan. 25, 2024).

A WEARABLE BELT DEVICE FOR POSTMENOPAUSAL WOMEN WITH OSTEOPENIA

Osteoboost, a device-based treatment that has been approved by the US FDA for postmenopausal women with osteopenia. It is the first nonpharmacological treatment available only on prescription for this specific group of individuals. Osteoboost is a wearable belt device that is worn on the hips, and it has a vibration pack on the back. This device delivers targeted calibrated mild vibrations to the hips and lumbar spine, which can help preserve bone strength and density... (Source: Medscape. Jan. 25, 2024).

PREDICTING A MORNING MIGRAINE ATTACK

Individuals with poor perceived sleep quality are 22% more likely to experience a headache the next morning. Similarly, lower than usual quality of sleep and lower than usual energy level the previous day were also associated with 18% and 16% increased chances of a headache the next morning, but not in the afternoon or evening. On the other hand, greater average levels of stress and substantially higher energy than usual the day before were associated with a 17% increased chance of headache in the following afternoon or evening... (Source: Neurology. Jan. 24, 2024).

ATOPIC DERMATITIS AND RISK OF INCIDENT ASTHMA

Children with mild atopic dermatitis (AD) are twice more likely to develop incident asthma than children without AD with hazard ratio (HR) of 1.82. The risk increased over threefold among children with moderate and severe AD with HRs of 3.24 and 3.7, respectively. Children with AD and asthma were also at higher risk of asthma exacerbations and asthma-related hospitalizations compared with asthmatic children without AD... (Source: *J Allergy Clin Immunol Pract.* Nov. 14, 2023).

LONG-STANDING MIGRAINE LINKED TO CROHN'S DISEASE

A study from South Korea has linked migraine to elevated risk of inflammatory bowel disease. A steep rise in the risk of inflammatory bowel disease, especially for Crohn's disease was observed after 5 years of follow-up in migraine patients. The risk of ulcerative colitis was more common in men than women... (Source: *Scientific Reports.* Jan. 12, 2024).

CANCER, A NEW RISK FACTOR FOR CARDIOVASCULAR DISEASE

A retrospective study presented at the 2023 American Heart Association (AHA) Congress has suggested cancer as a new risk factor for cardiovascular disease. After adjusting for traditional risk factors such as diabetes, smoking, hypertension, obesity, family history, a history of cancer was found to be significantly predictive of major cardiovascular events with HR of 1.66... (Source: *Medscape.* Jan. 25, 2023).

INCREASED INCIDENCE OF BPH IN GOUT PATIENTS

A Korean study suggests that men with gout are more likely to be diagnosed with benign prostatic hyperplasia (BPH). The incidence of BPH was 23.4% in gout patients versus 20.7% controls. Young adults, below 60 years of age, had higher probability than those older than 60 years. This association was independent of lifestyle factors and comorbid conditions... (Source: *Diagnostics.* Dec. 26, 2023).

CABO VERDE BECOMES THE 3RD AFRICAN COUNTRY TO BE MALARIA-FREE

Cabo Verde, a country in West Africa has been declared malaria-free by the World Health Organization (WHO). It is the third country to be so certified in the WHO Africa region. A total of 43 countries and 1 territory are now free of malaria... (Source: *WHO.* Jan. 12, 2024).

RISK FACTORS FOR YOUNG-ONSET DEMENTIA

A study involving 3,56,052 participants from the UK Biobank, with an average age of 54.6 years, without dementia has identified some risk factors other than the established factors that increase the risk of young-onset dementia. These include: vitamin D deficiency, raised C-reactive protein (CRP) levels and social isolation. Other factors such as orthostatic hypotension, lower socioeconomic status and having two apolipoprotein E ε4 alleles were also associated with greater risk... (Source: *JAMA Neurol.* Dec. 26, 2023).

STUDY LINKS SMOKING TO HAIR LOSS IN MEN

Likelihood of androgenetic alopecia or male-pattern hair loss is increased by 82% of men who smoke compared to never smokers. Those who smoked a minimum of 10 cigarettes a day were 96% more likely to experience hair loss. Disease progression was also 27% higher in ever smokers versus never smokers... (Source: *J Cosmet Dermatol.* Jan. 4, 2024).

DMARDs: A POTENTIAL TREATMENT FOR AUTOIMMUNE THYROID DISEASE?

Adults who have been diagnosed with rheumatoid arthritis may have a decreased risk for developing autoimmune thyroid disease. This risk is even lower for those who are receiving disease-modifying antirheumatic drugs (DMARDs), particularly in those receiving biologic DMARDs... (Source: *J Intern Med.* Nov. 22, 2023).

WHO LISTS NOMA AS A NEGLECTED TROPICAL DISEASE

Cancrumoris or noma, is now listed by the WHO as a neglected tropical disease. It frequently occurs in malnourished children, aged 2 to 6 years, with a background of extreme poverty. Also known as gangrenous stomatitis, this fatal disease begins as an inflammation of the gums, which spreads to involve and destroy the facial tissues and bones, if left untreated... (Source: *WHO.* Dec. 15, 2023).

CARDIAC BENEFITS OF EARLY BREAKFAST

Eating the first meal of the day after 9 am (vs. earlier than 8 am) is associated with an increased risk for cardiovascular disease, especially in women. A similar risk was observed if the last meal of the day was after 9 pm (vs. before 8 pm). Every 1 hour increase in nocturnal fasting was associated with a 7% lower risk for cerebrovascular disease... (Source: *Nat Commun.* Dec. 14, 2023).



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The Ramayana: Lessons for Health

"Humble is my lot, and my ambition high; my only hope is that all good men will be gratified to hear what I say, though the evil minded may laugh."

—Ramcharitmanas, Baalkaand, Doha 8

The Ramayana, our ancient epic, is much more than history. An integral part of the ethos of India, it shares wisdom that is relevant for all of humanity. Various versions of the Ramayana are available^{1,2} and experts have used these to expound upon the lessons that we gain from this epic.^{3,4} In this opinion piece, we view the Ramayana from a health perspective, and share learnings that we have gained.

PHYSICAL WELL-BEING

Physical health is clearly visible in the pages of the Ramayana. Lord Rama and his brothers were put through comprehensive education which included games, exercise and martial arts. Lord Rama and his family were able to traverse long distances in the forest on foot. Athletic prowess of various fighters including Lakshman and Hanuman has been described.

The importance of hygiene and self-care is also highlighted in the text. There are repeated references to appropriate care of one's clothes, skin and hair in the Ramayana, including use of natural cosmetics. The description of Lord Rama, and other characters, as well-proportioned, handsome/beautiful personae, reinforces the importance of physical health.

PSYCHOSOCIAL WELL-BEING

Mental, emotional and social health care has been described in the Ramayana. Lord Rama, when faced

with the stress of exile, handles it with confidence. When challenged by separation from Sita, he goes through various phases of grief, before moving towards optimism, planning and action.

The role of social relationships - family, friends, peers and public - in maintaining health and achieving desired outcomes, is portrayed beautifully.

The need for patience (for example, when the rains prevent Sugriv's army from launching the search for Sita), and perseverance (when his army that headed south faces multiple obstacles, they do not give up) is highlighted. Compassion towards fellow creatures, even during hard times (Kaushalya and Subhadra), as well as spirituality are shown as important aspects of health in the Ramayana.

ENVIRONMENTAL WELL-BEING

Apart from the learning related to the traditional biopsychosocial construct of health, the Ramayana shares wisdom regarding the need for environmental health. Urban planning (Ayodhya, Lanka Nagri), rural architecture (ashramas) and protection of greenery (Dandaka forest) are mentioned. The symbiotic role of plants (berries, lotus), birds (Jatayu, Sampati), and animals (vanara sena, Jambavan) in our life is illustrated with clarity.

HOLISTIC HEALTH

The World Health Organization definition of health focuses not only on physical health, but emotional, mental and social well-being as well. This operational construct of health is clearly evident in the Ramayana.

An analysis of the thoughts and action of its characters uncovers the integration of this definition of health in their daily routine and behavior.

Equal focus on body (physical well-being), mind (mental well-being) and soul (spiritual well-being) is evident in the upbringing of Lord Rama, in the behavior of his friends and family, and in the reactions of the various people he encounters during his travails. Similarly, coexistence with our environment, including flora and fauna is highlighted. The Ramayana reminds us that we have a bidirectional and symbiotic relationship with the plants, forests, animals and birds that co-habit our planet Earth. Resilience, i.e., taking life as it comes, while being prepared to manage unanticipated stresses and strains, is another lesson that we learn.⁵

HEALTHY ATTITUDE

Reading and reciting the Ramayana is just the first step towards enhanced realization. That imbibing and inculcating its wisdom needs a change in our attitude is described at various places in the holy book.

Self-confidence, as exemplified by Lord Rama, Lakshmana and Sita, is necessary for optimization of health. These heroes encountered many obstacles, and faced multiple trials and tribulations, but did not lose sight of their Karma. They maintained their confidence and composure, maintained their relationships and fulfilled their responsibilities.

Self-confidence, if not accompanied by hard work, is not enough. We note all characters of the Ramayana working hard, doing justice to their allotted roles. Whether it is Shabri who keeps her ashrama clean for Lord Rama's impending visit, or Bharata, who keeps the throne warm for his elder brother, these individuals exemplify action for the sake of action without desire for the fruit there of. This is especially true in the geriatric age group, as we see Jatayu, Sampati and Shabri add value to their years by serving the Lord. All these, and others, lived a meaningful, as well as fulfilling life.

CLINICAL VIGNETTES

The Ramayana's detailed description of some personalities serves as a teaching tool for modern students of medicine. Manthara, with her hump back, serves as an example of osteoporosis, while Kaikeyi may have had an acute episode of metabolic or infective encephalopathy.

King Dasharatha probably succumbed to Takotsubo cardiomyopathy or acute myocardial infarction, while

The Ramayana: Lessons for Health

Physical being

- Discipline
- Good nutrition and physical activity
- Hygiene and self-care

Emotional mental and social well-being

- Stress management
- Family and friends
- Compassion and spirituality

Environmental health

- Physical environment: urban and rural
- Flora: plants
- Fauna: birds and animals

Attitude

- Self-confidence
- Patience
- Perseverance

Holistic health

- Body, mind and soul balance
- Harmony with environment
- Take life as it comes

Bharata experienced malnutrition due to psychosocial deprivation.

The episode of Lakshmana regaining consciousness with the help of Sanjeevani booti, prescribed by Vaid Sushena, and procured by Hanuman, needs special mention. Lakshmana may have experienced hypoglycemia, hyponatremia or hypokalemic paralysis, and may have been revived by an ingredient like glucose or electrolytes. Similarly, Hanuman, when bound with the Brahmastra of Indrajeet, may have been anesthetized or sedated with a short-acting drug. The speedy recovery, and the fact that his burning tail did not hurt him, support this hypothesis.

LESSONS FOR US

What teaching does the Ramayana hold for us as health care professionals?

Emphasis on holistic health, while optimizing social and spiritual well-being in our daily life, are important aspects of not just our work, but also, we as society, and the world at large. Our focus should be on prevention of disease, disability and dysfunction. This can be achieved by promotion of health lifestyles, as described in the Ramayana.

We thank Lord Rama, for helping us explore newer facets of health through the Ramayana. This is the beginning of a never-ending journey, and we enjoin all readers to join us in health, happiness and harmony.

Acknowledgments

We thank our family and friends for having encouraged us in learning and understanding the wisdom of the Ramayana.

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Glycemic Status in the Young Type 1 Diabetes Patients

Suboptimal or inadequate glycemic control in young patients, children and adolescents, with type 1 diabetes is quite common and has been linked to an increased risk of future diabetes-related complications and mortality. Hence, it is crucial to maintain optimal blood glucose levels to minimize the potential complications. For this, regular monitoring, adherence to treatment plans and lifestyle modifications are essential.

A new study recently published in the journal *Diabetic Medicine* sought to define distinct HbA1c trajectories in 5,889 children and adolescents, aged 2 to 19 years, with type 1 diabetes; 47% of them were female.¹ Additionally, it examined the associations between these trajectories and clinical and socio-demographic factors. The goal was to understand the prevalence of inadequate glycemic control in this population and its potential impact on diabetes-related complications and mortality later in life.

The data for the study were obtained from the Danish Registry of Childhood and Adolescent Diabetes (DanDiabKids), which includes information on all Danish children and adolescents diagnosed with type 1 diabetes between 1996 and 2019. These children underwent a median of 6 HbA1c measurements per child resulting in a total of 36,504 measurements. To identify subgroups with distinct mean trajectories of HbA1c, data-driven latent class trajectory modeling was used. This approach allowed for the identification of different patterns of HbA1c levels over time in the study population.

The study identified four distinct trajectories of mean HbA1c levels: “Stable but elevated HbA1c” in 3%, “increasing HbA1c” in 5%, “late HbA1c peak” in 7% and “early HbA1c peak” in 5%.

In contrast to the “stable but elevated HbA1c” group, glycemic control was found to decline rapidly in the other three groups during late childhood or adolescence. These groups had higher HbA1c levels at the beginning of the study, fewer patients using insulin pumps, more frequent instances of inadequate blood glucose monitoring, and parents with lower educational status; hypoglycemic events were more severe. These groups also had fewer patients of Danish origin. Additionally, there were significant between-group differences based on the health care region.

This study demonstrates that although the majority of children and adolescents with type 1 diabetes show stable but elevated HbA1c trajectories on average, there are variations in the rate and severity of HbA1c level decline. It is necessary to address the causes and long-term repercussions of these heterogeneous trajectories on health.

Reference

1. Wibaek R, et al. Heterogeneity in glycaemic control in children and adolescents with type 1 diabetes: a latent class trajectory analysis of Danish nationwide data. *Diabet Med*. 2023 Dec 29:e15275.

Role of Cranberry in Urinary Tract Infections

ASHISH K SAXENA*, NEELAM BALA†, RAKA SHEOHARE‡, BIJAY PATNI#

ABSTRACT

Urinary tract infection (UTI), both symptomatic and asymptomatic, occurs very frequently in the population, especially among patients with diabetes. With the advent of newer medications such as sodium-glucose co-transporter 2 (SGLT2) inhibitors, there is greater focus on this disease. Cranberry products have been used earlier in various forms as a natural remedy for this disease. Certain compounds like flavonoids, distinctive proanthocyanidins with prominent active ingredients like phenolic acid inhibit the adherence of fibrillae of *Escherichia coli* to the urothelial cells lining the urinary bladder. This article takes a brief look at the disease and the role of cranberry as a natural remedy for UTI.

Keywords: Urinary tract infection, cranberry, diabetes mellitus, recurrent UTI treatment

Urinary tract infection (UTI) is very commonly seen in our populations, especially in patients with diabetes. With the advent of newer oral hypoglycemic agents (OHAs) like sodium-glucose co-transporter 2 (SGLT2) inhibitors, the incidence and focus on this disease has increased.¹

In fact, 12% of men and 50% of women will experience UTI at some point in their lives. Additionally, up to 30% of young women experience recurrent UTIs, which can have a negative impact on their quality of life.² Recurrent and persistent UTI has been seen in patient population and the role of natural food substances such as cranberry in UTI has been explored.³

Cranberry juice may delay the onset of chronic diseases, lessen their severity and guard against oxidative damage brought on by aging. Cranberry juice is safe for majority of healthy people, but it can interact with several medications.³

THE CRANBERRY FRUIT

Cranberry is scientifically known as *Vaccinium macrocarpon*. The name “cranberry” originates from the word

“cranberry” and refers to the shape of its flower,⁴ which bears a resemblance to head and neck of sand crane. Cranberries belong to the Ericaceae family and typically thrive in wet forests characterized by acidic swamps containing ample peat moss.⁵

Large cranberry, Indian cranberry and American cranberry are all synonyms for cranberry. The following 9 varieties of cranberries are available: Ben Lear, Crimson Queen, Early Black, Franklin, Howes, McFarlin, Pilgrim, Scarlet Knight and Stevens.⁶ Cranberries are harvested for use in products throughout September and October.³

Native Americans did not grow plants, but they did collect berries and use them in their cuisine. They were the first to employ maple sugar to sweeten cranberry juice.⁷

Cranberry contains 10% carbohydrates and about 80% water by weight along with flavonoids, anthocyanins, catechin, triterpenoids, organic acids and just a little quantity of ascorbic acid. Citric, malic and quinic acids make up the majority of organic acids.⁸

There has been a significant focus on flavonoids, particularly colored anthocyanins and distinctive proanthocyanidins with prominent active ingredients include phenolic acids, benzoates, hydroxycinnamic acids, terpenes and organic acids for their role in inhibiting the adherence of *Escherichia coli* to the urothelial cells of the urinary bladder.⁸

BENEFICIAL PROPERTIES OF CRANBERRIES

Cranberries promote good oral health. They are used in the treatment of bladder and renal problems, urethritis and

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help people lose weight. They also help reduce pulmonary inflammation.⁷

Cranberries contain various antioxidants such as anthocyanins, proanthocyanidins and quercetin that may be beneficial for heart health.⁹

They are one of the best food sources for ursolic acid, which has potential anti-cancer, anti-inflammation and antioxidant properties. It has also been seen to be particularly useful in prostate cancer.¹⁰

Cranberry juice helps in managing UTIs. The proanthocyanidins in cranberries have natural bactericidal effects and may inhibit the adherence of *E. coli* to the inner membrane of bladder and urinary system preventing infection.¹¹

Cranberries stop kidney stone production by preventing the build-up of calcium oxalate crystals.¹²

Common cold symptoms can be managed using cranberries and honey.¹³ Because of its antioxidant and anti-aging characteristics, applying cranberries as a face pack also aids in protecting the skin against the damaging effects of free radicals.¹⁴

THE URINARY BLADDER

Although the shape and size of the urinary bladder varies from person to person and is significantly influenced by the amount of urine that it holds, it has a broadly spherical shape.¹⁵ The urinary bladder is situated in the pelvic cavity above the pelvic reproductive organs and in front of rectum.¹⁶ It shares the small pelvic cavity with the uterus, which sits above and behind it, because the urinary bladder is somewhat smaller in females. The enlargement of the urinary bladder is severely limited by the enlarged uterus during pregnancy.¹⁷

There are various different tissue layers that make up the urinary bladder.¹⁸ The mucosa layer that lines the hollow lumen of the bladder is its deepest layer. The mucosa of other hollow organs is not as flexible as the transitional epithelial tissue that lines the urinary bladder, which can hold a lot of urine.¹⁹

UTI

Any region of urinary system can become infected, which is known as UTI. The bladder and urethra, which are parts of lower urinary tract, are most commonly infected.²⁰

Women are more likely than men to experience a UTI.²¹ A bladder specific infection may be uncomfortable and unpleasant. However, if a UTI spreads to the kidneys,

major health issues like pyelonephritis and pyoma may occur.²²

For young boys, older men and women of all ages, UTIs are a significant cause of morbidity. In addition to frequent recurrences, other serious repercussions include pyelonephritis with sepsis, renal injury in young infants, preterm birth and difficulties brought on by constant antimicrobial usage, such as high-level antibiotic resistance and *Clostridium difficile* colitis.²³

Common Pathogens Causing UTI

Both Gram-positive and Gram-negative bacteria, as well as some fungi, can cause UTIs, which are among the most prevalent bacterial infections.²⁴

E. coli, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus faecalis* and *Staphylococcus saprophyticus* are the micro-organisms most frequently responsible for UTI.²⁵ Uropathogenic *E. coli* is the most common causative agent for both simple and complex UTIs.²⁶

Symptoms of UTI

The symptoms associated with a lower UTI include increased frequency of urination without passing a significant amount of urine, a burning sensation during urination, cloudy urine, a change in the color of urine, a strong odor and pain while urination.²⁷

The symptoms indicative of an upper UTI include pain and tenderness in upper back area, accompanied by chills, headache, intermitted fever, feelings of nausea, vomiting and presence of blood in urine.⁸

Pathogenesis of UTI

Uropathogens that live in the gut contaminate the periurethral region and are able to colonize the urethra to cause uncomplicated UTI. The superficial umbrella cells are colonized and invaded as a result of their subsequent passage to the bladder and the expression of pili and adhesins.²⁵ Extracellular bacteria are removed by host inflammatory responses, including neutrophil infiltration. Some bacteria multiply and develop biofilms in order to avoid the immune system, either by attacking host cells or through structural modifications that make them resistant to neutrophils.²⁸

The toxins and proteases secreted by these bacteria cause host cell destruction, releasing vital nutrients that aid in bacterial survival and colonization of the kidneys. This causes host tissue damage and the generation of bacterial toxins. UTIs can eventually result in serious health problems if they are not treated.²⁹

These initial steps of periurethral colonization, advancement to the urethra and migration to the bladder also occur in complex UTIs. The bladder must be weakened for the viruses to invade the body though. Catheterization is the most prevalent reason for a weakened bladder. Because catheterization triggers a strong immune response, fibrinogen builds up on the catheter creating perfect habitat for uropathogens that express fibrinogen-binding proteins to attach.³⁰

Urinary pH

The pH of urine falls within the range of 6.0 to 7.5, while values between 4.5 and 8.0 are typically not reason for anxiety; 1 being the most acidic and 14 being the most basic on the pH scale.

The urea-splitting bacteria *Proteus*, *Klebsiella* or *Ureaplasma urealyticum* are frequently found in urine with pH of 8.5 or 9. An alkaline urine pH can indicate struvite kidney stones or infection stones.³¹

The nitrate test is considered the most reliable method for detecting the presence of bacteria in urine, as bacteria need time to convert nitrates to nitrites, which takes approximately 6 hours. This is why urologists often request testing of the first urine sample in the morning, especially in males. The nitrate test has a specificity of over 90% meaning it is highly accurate in identifying the presence of bacteria. However, it is worth nothing that certain type of bacteria, such as *Enterococcus*, *Pseudomonas* and *Acinetobacter*, do not convert nitrates despite being implicated in complicated UTIs.³²

Duration and Time of Action of Bacteria in UTIs

UTI can be influenced by multiple factors, including diabetes, the use of drugs like SGLT2 inhibitors, anatomical considerations such as short ureters, infrequent voiding of urine and a history of recurrent UTIs. Additionally, factors such as particular bacteria causing the infection, the individual's immune response and the efficacy of treatment play significant roles in UTI development and management.³⁰

Typically, bacteria enter the urinary tract through the urethra and begin to multiply, leading to infection. The time of infection refers to the period during which bacteria actively replicate and cause symptoms. This period can range from a few hours to a few days, depending on bacterial load and the susceptibility of the individual.

If left untreated, a UTI can persist and potentially spread to the upper urinary tract, such as the kidneys, leading to a more severe infection. In some cases, the

bacteria can form biofilms or hide within the urinary tract, making eradication more challenging.³³

Once appropriate treatment, such as antibiotics, is initiated, the duration of the infection can vary. In many cases, symptoms may start to improve within a few days of treatment. However, it is crucial to complete the full course of antibiotics as prescribed by a health care professional to ensure complete eradication of the bacteria and prevent recurrence. It is important to note that the duration of a UTI can vary from person to person and seeking medical advice is essential for proper diagnosis, treatment and monitoring of the infection.³⁴

MECHANISMS OF ACTION OF CRANBERRY

Inhibition of Bacterial Adhesion

Proanthocyanidins have anti-adhesive properties and might help in reducing the probability of bacteria, particularly *E. coli*, attaching to the walls of the urinary tract. They make it more difficult for the bacteria to create an infection by interfering with their ability to bind to the lining of the urinary system.³⁵

Acidification of Urine

Consuming cranberry products may cause urine to become more acidic as cranberries are acidic in nature. By creating a less favorable environment for the bacteria to grow, the increased pH may be able to reduce the risk of infection.³⁶

Anti-inflammatory Effects

Cranberries contain a number of phytochemicals, including flavonoid and anthocyanins, which have anti-inflammatory properties. These phytochemicals help in lowering urinary tract inflammation, which could assist in preventing UTI symptoms.³⁷

Immunological Effects

The high content of antioxidant phenolic compounds in cranberries assists in the natural antioxidant defense system of an individual by preventing formation of reactive oxygen specific. They also stimulate immune cells and promote the production of cytokines by modulating the immune system; cranberry may support the body to fight off UTI more effectively causing bacteria.³⁸

SIDE EFFECTS

The potential side effects of consuming high amounts of cranberry juice or supplements, particularly in people prone to these illnesses, include gastrointestinal irritation and increased chances of kidney stones.³⁹

DYSURIA AND HEMATURIA

Dysuria and hematuria are two common symptoms of UTIs.

Dysuria: Urination that is difficult and uncomfortable is called dysuria. Typically, the patient presents with lower UTI symptoms like cystitis. Infection can produce inflammation and irritation, which can make urinating feel hot or stinging. Also, an insatiable desire to urinate may be indicative of dysuria.⁴⁰

Hematuria: Blood in urine is termed hematuria, which typically occurs due to UTI and inflammation. The infection can irritate the blood vessels in the urinary system, leading to leakage of blood. The severity of hematuria can vary, ranging from tiny amounts of blood visible only through a microscopic to noticeable amounts that cause the urine to appear pink, red or brown in color.⁴¹

When these symptoms occur together, especially when accompanied by other UTI-related symptoms like frequent urination, urgency, cloudy urine and lower abdominal pain, strongly indicate the presence of a UTI.⁴²

POST-COITAL DYSURIA

Post-coital dysuria refers to the condition where an individual experiences pain or discomfort during or after sexual intercourse, specifically in the urinary tract. It is often characterized by symptoms such as burning or stinging sensation while urinating, increased frequency of urination and general discomfort in the pelvic region following sexual activity.⁴³

Post-coital dysuria can have other potential causes such as:

- Irritation or injury to the urethra during vigorous or rough sexual activity, resulting in pain or discomfort during urination.
- Allergic reactions to certain lubricants, latex condoms or other materials used during sexual activity, leading to ureteral irritation or inflammation and subsequent dysuria.
- Vaginal infections like yeast infections or bacterial vaginosis, which can cause inflammation and irritation in genital area resulting in dysuria after intercourse.⁴⁴

DIABETES AND UTI

Individuals with diabetes have a higher risk of developing UTIs compared to those without diabetes. Various factors contributing to this increased risk

include immune system dysfunction, elevated blood sugar levels and urinary tract abnormalities. Patients with diabetes may experience more frequent, persistent and severe UTIs. Proper blood sugar control, good personal hygiene and prompt medical attention are essential for managing UTI risk in diabetes.⁴⁵

Frequency of UTI in Diabetes

Frequency of UTIs in individuals with diabetes can vary depending on various factors such as age, sex, duration of diabetes and glycemic control. A prospective study investigated the prevalence of asymptomatic bacteriuria in women with diabetes and the likelihood for asymptomatic bacteriuria in women with diabetes was increased by 1.9-fold.⁴⁶

ASYMPTOMATIC AND SYMPTOMATIC UTIs

UTIs can be classified into two main categories:

- Symptomatic UTIs
- Asymptomatic UTIs

Symptomatic UTIs: Symptomatic UTIs present with symptoms such as constant and pressing urge to urinate, dysuria, a painful or uncomfortable micturition, sensation of incomplete emptying of bladder, pelvic or lower abdominal pain, urine that is cloudy, red or has a strong odor, burning sensation in the urinary tract, tiredness, fever or chills.⁴⁷

Asymptomatic UTIs: Asymptomatic UTI is a condition in which bacteria are present in the urinary tract without causing noticeable symptoms. In such cases, individuals may be unaware that they have an infection unless it is detected through a urine test. Asymptomatic UTIs is more commonly found in certain populations, such as the elderly, individuals with indwelling urinary catheters, or those with compromised immune system.⁴⁸ It is important to remember that, despite the absence of overt symptoms, asymptomatic UTIs can still be dangerous if left untreated. The presence of bacteria in the urinary tract increases the risk of problems, such as kidney damage or infection spreading to the kidneys.⁴⁹

CRANBERRY AND UTI

Cranberry products such as cranberry juices or supplements, have been used in the treatment of urinary infections. It is important to note that cranberry products should not be considered a substitute for appropriate medical treatment for UTIs. It is crucial to seek medical attention and follow the prescribed treatment, which usually involves antibiotics.⁵⁰

CONCLUSION

Cranberry products are helpful in patients with symptomatic and asymptomatic UTIs by the action of various phenolic compounds present in this fruit. This is an insight into the occurrence of the disease and mechanisms of action of cranberry. More studies and observations are required to unlock the potential of this fruit and establish its appropriate use in patients suffering from this disease. Further assessment with well-designed randomized controlled clinical trials can further classify the use and benefit of cranberry products in UTIs.

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Post-Traumatic Renal Artery Pseudoaneurysm Managed Successfully with Angioembolization

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ABSTRACT

Introduction: Renal artery pseudoaneurysm is a rare complication of blunt renal trauma. Super-selective angioembolization is a minimally invasive, effective procedure to manage traumatic renal artery pseudoaneurysm, in patients who are hemodynamically stable. We report our experience in the management of patients with post-traumatic bleeding pseudoaneurysm with angioembolization. **Materials and methods:** We retrospectively reviewed the inpatient and outpatient records and imaging data of our hospital, of all patients with history of blunt injury to kidneys, admitted with massive hematuria and underwent angioembolization to control the bleeding. **Results:** During the study period, 3 patients (all male) with a mean age of 26.66 years presented to us with blunt injury abdomen. Contrast computed tomography (CT) revealed Grade IV renal injury in 2 patients and Grade V injury in 1 patient. Focal intensively enhancing areas were noted at the site of renal parenchymal lacerations suggestive of pseudoaneurysms. Super-selective catheterization was performed and embolization done using 50% N-butyl-2-cyanoacrylate (NBCA) + Lipiodol. **Conclusions:** Angioembolization, a radiographic intervention, is an effective and minimally invasive technique to stop active bleeding from renal artery pseudoaneurysms.

Keywords: Delayed hematuria, blunt renal trauma, minimally invasive technique

Over the last few decades, there has been a clear transition towards a nonoperative approach in the management of renal trauma.¹⁻³ A combination of several factors has probably led to this transition namely i) the accumulated knowledge about the safety and outcome of the nonoperative approach in renal trauma; ii) improvement in imaging modalities such as computed tomography (CT)⁴ and iii) advances in minimally invasive treatment techniques such as angioembolization in cases of active bleeding,^{5,6} and endourological stenting in cases of urine extravasation.^{7,8}

As per the current guidelines (American Urological Association [AUA]⁹ and European Association of

Urology [EAU]¹⁰), the absolute indications for renal intervention include hemodynamic instability unresponsive to aggressive resuscitation secondary to renal hemorrhage, Grade V vascular injuries and an expanding or pulsatile perirenal hematoma identified at the time of laparotomy performed for associated injuries. Relative indications for renal intervention include¹¹ a large laceration of the renal pelvis, avulsion of the ureteropelvic junction (UPJ), co-existing bowel or pancreatic injuries, persistent urinary leakage and post-injury urinoma or perinephric abscess with failed percutaneous or endoscopic management. Nonoperative management includes observation with supportive care, bed rest with monitoring of vital signs and laboratory tests and reimaging (whenever felt necessary or in cases of deterioration), with the appropriate use of minimally invasive procedures (angioembolization or ureteral stenting) whenever indicated.

Complications following renal trauma usually depend on the grade of the initial renal injury and the method of management.¹² The resulting complications are usually of minimal long-term morbidity, that can be successfully managed using end urologic and percutaneous techniques, and do not significantly prolong the mean days of hospitalization.^{13,14} Early complications are those that occur within 1 month of injury, and include urinoma, delayed bleeding, urinary fistula, abscess and

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hypertension. Prolonged urinary extravasation is the most common complication after renal trauma.^{13,15} Delayed renal bleeding most commonly occurs within 2 weeks of injury. When bleeding is heavy or symptomatic, transfusions, angiography and super-selective embolization may be required.¹⁶ Herein, we report our experience in the management of patients with post-traumatic bleeding pseudoaneurysm with angioembolization.

MATERIALS AND METHODS

We retrospectively reviewed the inpatient and outpatient records including imaging data of our hospital, of all patients with history of blunt injury to kidneys who were admitted with massive hematuria and underwent angioembolization to control bleeding.

Ethical Considerations: The protocol of the study was approved by Ethics Committee of the Institute. The design and objectives of the study were explained and a written permission obtained from the Ethical Committee.

RESULTS

During the study period, from July 2015 to June 2021, 3 patients (all male) with a mean age of 26.66 years presented to us with blunt injury abdomen. Fall from a two-wheeler, collapse of wall and being hit by a four-wheeler were the causes of trauma. All 3 had received primary care at a local hospital and were managed conservatively. They were referred to our hospital for delayed bleeding (hematuria) at a mean duration of 23 days after trauma. All the 3 patients appeared pale and had low hemoglobin values as seen in Table 1.

Contrast CT (Fig. 1) done revealed Grade IV renal injury in 2 patients and Grade V injury in 1 patient.

Focal intensely enhancing areas were noted at the site of renal parenchymal lacerations suggestive of pseudoaneurysms. Perirenal collection was also noted.

Table 1. Details of Patient Demographics

Age (years)	Gender	Renal injury	Other abdominal injuries	Delayed bleeding	Hb (gm%)
18	M	Right Grade IV	Liver	21 days	7
33	M	Left Grade V	Mesentery	30 days	6.2
29	M	Left Grade IV	Spleen	18 days	8
26.66 (mean)				23 (mean)	

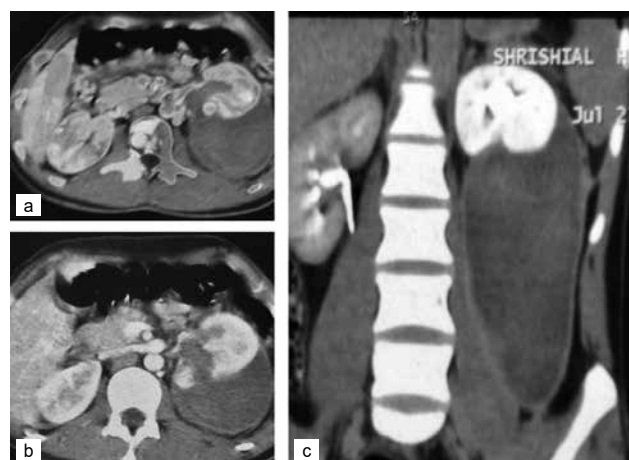


Figure 1. (a) CT scan showing a huge perirenal collection. (b) scan showing lower polar laceration communicating with renal pelvis. (c) CT scan showing a huge perirenal collection trickling down the fascia of Gerota.

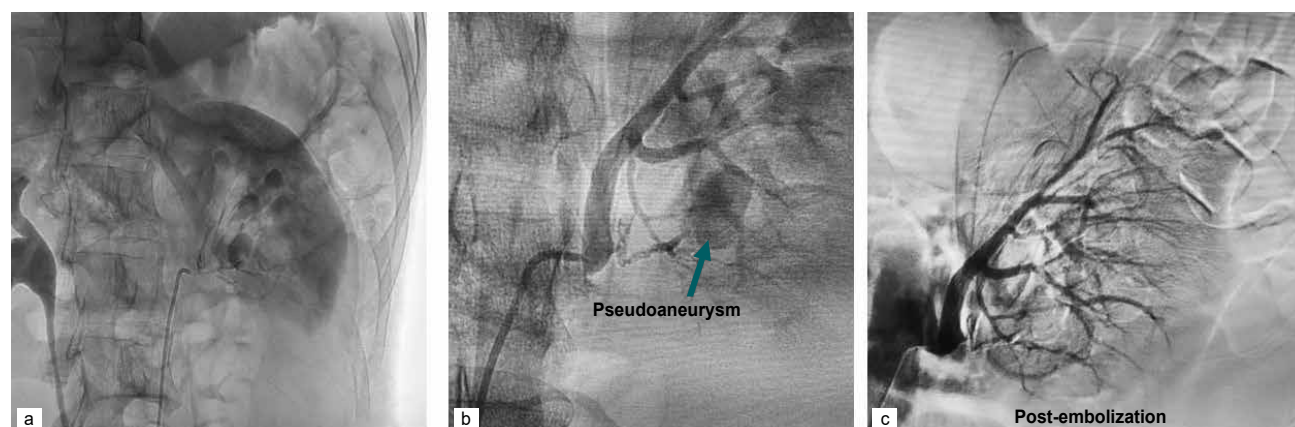


Figure 2. (a and b) Diagnostic renal angiogram showing a pseudoaneurysm involving the lower pole. (c) Post-embolization renal angiogram.

CLINICAL STUDY

In view of the persistent bleeding and presence of pseudoaneurysms, the patients were counseled for complete endovascular embolization.

The embolization procedure was performed under local anesthesia. Retrograde Seldinger technique was utilized through the opposite femoral arterial access. A diagnostic renal angiogram was performed using a Cobra catheter. Once the pseudoaneurysm was confirmed, the 5 Fr Cobra catheter and Progreat catheter were used to perform super-selective catheterization and embolization using 50% N-butyl-2-cyanoacrylate (NBCA) + Lipiodol (Fig. 2). Check angiogram of the renal artery showed complete embolization of the pseudoaneurysm with normal opacification of the rest of the renal arterial branches.

The post-embolization period was uneventful. Patients were discharged after 72 hours and were followed up for at least 12 months after embolization.

DISCUSSION

Blunt trauma remains the most common cause of renal injuries (90%) and only 10% to 15% of these can be classified as major injuries.¹⁷ Renovascular injuries, such as transection, thrombosis, dissection and arteriovenous fistula formation are well-recognized but rare consequences of blunt renal trauma.^{18,19} Renal artery pseudoaneurysms usually result after iatrogenic renal procedures, although they can also occur as a rare complication of blunt renal trauma.^{19,20} Renal artery pseudoaneurysm is believed to result from rapid deceleration-induced, full- or partial-thickness injury to arteries supplying the renal parenchyma.^{18,20,21} Following complete or partial injury of an artery, blood seeps through the surrounding tissues namely vascular adventitia, renal parenchyma and Gerota's fascia.

Temporary cessation of bleeding occurs immediately after the injury due to hypotension and local coagulation. As the clot undergoes lysis and the surrounding necrotic tissue degrades, it results in recanalization between the intravascular and extravascular spaces and, subsequently, the formation of a pseudoaneurysm. Restoration of normal blood flow and pressure, leads to the growth of the pseudoaneurysm, which eventually ruptures into the pyelocalyceal system or the perirenal space.^{18,20,22} Gross hematuria from blunt parenchymal injury, typically resolves within several hours and can be effectively managed with bed rest and transfusion support, until the urine clears and vital signs are stable. However, persistent bleeding or delayed gross hematuria should raise the suspicion of segmental

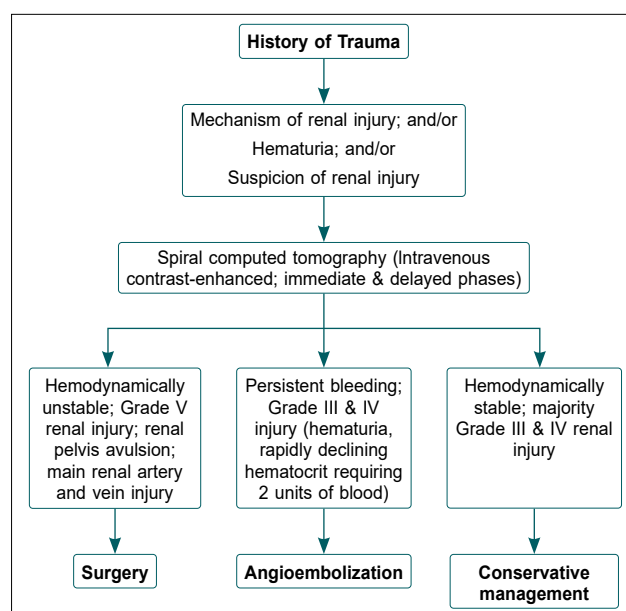


Figure 3. Flowchart showing management of renal trauma.

vascular injury, including pseudoaneurysm formation and prompt further investigation and management.¹⁹⁻²¹

In broad terms, it is preferable to use noninvasive techniques or strategies such as angioembolization for cases of persistent bleeding in hemodynamically stable patients. Breyer et al²³ suggested a treatment algorithm, which complements the current AUA guidelines for management of renal trauma.⁹ A contrast-enhanced CT imaging with delayed and immediate phases is the first step that would provide the grade of renal trauma as well as help into visualize the renal arteries, veins and parenchyma. Primary angioembolization interventions are ideally suited for patients with persistent bleeding, and an intact main renal artery and vein. All patients managed conservatively for renal trauma should be monitored and observed for a change in hemodynamic status, as delayed hemorrhage is known to occur from a pseudoaneurysm.^{20,22} Figure 3 depicts an algorithm for the management of renal trauma. A prospective study found that 18% of those treated with nonoperative intent ultimately needed surgical intervention.²⁴ In these cases of delayed hemorrhage, angioembolization is a good first-line choice of treatment.

CONCLUSION

Renal artery pseudoaneurysm formation following a blunt abdominal trauma is rare. However, whenever there is delayed gross hematuria, the possibility of pseudoaneurysm should be considered, and managed by angioembolization.

Conflict of Interest: None.

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Spectrum of Opportunistic Infections in People Living with HIV: A Tertiary Care Center Experience from North India

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ABSTRACT

Introduction: Patients with human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS) are prone to opportunistic infections (OIs) given their immunosuppressed state. OIs continue to cause morbidity and mortality in HIV/AIDS patients even after highly-active antiretroviral therapy (HAART); hence, attainment of the goals on health care programs, particularly in resource-poor countries, is hard to achieve. The prevalence of specific OIs varies in different countries and even in different areas within the same country. Little information is available about the prevalence of OI in HIV patients from developing countries, especially India. Early diagnosis and prompt treatment contribute to increased life expectancy among infected patients delaying progression to AIDS. Hence, the present study was carried out to elucidate current frequencies and spectrum of OIs in HIV seropositive adult patients in Haryana and to evaluate the associated risk factors for OIs. **Materials and methods:** This was a cross-sectional study carried out at the Dept. of General Medicine in a tertiary care hospital in North India. Basic demographic details, anthropometric measurements, symptoms of HIV/OI, clinical examination, biochemical investigations and treatment details were recorded. Patients aged 18 to 70 years and HIV seropositive subjects were included in the study. **Results:** The study found that about 53.21% of HIV/AIDS patients on ART had one or more OIs. Tuberculosis (TB) was the predominant OI identified, with a prevalence of 25.71%. Candidiasis and herpes zoster were the second and the third most prevalent OIs at 13.8% (101/731) and 7.25% (53/731), respectively. Age (43.4 ± 10.7 years), low income, illiteracy, low socioeconomic status, initial 4 months since initiation of ART, CD4 count $<200/\text{mm}^3$, body mass index of $<18.5 \text{ kg/m}^2$, poor ART adherence, hemoglobin, albumin were strongly associated with OIs. **Conclusion:** The present study shows that TB is the commonest OI in adults and the overall population of people living with HIV (PLHIV) in Haryana and proves that OIs across different patient groups vary significantly. Various factors like adherence to HAART, socioeconomic and education status of patients can influence the occurrence and outcome of these deadly infections.

Keywords: Spectrum, opportunistic infections, PLHIV

Human immunodeficiency virus (HIV) infection is one of most studied infectious diseases since it was first recognized clinically in 1981 in the United States of America. HIV-related opportunistic infections (OIs) have been defined as infections that

are more frequent or more severe because of HIV-mediated immunosuppression.¹ OIs are the first clinical manifestations that alert clinicians to the occurrence of the acquired immunodeficiency syndrome (AIDS). These OIs occurs on average 7 to 10 years after infection with HIV.^{2,3} Until effective antiretroviral therapy (ART) was developed, patients generally survived for only 1 to 2 years after the initial manifestation of AIDS.⁴ However, OIs continue to cause morbidity and mortality in HIV/AIDS patients even after highly-active antiretroviral therapy (HAART); hence, the attainment of the goals on health care programs, particularly in resource-poor countries, is hard to achieve. OIs shorten the life span of people with HIV infection and require expensive treatments, which carry a substantial financial burden, especially for a developing country like India. Timely intervention helps HIV-positive persons live longer and also helps to prevent transmission in the community.⁵

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Estimating the cost of necessary health care as accurately as possible must be the first step in planning specialized health services, which is only possible if we know how the OIs are distributed in a given place. Also, there is no denying that HIV-related OIs affect a person's quality of life and contributes to the overall disability-adjusted life years (DALY) caused by AIDS. The prevalence of specific OIs varies in different countries and even in other areas within the same country. Identifying such OIs is especially important for HIV and AIDS case management. Little information is available about the prevalence of OI in HIV patients from developing countries, especially India. Early diagnosis of OIs and prompt treatment contribute to increased life expectancy among infected patients delaying progression to AIDS. Hence, this study was carried out to elucidate current prevalence and spectrum of OIs infecting HIV-seropositive adult patients in Haryana, a northern state in India, and to evaluate the associated risk factors of OIs. Identifying such pathogens is very important for clinicians and health planners to tackle the AIDS epidemic more effectively.

MATERIALS AND METHODS

This was a cross-sectional study carried out at a tertiary care center in North India. Adult patients between 18 to 70 years attending the Nodal ART Centre, admitted under Dept. of Medicine PGIMS, Rohtak, Haryana, and admitted under clinics were enrolled in this study. Patients who did not consent to participate in the study, those with psychiatric illness taking regular medications, pregnant and lactating mothers, those with non-HIV/AIDS-related malignancy, known cases of chronic kidney and liver disease prior to diagnosis of HIV and patients with an altered sensorium or cognitive impairment severely affecting communication were excluded from the study. Our Nodal ART Centre has all the adequate facilities and investigations for detecting the OI before commencing ART.

Detailed information of all enrolled patients was filled in a proforma designed for the study purpose. This included basic demographic details, anthropometric measurements, symptoms of HIV/OI, clinical examination and treatment. At baseline, each patient underwent hematological and biochemical investigations. Patients were assessed for OI risk factors. These included age, weight at last visit, serum albumin at diagnosis of OI, World Health Organization (WHO) clinical stage III and IV, CD4 count at the time of diagnosis of OI, initiation of ART since diagnosis of HIV and adherence to ART. The Center for Adherence Support Evaluation (CASE)

Adherence Index, a simple composite measure of self-reported ART adherence, was utilized to assess adherence to ART.⁶ Informed consent was taken from all participants and study was approved from ethical committee of the institute and Haryana state division of National AIDS Control Society.

The diagnosis of OI was made following standard guidelines where possible and facilities available. Where diagnosis was based on clinical grounds alone, the opinion of two independent physicians involved in enrolled patient care and management was required before such diagnosis was accepted.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) Version 23 was used for all descriptive and statistical analysis. Association of OIs was done by subgroup analysis of WHO staging, CD4 count, demographic and biochemical/hematological profile and treatment adherence. The distribution of data was analyzed and appropriate parametric/nonparametric tests were used for statistical analysis. Continuous data were expressed as means $\pm$ standard deviation (SD), and the means were compared using a *t*-test. Nominal data were expressed as frequencies or proportions, and the Chi-square test and Fisher's exact test were used to compare the differences in frequency. For all tests, a *p*-value of <0.05 will be considered significant, and the confidence interval will be kept at 95%.

RESULTS AND OBSERVATIONS

The study was conducted in the Dept. of General Medicine, PGIMS, Rohtak, Haryana, India. A total of 731 patients aged 18 to 70 years and HIV seropositive subjects were included in the study. The baseline characteristic of the study participants is presented in Table 1.

The study found that about 53.21% of HIV/AIDS patients had one or more OIs compared to 46.79% who had no OI. Tuberculosis (TB) (48.32% of total OIs) was the predominant OI identified, with a prevalence of 25.71% (200/731). Of these, 71.80% ($n = 135/188$) were pulmonary TB and 31.3% were extrapulmonary TB ($n = 59/188$). Among the extrapulmonary TB cases, 35 were abdominal TB and 24 were TB meningitis. Candidiasis and herpes zoster were the second and the third most prevalent OIs in the present study, at 13.8% (101/731) and 7.25% (53/731), respectively (Table 2).

There were 63 co-infections of different OIs observed in the current study. Of these, 55 had 2 co-infections,

Table 1. Distribution of Demographic Characteristics of Study Subjects

Demographic characteristics	Frequency	Percentage (%)
Gender		
Female	284	38.85
Male	438	59.92
Transgender	9	1.23
Area of residence		
Rural	534	73.05
Urban	197	26.95
Religion		
Christian	3	0.41
Hindu	717	98.08
Muslim	10	1.37
Sikh	1	0.14
Income		
<2,000	135	18.47
2,000-5,000	232	31.74
5,001-20,000	298	40.77
>20,000	66	9.03
Socioeconomic status		
Lower	51	6.98
Upper lower	113	15.46
Lower middle	377	51.57
Upper middle	120	16.42
Upper	70	9.58
Education		
Illiterate	172	23.53
Primary school	271	37.07
Secondary school	208	28.45
College and Above	80	10.94
Marital status		
Married	655	89.60
Unmarried	23	3.15
Widow/Widower	53	7.25
Spouse		
Expired	52	9.65
Nonreactive	289	53.62
Reactive	198	36.73
Age (years)		
Mean $\pm$ SD	40.02 $\pm$ 11.17	
Median (25th-75th percentile)	38 (32-48)	
Range	19-70	

Table 2. Distribution of Opportunistic Infections of Study Subjects

Opportunistic infections	Frequency	Percentage (%)	Percentage (%) from total OI
No OI	342	46.79	-
Skin	73	9.99	18.77
Herpes zoster	53	7.25	13.62
Kaposi sarcoma	20	2.74	5.14
CNS	56	7.66	14.40
TBM	24	3.28	6.17
Primary CNS lymphoma	3	0.41	0.77
PMLE	2	0.27	0.51
Cryptococcal meningitis	15	2.05	3.86
Cerebral toxoplasmosis	12	1.64	3.08
GIT	166	22.71	42.67
Abdominal TB	35	4.79	9.00
Chronic mucocutaneous candidiasis	100	13.68	25.71
Candidal esophagitis	1	0.14	0.26
HSV oral ulcers	16	2.19	4.11
Chronic diarrhea	20	2.74	5.14
Cryptosporidiosis	14	1.92	3.60
Giardiasis	1	0.14	0.26
Isosporiasis	2	0.27	0.51
Schistosomiasis	3	0.41	0.77
Respiratory	161	22.02	41.39
Pulmonary TB	135	18.47	34.70
Other bacterial	12	1.64	3.08
<i>Klebsiella pneumoniae</i>	3	0.41	0.77
<i>Pseudomonas aeruginosa</i> pneumonia	1	0.14	0.26
<i>Streptococcus pneumoniae</i>	8	1.09	2.06
Fungal	8	1.09	2.06
<i>Aspergillus fumigatus</i> pneumonia	1	0.14	0.26
<i>Histoplasma capsulatum</i> pneumonia	1	0.14	0.26
<i>Cryptococcus neoformans</i> pneumonia	1	0.14	0.26
<i>Pneumocystis jirovecii</i> pneumonia	5	0.68	1.29

Table 2. Distribution of Opportunistic Infections of Study Subjects

Opportunistic infections	Frequency	Percentage (%)	Percentage (%) from total OI
Hematology	10	1.37	2.57
Diffuse large B-cell lymphoma	10	1.37	2.57
Eye	1	0.14	0.26
CMV retinitis	1	0.14	0.26
Total pulmonary and extrapulmonary	188	25.71	48.32

OI = Opportunistic infection; TB = Tuberculosis; CNS = Central nervous system; TBM = Tuberculosis meningitis; PMLE = Polymorphous light eruption; GIT = Gastrointestinal tract; HSV = Herpes simplex virus; CMV = Cytomegalovirus.

7 had 3 co-infections and 1 patient had 4 co-infections. TB with candidiasis were the most common co-infection (32 cases) followed by TB with cryptosporidiosis (4 cases).

The mean $\pm$ SD of age (years) in patients with OI was 43.4 ± 10.7 , which was significantly higher than patients without OI (36.18 ± 10.43). The proportion of patients with OI was significantly higher in patients with income (in Rupees) (<2,000 [68.15.52%] and 2,000-5,000 [60.34%]) as compared to 5,000-20,000 (45.97%) and >20,000 (30.30%). OIs were significantly higher in illiterate people (66.86%) as compared to those with primary school education (52.40%), secondary school education (54.33%) and college and higher education (23.75%) with a p-value of <0.0001. It was found that 90.20% of patients in the lower Kuppaswamy class had OIs as compared to upper-lower (57.52%), lower-middle (52.25%), upper-middle (41.67%) and upper class (44.29%) with a p-value <0.0001. OIs were significantly higher in patients with body mass index (BMI) (kg/m^2) of <18.5 (underweight; 83.94%) as compared to 18.5-24.99 (normal BMI; 44.23%), 25-29.99 (overweight; 3.85%), ≥ 30 (obese; 0%) with p value of <0.0001. Significant association was seen between weight (kg) and OIs. Mean $\pm$ SD of weight (kg) in patients without OI was 58.7 ± 9.17 , which was significantly higher as compared to patients with OI (52.72 ± 7.21) with p value of <0.0001.

The proportion of patients with OI was significantly higher in time since ART initiation (months) ≤ 12 months (71.84%) as compared to 13 to 24 months (30.19%), 25 to 36 months (26.67%), 37 to 48 months (57.64%), 49 to 60 months (53.33%), 61 to 72 months (55.56%) and ≥ 73 months (52.21%) ($p < 0.0001$). The proportion of patients with OI was significantly higher within

1 to 4 months (83.33%) as compared to 5 to 8 months (66.67%), 9 to 12 months (50%) after HAART initiation with p value of 0.011. This signifies that as the viral load decreases and CD4 count improves, the risk of OIs reduces significantly.

The highest prevalence was seen in patients categorized as WHO clinical stage IV and III ($n = 135/135$, 100%) and ($n = 193/193$, 100%), respectively, while the lowest prevalence was observed among clinical stage I patients ($n = 1/342$, 0.29%). Statistically, a significant association was depicted between the prevalence of OIs and WHO clinical stages II, III and IV.

The prevalence of OIs was found to be highest ($n = 225/225$, 100%) among HIV-infected patients with CD4 count $<200/\text{mm}^3$ followed by CD4 count 200-349/ mm^3 and count 350-499/ mm^3 with a prevalence of ($n = 122/157$, 77.71%) and ($n = 30/127$, 23.62%), respectively whereas, the prevalence was significantly lower in patients with CD4 count more than 500/ mm^3 with a prevalence of only 5.41% (Fig. 1). The mean $\pm$ SD CD4 count/ mm^3 in patients without OI was 600.37 ± 246.8 , which was significantly higher than patients with OI (199.07 ± 116.88).

Good adherence to ART was seen in 503 (68.81%) patients, and poor adherence was present in 228 patients (31.19%). OIs were significantly higher in patients with poor ART adherence (99.12%) as compared to good adherence (32.41%).

A significant association was seen between low hemoglobin, protein (g/dL), albumin (g/dL) and OI. Mean $\pm$ SD protein (g/dL) and albumin (g/dL) in patients without OI was 7.51 ± 0.86 , 3.9 ± 0.51 , respectively, which was significantly higher as compared to patients with OI (7.29 ± 0.88 ($p = 0.0006$), 3.63 ± 0.6 ($p < 0.0001$)), respectively.

On univariate analysis, co-factors that had significant association with OIs were low-income education/socio-economic status, age, weight/BMI, hemoglobin, albumin, CD4 count, WHO staging, adherence to ART (Table 3).

On performing multivariate regression, CD4 count, low case adherence index score (poor adherence) and WHO staging (stage II, stage III and stage IV) were significant independent risk factors of OI after adjusting for confounding factors. Patients with low case adherence index score (poor adherence), WHO staging (stage II, stage III, stage IV) had significantly high risk of OI with adjusted odds ratio (OR) of 913.992 (21.282-39,252.803), 20.188.208 (678.408-60,0764.698), 26.264.032 (640.880-1076331.334), respectively. With the increase in CD4, risk of OI significantly decreased with adjusted OR of 0.989 (0.98-0.999) (Table 3).

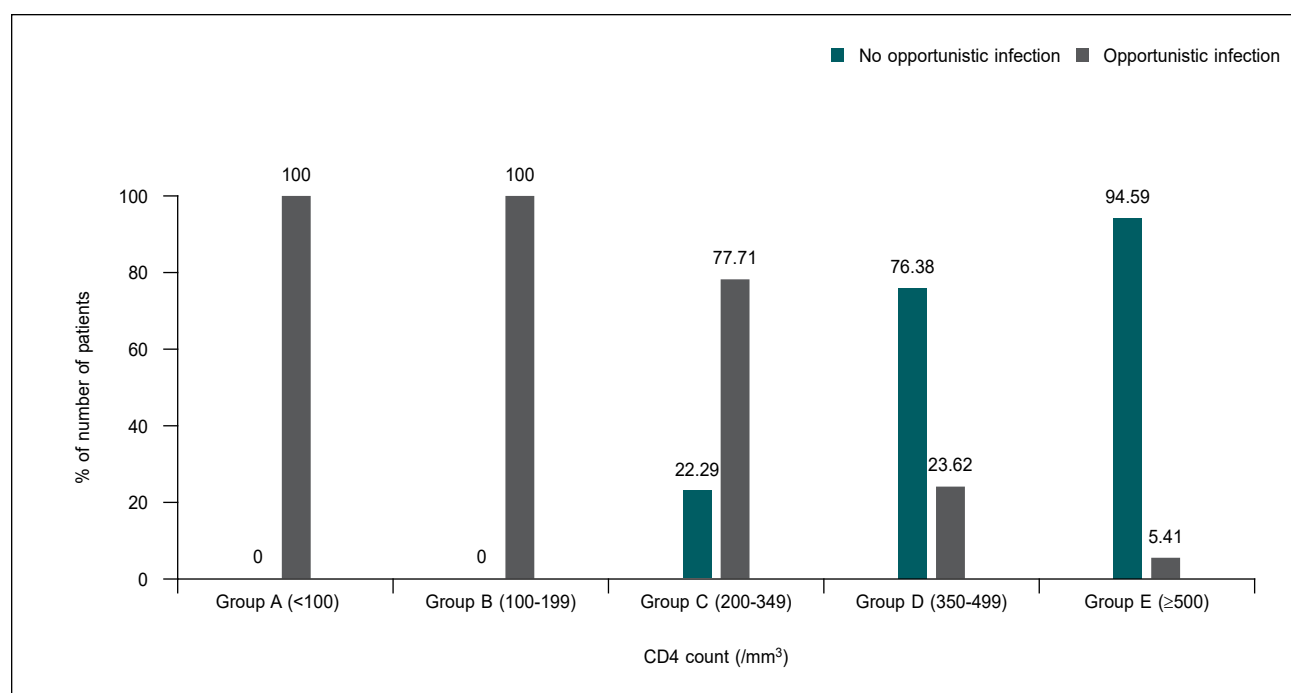


Figure 1. Association of CD4 count (/mm³) with opportunistic infection.

Table 3. Baseline Characteristics and Univariate and Multivariate Risk Factor Analysis for Opportunistic Infection

Characteristics	No OI (n = 342)	OI (n = 389)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	P value	OR	P value
Age (years)						
Mean ± SD	36.18 ± 10.43	43.39 ± 10.73	1.066 (1.05-1.082)	<0.0001		
Income						
<2,000	43 (31.85%)	92 (68.15%)	1	<0.0001		
2,000-5,000	92 (39.66%)	140 (60.34%)	0.714 (0.457-1.117)			
5,001-20,000	161 (54.03%)	137 (45.97%)	0.4 (0.261-0.614)			
>20,000	46 (69.70%)	20 (30.30%)	0.207 (0.11-0.392)			
Socioeconomic status						
Lower	5 (9.80%)	46 (90.20%)	1	<0.0001		
Upper lower	48 (42.48%)	65 (57.52%)	0.16 (0.061-0.42)			
Lower middle	180 (47.75%)	197 (52.25%)	0.129 (0.052-0.323)			
Upper middle	70 (58.33%)	50 (41.67%)	0.085 (0.032-0.222)			
Upper	39 (55.71%)	31 (44.29%)	0.094 (0.034-0.259)			
Education						
Illiterate	57 (33.14%)	115 (66.86%)	1	<0.0001		
Primary school	129 (47.60%)	142 (52.40%)	0.548 (0.368-0.815)			
Secondary school	95 (45.67%)	113 (54.33%)	0.592 (0.389-0.899)			
College and above	61 (76.25%)	19 (23.75%)	0.158 (0.086-0.288)			
Weight (kg)						
Mean ± SD	58.7 ± 9.17	52.72 ± 7.21	0.913 (0.895-0.932)	<0.0001		

Table 3. Baseline Characteristics and Univariate and Multivariate Risk Factor Analysis for Opportunistic Infection

Characteristics	No OI (n = 342)	OI (n = 389)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	P value	OR	P value
BMI (kg/m²)						
18.5-24.99 (Normal)	285 (55.77%)	226 (44.23%)	1	<0.0001		
<18.5 (Underweight)	31 (16.06%)	162 (83.94%)	0.15 (0.101- 0.234)			
25-29.99 (Overweight)	25 (96.15%)	1 (3.85%)	0.01 (0.002-0.064)			
≥30 (Obese)	1 (100%)	0 (0%)	0.06 (0.001-6.069)			
WHO clinical staging						
I	341 (99.71%)	1 (0.29%)	1	<0.0001	1.000	
II	1 (1.64%)	60 (98.36%)	9182.5 (929.2-90739.2)		20188.20	<0.0001
III	0 (0%)	193 (100%)	88107 (3545.5-2189448.1)		26264.03	<0.0001
IV	0 (0%)	135 (100%)	61697.667 (2472.9-1539321.7)		116.37	0.050
CD4 count (/mm³)						
Group A (<100)	0 (0%)	60 (100%)	1	<0.0001		
Group B (100-199)	0 (0%)	165 (100%)	2.73 (0.05-142.5)		0.98	0.02
Group C (200-349)	35 (22.29%)	122 (77.71%)	0.029 (0.002-0.48)			
Group D (350-499)	97 (76.38%)	30 (23.62%)	0.003 (0-0.04)			
Group E (≥500)	210 (94.59%)	12 (5.41%)	0 (0-0.009)			
Hemoglobin (g/dL)	12.51 ± 2.31	9.87 ± 1.83	0.56 (0.5-0.6)	<0.0001		
ART adherence						
Good adherence	340 (67.59%)	163 (32.41%)	1	<0.0001	-	-
Poor adherence	2 (0.88%)	226 (99.12%)	188.681 (53.3- 667.1)		913.992	0.0004
Albumin (g/dL)	3.9 ± 0.51	3.63 ± 0.6	0.412 (0.3-0.5)	<0.0001		

DISCUSSION

HIV is a major global public health issue, which has claimed more than 40 million lives so far with ongoing transmission globally. Despite the availability of ART, it is not a 100% curable disease. OIs and associated complications account for considerable morbidity and mortality in people living with HIV (PLHIV). The present study involving 731 patients on ART was carried out to elucidate current frequencies and spectrum of OIs infecting HIV seropositive adult patients in Haryana and to evaluate the associated risk factors of OIs.

The most common self-reported risk factor for the occurrence of HIV was the heterosexual route of transmission (94.53%), followed by unsafe sex with high-risk partners 6.16% and men who have sex with men (MSM) 3.01%. This can be explained by the mode of sexual activity practiced in the population. The study

found that about 53.21% of HIV/AIDS patients on ART had one or more OIs compared to 46.79% who had no OI. This agrees with the prevalence of 48%, 46.7% and 58% documented by Mitiku et al, Sun et al and Balkhair et al, respectively.⁷⁻⁹ However, prevalence in the present study is higher than various studies conducted in Nigeria and Southern India, which documented 22.4%, 35.7% and 8.3% prevalence, respectively.¹⁰⁻¹² This might be due to methodological differences in selecting study subjects. Moreover, South India's literacy rate is comparatively higher as compared to Haryana's; the present study found a significant association between education and OIs. This may explain the lower prevalence of OIs in the South. Also, it was lower as compared to the South Ethiopia study with a prevalence of 88.4%.¹³ This could be due to differences in availability and duration of HAART, the difference in CD4 level, clinical staging and the difference in host immunity of study subjects.

Table 4. Comparison Between Different Studies Vis-a-Vis Present Study

Study	Prevalence of OIs	Most common OIs		
		Most common	2nd most common	3rd most common
Our study (2022)	53.21%	Tuberculosis (48.32%)	Candidiasis (25.7%)	Herpes zoster (13.6%)
International studies				
Mitiku et al ⁷ (2015)	48%	Tuberculosis (21.23%)	Herpes zoster (11.2%)	Oral candidiasis (9.5%)
Solomon et al ¹³ (2018)	88.4%	Tuberculosis (18%)	Community-acquired pneumonia (16.3%)	Oral candidiasis (15.3%)
Balkhair et al ⁹ (2012)	58%	<i>Pneumocystis jirovecii</i> pneumonia (25%)	Cryptococcal meningitis (22%)	CMV retinitis (17%)
Iroezindu et al ¹⁰ (2013)	22.4% (76/339)	Candidiasis (8.6%)	Tuberculosis (7.7%)	Dermatitis (5.6%)
Chanie et al (in children) ¹⁷ (2021)	5.53%	Pneumonia (35.63%)	Tuberculosis (28.74%)	Oral Candidiasis (10.34%)
Indian studies				
Vinod et al ¹⁵ (2018)	23.5%	Candidiasis (52%)	Tuberculosis (50%)	
Ghate et al ¹¹ (2009)	35.7%	Tuberculosis (15.4%)	Oral Candidiasis (11.3%)	Herpes zoster (10.1%)
Srirangaraj et al ¹² (2011)	8.3%	Tuberculosis (53.4%)	Oral Candidiasis (27.2%)	Herpes zoster (14.7%)
Singh et al ¹⁶ (2003)		Oral candidiasis (59%)	Tuberculosis (56%)	Cryptosporidiosis (47%)
Bariha et al ¹⁸ (2018)		Tuberculosis (51%)	Oral Candidiasis (43%)	Cryptosporidiosis (6.8%)
Saldanha et al ¹⁹ (2008)		Tuberculosis (45.3%)	Candidiasis (34.5%)	Cryptosporidiosis (17.5%)
Sharma ²⁰ (2004)		Tuberculosis (71%)	Candidiasis (39.3%)	<i>Pneumocystis jirovecii</i> pneumonia (7.4%)

The present study revealed that TB (48.32% of total OIs) is the predominant OI identified, with a prevalence of 25.71% (188/731). Other studies done worldwide also had the same observation and TB was the most common OI found in PLHIV.^{7,13,14} TB enhances the progression of HIV infection by inducing immune activation. Candidiasis and herpes zoster were the second and the third most prevalent OIs in the present study, at 13.8% (101/731) and 7.25% (53/731), respectively. However, in many other studies, Candidiasis was found to be the most common OI as summarized in Table 4.^{7,9-13,15-20}

In the present study, the prevalence of cryptococcal meningitis was 2.05%, significantly higher than in the study conducted by Mitiku, with a prevalence of 0.28%.⁷ This could be due to increasing diagnostic availability (radiological and serology) and high suspicion of disease. There were 63 co-infections of different OIs observed in the present study. Of these, 55 had 2 co-infections, 7 had 3 co-infections and 1 patient had 4 co-infections. Also, TB with candidiasis was the most common co-infection (32 cases), followed by TB with cryptosporidiosis (4 cases). This was similar to studies conducted in Eastern Ethiopia and Northwest Ethiopia.^{7,21}

A higher proportion of TB and candidiasis co-infection in the present study may be explained by a higher prevalence of these two OIs among the study participants. Double and triple OIs have also been reported from studies in India and Nigeria.^{5,10} Prevalence of OIs among patients with comorbid viral hepatitis was comparable. No statistically significant association was observed ($p = 0.053$). This could be due to the small sample size of hepatitis B virus (HBV) and hepatitis C virus (HCV) reactive patients. However, the highest prevalence of OIs was depicted among hepatitis B surface antigen (HBsAg) reactive patients ($n = 14/18$, 77.78%).

The present study was conducted among HIV patients taking ART for 1 month or more. The prevalence of OIs was significantly higher in patients on ART for <4 months (83.33%), and the prevalence decreased in the subsequent months. This was similar to various previous studies and may be because HAART improves patient's CD4 count and therefore the prevalence of OIs decreases overtime.^{22,23} HIV-associated OIs and other related infections continue to occur in HIV-positive patients, but since the introduction of HAART, most infections occur at rates that are substantially lower than those seen in the pre-HAART era.

WHO clinical stage IV and III showed highest prevalence while least prevalence was observed among clinical stage I patients. This was similar to study in Northwest Ethiopia.²¹ In WHO stages II, III and IV, there is marked reduction in CD4 count, which may be the reason for the increased prevalence of OIs as in our study. The prevalence of OIs was highest ($n = 225/225$, 100%) among HIV-infected patients with CD4 count $<200/\text{mm}^3$. In contrast, the prevalence was significantly lower in patients with a CD4 count of $>500/\text{mm}^3$, with a prevalence of only 5.41%. Other studies from India have also reported a high risk of developing OIs such as TB, *Pneumocystis jirovecii* pneumonia and cryptococcal meningitis among patients with CD4 counts <200 cells/ mm^3 .²³ This finding appears accurate since CD4 cells play a central role in the activation of humoral and cellular immune response in the fight against infection. Hence, low CD4 count increases susceptibility to OIs.²¹

In the present study, OI was significantly higher in patients with BMI (kg/m^2) of <18.5 (underweight; 83.94%). BMI is an important indicator of nutritional status in patients with HIV infection. Emaciation is a common condition during the early period of HIV, and there is some evidence that higher BMI is associated with more robust CD4+ T-cell recovery in HAART-treated patients.²⁴ Li et al demonstrated that HIV-infected patients with higher BMI at pre-treatment exhibit better immune reconstitution overtime after HAART initiation.²⁵ Also, patients with body weight 52.72 ± 7.21 kg were more prone to develop OIs. This finding was similar to a study conducted by Inamdar et al.¹⁴

Opportunistic infections were significantly higher in patients with poor adherence to ART (99.12%). This was similar to the findings in the study conducted by Iroezindu et al.¹⁰ Fonsah et al conducted a study where subjects with CD4 cell counts <200 cells/ μL had a lower proportion of good adherence than subjects with CD4 cell counts ≥ 200 cells/ μL .²⁶ Therefore, people with poor adherence have a low CD4 count that translates to an increased incidence of OIs. Poor adherence to ART also causes progression of HIV, decreased CD4 count and hence can result in more OIs as already discussed.

Significant association was seen between hemoglobin (g/dL) and patients with OI with mean $\pm$ SD of hemoglobin (g/dL) 9.87 ± 1.83 g/dL. This was similar to a study by Iroezindu et al.¹⁰ Srikanthia et al demonstrated that both the cell-mediated immune response and bactericidal capacity of leukocytes in children with hemoglobin levels below 10 g/dL were significantly depressed.²⁷

Significant association was seen between protein, albumin and OIs. Studies in the past decade have suggested that low albumin levels in HIV-infected patients are associated with rapid progression to AIDS and may account for increased mortality. Studies have suggested baseline albumin levels to be a good predictor of survival in patients with low CD4 count.²⁸⁻³⁰ This may be attributable to nutritional factors, enteropathy and acute phase reactant proteins. Hence, the National AIDS Control Organization (NACO) in India provides nutritional supplements to those HIV-infected cases inducted for ART and nutritional counseling for others as a part of a national policy.³¹ In developing countries where many people live below the poverty line, serum albumin would be a useful surrogate test for predicting the severity of HIV infection and the clinical monitoring of response to ART.

There were some limitations of the present study. As a cross-sectional study, cause-effect relationships cannot be assessed. Therefore, the data on the natural history pattern of disease and survival of hospitalized patients with HIV/AIDS could not be established. The study's endpoint is restricted to the in-hospital period; hence, the full access to patient's follow-up clinical data after being discharged was not always available.

The present study shows TB as the commonest OI in overall population of PLHIVs in Haryana followed by candidiasis and herpes zoster. Baseline CD4 cell count <200 cells/ mm^3 , baseline WHO clinical stages III and IV and ART nonadherence were strongly associated with the prevalence of OIs. Lower income, education and socioeconomic status were also associated with a higher prevalence of OIs. Weight, BMI, albumin, hemoglobin level are strong predictors for the occurrence of OIs.

CONCLUSION

Presently, India has the third-largest population of HIV-infected individuals after South Africa and Nigeria. HIV patients are susceptible to a variety of OIs depending upon clinical status, WHO grading and CD4 count. It is noteworthy that OIs can have atypical presentations and multisystem involvement. Various factors like adherence to ART, socioeconomic and education status of patients can influence the occurrence and outcome of these deadly infections. Hence, there is a need for surveillance and a high degree of suspicion of these infections in HIV patients to ensure early diagnosis and intervention. Moreover, interventions need to be designed to promote easy and early access to HIV testing and early enrollment of HIV-infected individuals into ART services seeing that the use of ART was found to reduce the prevalence of

OIs by 4th month. Individuals who continue to have low CD4 cell counts while on ART should be aggressively evaluated for OIs and practical efforts to optimize their immunological recovery should be made.

Conflict of Interest: Nil.

External Funding Support: Nil.

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Carotid Plaque in Type 2 Diabetes Patients

Older type 2 diabetes patients and those with long diabetes duration, increased waist-to-hip ratio and high lipoprotein(a) [Lip(a)] levels have a higher likelihood of developing carotid atherosclerotic plaque, according to a study published in the *Journal of Translational Medicine*.¹

In the study, a total of 949 hospitalized patients with type 2 diabetes were included. Carotid ultrasound was performed to identify the presence of carotid atherosclerotic plaque in these patients, and it was found that 531 patients had such plaques, while 418 did not. The participants were assessed for waist-to-hip ratio, blood glucose levels, liver and kidney function, blood lipid profile, islet function, among other relevant indicators to determine the risk factors that contribute to the development of carotid plaque and to evaluate the predictive significance of carotid plaques in patients with type 2 diabetes. It was observed that the carotid plaques were significantly more prevalent in male patients with type 2 diabetes. The prevalence of diabetic nephropathy and hypertension was also significantly higher in patients with carotid plaque compared to those without carotid plaque. Patients with carotid plaque were older and had long-standing diabetes than those without carotid plaque. They also had higher waist-to-hip ratio, elevated postprandial glucose, increased Lp(a), higher levels of carcinoembryonic antigen and lower estimated glomerular filtration rate (eGFR) compared to those without plaque.

Furthermore, age, waist-to-hip ratio, duration of diabetes, hypertension, male gender and Lp(a) were identified as independent risk factors. After adjustment for confounding variables, eGFR was not found to be a risk factor for carotid plaque. Age, waist-to-hip ratio, duration of diabetes and Lp(a) demonstrated higher area under the curve (AUC) values for predicting the presence of carotid artery plaque in this group of patients (AUC: 0.750, 0.640, 0.678, 0.552, respectively). By constructing the logit (P) value using the aforementioned risk factors, the area under the receiver operating characteristic (ROC) curve was calculated to be 0.816, indicating a relatively good predictive ability for the presence of carotid plaque in patients with type 2 diabetes.

Cardiovascular disease is a major cause of death in patients with type 2 diabetes. Carotid atherosclerosis has shown significant correlation with cardiovascular events in these patients. Hence, early prediction of these macrovascular complications is critical. In this study of type 2 diabetes patients, several risk factors have been identified as being significantly predictive of the risk of formation of carotid plaque. These factors can be evaluated clinically and include advanced age, waist-to-hip ratio, duration of diabetes, hypertension, male gender and Lp(a) levels. Identification of these risk factors and their collective assessment allows better prediction of likelihood of carotid plaque formation in these patients and devise strategies for its prevention and management.

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A Case of Idiopathic Autoimmune Hemolytic Anemia: Every Anemia – First Type It and Then Treat It

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ABSTRACT

Autoimmune hemolytic anemia (AIHA) is a medical disorder where the immune system erroneously targets and destroys red blood cells (RBCs), causing a reduction in their longevity. This results in an inadequate supply of RBCs to carry oxygen, leading to symptoms like fatigue, weakness and jaundice. AIHA is categorized into warm and cold types based on the optimal temperature for antibody activity. A comprehensive grasp of the immunological mechanisms involved is essential for accurate diagnosis and effective management of this autoimmune condition. AIHA is a frequently missed diagnosis as patient are not fully investigated, and treated with vitamin B12, folic acid and iron in outpatient department.

Keywords: Autoimmune hemolytic anemia, reticulocyte count, lactate dehydrogenase, peripheral smear

Idiopathic autoimmune hemolytic anemia (IAIHA) refers to a subtype of autoimmune hemolytic anemia (AIHA) where the underlying cause of the immune system's attack on red blood cells (RBCs) cannot be identified. This form of AIHA presents a diagnostic challenge, as it lacks a clear association with known triggers or underlying conditions.¹

Patients with IAIHA experience the hallmark symptoms of AIHA, including fatigue, weakness and jaundice, stemming from the destruction of their own RBCs by autoantibodies.

CASE REPORT

A 39-year-old female presented to hospital on 20th October 2023 with complaint of abdominal pain since 6 to 7 days, predominant in epigastric and left upper quadrant, associated with generalized weakness, easy fatigability since last 15 days.

All the vitals were within normal limits. On general examination, there was pallor and icterus. On abdominal examination, the spleen was palpable 2 fingers below the costal margins.

There was no history of any drug intake or recent infection/fever.

Patient was treated empirically with parenteral vitamin B12 1,000 µg IV × 5 doses, oral folic acid 5 mg once daily and blood transfusion 1 unit packed cell volume. The patient was discharged on oral iron, B12 and folic acid.

Patient again presented after 2 months with similar complaints, with pallor and icterus and falling hemoglobin.

Detailed examination and investigation turned out to be a hemolytic anemia, with high indirect bilirubin, raised lactate dehydrogenase (LDH), high reticulocyte count, positive direct Coombs test and hemolysis on peripheral smear (Fig. 1). After thorough investigation on second admission, a diagnosis of idiopathic warm AIHA was made.

Investigation

Diagnosis involves a comprehensive assessment, including blood tests such as the direct and indirect Coombs tests to detect the presence of antibodies on RBCs. Distinguishing IAIHA from secondary forms requires ruling out underlying causes such as infections, medications or other autoimmune disorders.²

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Investigations	20-Oct-23	22-Oct-23	14-Dec-2023	6-Jan-23	18-Jan-23
Hb (g/dL) (12-15g/dL)	7.6	8.9	7.2	9.8	10.2
WBC(cells/cu mm) (4,000-11,000 cells/cu mm)	6,800	7,200	9,400	7,400	8,200
Platelet (cells/cu mm) (1,50,000-4,00,000 cells/cu mm)	1,97,000	2,12,000	2,02,000	2,30,000	2,32,300
Creatinine (mg/dL) (<1.2 mg/dL)	1.0	0.9	0.8	0.9	0.9
Upper GI endoscopy	Normal				
Serum SGPT (U/L) (10-56 U/L)	78	74		43	
Bilirubin (total/indirect)	2.3/1.8		2.8/2.2	1.1/0.9	1.0/0.8
LDH (U/L) (140-280 U/L)	623		1,142	212	198
dsDNA (0-29.9 IU/mL)			Negative		
ANA - Immunofluorescence (Normal <1:160 titer)			Negative (1:40 titer)		
ESR (mm/1st hr) (0-20 mm/1st hr)		45			
PSCM, reticulocyte count (RC)			Moderate anisocytosis, spherocytosis & nucleated RBC, RC-4.2%		
HIV, HBV, HCV, EBV IgM			Negative		
C-reactive protein		Negative	Negative		
Direct Coombs test (DCT)		DCT+2	DCT+4		
Ultrasonography abdomen			Splenomegaly, 16 cm length		

Hb = Hemoglobin; WBC = White blood cell; GI = Gastrointestinal; SGPT = Serum glutamic-pyruvic aminotransferase; LDH = Lactate dehydrogenase; dsDNA = Double-stranded deoxyribonucleic acid; ANA = Antinuclear antibody; ESR = Erythrocyte sedimentation rate; PSCM = Peripheral smear cell morphology; RBC = Red blood cell; HIV = Human immunodeficiency virus; HBV = Hepatitis B virus; HCV = Hepatitis C virus; EBV = Epstein-Barr virus; IgM = Immunoglobulin M.

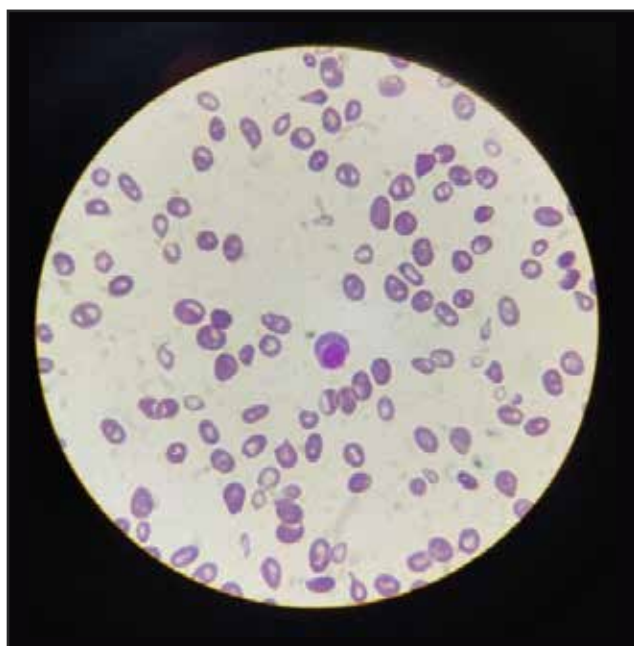


Figure 1. Peripheral smear.

Treatment

Treatment strategies for IAIHA often parallel those for other forms of AIHA. Corticosteroids remain a primary therapeutic choice, aiming to suppress the immune response and alleviate hemolysis. In more resistant cases, immunosuppressive agents or other advanced therapies may be considered to manage the condition.³

From 15th December 2023, patient was started on tablet prednisolone 20 mg once daily, for 2 weeks, followed by tapering dose 5 mg/2 week for next 4 weeks. By 15th January 2024, after 1 month of steroid, patient is currently on 10 mg prednisolone, having clinical improvement with resolution of easy fatigability, shortness of breath on exertion and recovery in laboratory signs of hemolysis. No side effects of steroids were noted during the course of treatment.

Prednisolone is planned to be slowly tapered over the next 1 month and to be stopped after a total of 8 weeks.

DISCUSSION

Among various types of AIHA,⁴ warm antibody hemolytic anemia (WAHA), is the most common type of AIHA, where the immune system targets RBCs at normal body temperature (37°C). Antibodies, usually immunoglobulin G (IgG), attach to RBCs, leading to their destruction by macrophages in the spleen and liver.

Cold antibody hemolytic anemia (CAHA) is less common than WAHA. It involves the immune system attacking RBCs at lower temperatures and is typically triggered by exposure to cold. Cold agglutinins, often IgM antibodies, bind to RBCs in colder areas of the body, causing clumping and destruction.

Mixed-type antibody hemolytic anemia: Some individuals may exhibit characteristics of both WAHA and CAHA, making it a mixed-type presentation.

Drug-induced hemolytic anemia:⁵ Certain medications can trigger an immune response against RBCs, leading to hemolysis. Drugs can either induce the formation of antibodies that attack RBCs directly or cause a drug-induced immune reaction.

Secondary AIHA: AIHA can occur secondary to underlying conditions such as autoimmune diseases (e.g., lupus), infections or malignancies. Underlying diseases or conditions stimulate the immune system to produce antibodies that target RBCs.

IAIHA: In some cases, as described in this case, the exact cause of AIHA remains unknown, leading to the classification of IAIHA. The immune system appears to spontaneously target and destroy RBCs without any apparent triggering factor.

Management of AIHA involves addressing the underlying cause, if known, and utilizing immunosuppressive therapies to modulate the immune response and reduce destruction of the RBCs.

The idiopathic nature of IAIHA underscores the complexity of autoimmune disorders, highlighting the need for ongoing research to unravel the precise mechanisms triggering immune dysregulation in these cases. As our understanding of autoimmune diseases evolves, advancements in targeted therapies may offer more tailored and effective treatments for individuals with IAIHA.

CONCLUSION

This case highlights the importance of thorough investigation in new-onset anemia, particularly when standard

treatments fail. It highlights the pitfalls of empiric treatments like iron, B12 and folic acid in outpatient settings for anemic patients. The successful management of IAIHA with corticosteroids showcases the significance of tailored therapies based on accurate diagnoses.

This case contributes to our understanding of IAIHA, emphasizing the need for continued research to advance treatment modalities. It also reinforces the critical role of comprehensive investigations in managing AIHA effectively.

Declaration

- **Funding:** The author(s) received no financial support for the research, authorship and/or publication of this article.
- **Conflicts of interest/Competing interests:** All authors declare that they have no conflicts of interest.
- **Ethics approval:** Ethical approval is not applicable for this article.
- **Consent to participate:** Written informed consent was obtained from the patient; the patient was informed of the potential risk-benefits and side effects of steroid treatment.
- **Consent for publication:** Written informed consent was obtained from the patient for their anonymized information to be published in this article.
- **Availability of data and material:** All data underlying the results are available as part of the article and no additional source data are required.
- **Code availability:** Not applicable.
- **Authors' contributions:** Drafting of the manuscript content, including medical writing of content – Dr Darpan Kothia and Analysis & interpretation of data - Dr Hemang K Acharya.

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Extended Use of Ivabradine in Heart Failure with Preserved Ejection Fraction and Inappropriate Sinus Tachycardia

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ABSTRACT

Ivabradine has been used for over a decade in managing chronic coronary syndromes and heart failure (HF) with reduced ejection fraction (HFrEF). HF with preserved ejection fraction (HFpEF) accounts for 50% of the total HF cases carrying equal mortality and morbidity risk as HFrEF. Increased heart rate (HR) in such cases has been shown to be associated with poor clinical outcomes. Clinical conditions like inappropriate sinus tachycardia (IST) manifest with elevated HR without any specific triggers. Beta-blockers have been the preferred treatment of choice for both HFpEF and IST but are often ineffective or present with side effects due to their negative inotropic effects. Ivabradine, through its inhibitory action on funny current (I_f), reduces HR without altering the inotropic mechanism. Few case reports and small case series have documented its extended use and efficacy in reducing HR in these cardiac conditions. In this article, we present two cases who needed HR control, one with HFpEF and another case of IST syndrome. Ivabradine was successfully used in both these cases to control the elevated HR.

Keywords: Ivabradine, HFpEF, inappropriate sinus tachycardia

Ivabradine is a selective inhibitor of funny channel (I_f), which are located in the sinoatrial node and are responsible for controlling the diastolic depolarization termed as I_f current and its activity can vary by the sympathetic and parasympathetic stimuli. Ivabradine, through a concentration-dependent mechanism, selectively inhibits the I_f channels and reduces the heart rate (HR) without altering the blood pressure (BP) or contraction or relaxation activity of the myocardium.¹ It is a novel antiarrhythmic drug approved for the treatment of select heart failure (HF) patients.²

It was initially used as an antianginal drug and was later approved for use in HF with reduced ejection fraction (HFrEF) cases (EF <35%). The European Society of Cardiology (ESC) has recommended its application for reducing the risk of hospitalizations due to HF and

cardiovascular death in New York Heart Association (NYHA) Class II-IV with left ventricular ejection fraction (LVEF) of $\leq 35\%$ despite maximally tolerated doses of beta-blocker (BB). Nearly 50% of cases of HF patients have preserved EF (HFpEF) and bear similar mortality and morbidity outcomes as HFrEF.³

Increased HR in patients with HF is associated with poor outcomes. Patients with HFpEF have impaired left ventricular (LV) relaxation and increased HR during exercise, reducing the LV filling, which increases the LV filling pressure and causes reduced exercise tolerance. Since ivabradine reduces HR without causing any effect on BP, it has been used in specific cases for managing HR when BB or calcium channel blockers (CCBs) are contraindicated.⁴

Ivabradine has established itself as an HR-modulating agent with its prime role in chronic coronary syndromes and HFrEF. It has also been recognized for its extended use in other unapproved conditions like inappropriate sinus tachycardia (IST) and cases of HFpEF.

The two cases presented here are examples of extended use of ivabradine in HFpEF and IST. Off-label indications are fully justified when necessary, as the side effects are rare and not serious.

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CASE REPORTS

Case 1

A 63-year-old female presented with history of Class IV dyspnea, cough, wheezing, pedal edema and extreme fatigue in June 2022. She was normotensive and nondiabetic with a history of chronic obstructive pulmonary disease (COPD). She was on oral bronchodilators, nebulizers and continuous positive airway pressure (CPAP) at night on the advice of a pulmonologist. She was on thyroid supplements and was euthyroid at presentation. Past medical history revealed repeated admissions in the last 13 years for episodic bronchospasm, worsening dyspnea and HF.

On examination, the patient had sinus tachycardia (HR 130/min), BP was 96/70 mmHg, jugular venous pressure (JVP) was elevated; pedal edema was noted. Cardiovascular examination revealed right ventricular (RV) heave, loud pulmonic closure sound (P2), Grade 2/6 ejection systolic murmur at the left sternal border and pansystolic tricuspid regurgitation murmur was heard. Routine blood tests were normal, thyroid-stimulating hormone (TSH) was normal and there was a 10-fold increase in N-terminal pro-brain natriuretic peptide (NT-proBNP) levels.

An electrocardiogram (ECG) showed sinus rhythm, HR 133/min, right axis deviation and RV hypertrophy with strain (Fig. 1A). X-ray chest showed cardiomegaly, a prominent pulmonary artery segment and evidence of pulmonary hypertension. Lung fields showed peribronchiolar haze. The echocardiogram revealed normal LV size, no regional wall motion abnormalities (RWMA) and an LVEF of 62%. There was evidence of severe pulmonary arterial hypertension (PAH) with RV dysfunction. She was diagnosed with COPD, severe PAH with RV dysfunction, preserved LV systolic function (HFpEF) and right-sided HF.

The patient was started on digoxin, diuretics and pulmonary vasodilators (tadalafil), oral bronchodilators, as well as nebulizers, antibiotics and bilevel-positive airway pressure (BiPAP). On day 3, she developed persistent sinus tachycardia; hence, ivabradine 5 mg twice daily was added as BB were contraindicated due to COPD. Three days later, ECG revealed a sinus rhythm rate of 82/min (Fig. 1B).

Case 2

A 70-year-old female, NRI, from USA, came for a routine annual review in September 2022. She had a history of intermittent episodic palpitations with sweating

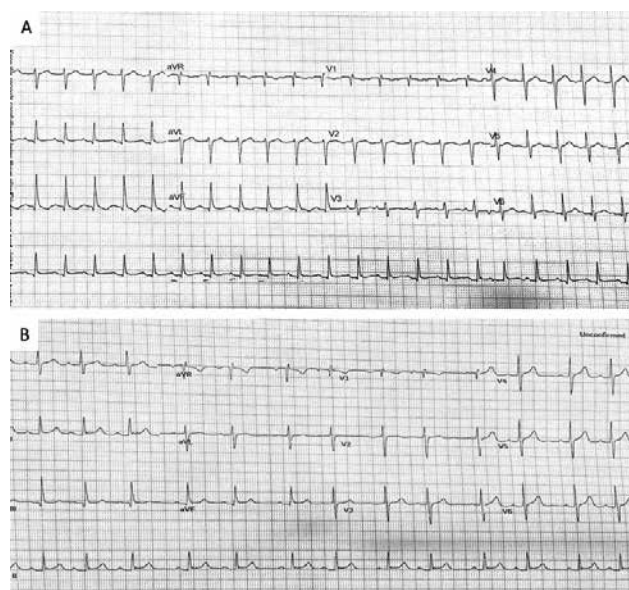


Figure 1. ECG at admission showing sinus rhythm, 133/min, right axis deviation (A). ECG 3 days after starting ivabradine showing sinus rhythm, 82/min (B).

for a short duration for the past 5 years. There were 3 episodes of presyncope, mainly on effort and emotion associated with severe palpitations. She was a known case of mild hypertension for 20 years and had a history of intermittent bronchospasm requiring bronchodilator inhalers.

She had undergone a complete cardiac evaluation in USA. Her ECG showed a left bundle branch block (LBBB). Biochemical parameters including thyroid profile were normal. Echocardiogram did not show any RWMA and LVEF was normal. A treadmill test (TMT) showed normal effort tolerance with no symptoms or evidence of arrhythmias except sinus tachycardia and LBBB. In August 2019, she underwent 14 days of patch monitoring, which revealed sinus rhythm, rate 61-126/min and occasional supraventricular ectopics. There were no ventricular arrhythmias or pauses. During episodes of symptomatic palpitations, monitoring revealed sinus tachycardia, which lasted for 10 to 15 minutes.

She was diagnosed with symptomatic IST syndrome. The patient was started on oral ivabradine 5 mg twice daily, spironolactone for hypertension and bronchodilator inhalers whenever needed. She came for an annual review in September 2022 and expressed 90% symptomatic improvement with medication. Her pulse rate was 76/min, regular and her BP was 130/70 mmHg.

The cardiovascular and chest examinations were normal. ECG revealed sinus rhythm, 76/min and LBBB. Her

echocardiogram was normal; 640 slice computerized tomography (CT) coronary angiogram revealed evidence of insignificant CAD. She was reassured and continued on ivabradine and was advised to come for a follow-up every 6 months or earlier, if warranted, by symptoms.

DISCUSSION

In HF, there is an increase in HR as a response to the reduced cardiac output. But this elevated HR leads to increased oxygen demand by the myocardium resulting in the worsening of hemodynamic mechanism resulting in ventricular dysfunction and poor clinical outcomes. Patients with HFpEF have impaired LV relaxation and increased HR during exercise, reducing the LV filling, which in turn increases the LV filling pressures and decreases exercise tolerance. Drugs like BBs have not shown any reduction in mortality due to cardiovascular causes in HFpEF.⁴ Due to their negative inotropic effect, no improvement was observed in exercise tolerance or peak oxygen uptake.⁵ Ivabradine has shown promising results as it reduces HR by selectively acting only on the I_f channels.⁶

Ivabradine exerts a negative chronotropic effect by reducing the spontaneous phase IV depolarization in the sinoatrial node by blocking the I_f channels, which causes an increase in the diastolic time.⁶ Data from a study by Kosmala et al comparing ivabradine and placebo in 61 patients with HFpEF for 7 days has shown significant improvement in exercise capacity in the former group (metabolic equivalents [METs] was 1.5 ± 1.2 vs. 0.4 ± 1.2 ; $p = 0.001$) along with improvement in peak VO_2 (3 ± 3.6 mL/kg/min vs. 0.4 ± 2.7 mL/kg/min; $p = 0.003$).⁷ Another study by Pal et al has shown significant improvement in VO_2 ($p = 0.003$) and reduced submaximal exercise capacity with dose titration.⁸

Ivabradine has been routinely used to control HR in cases of HFrEF, angina and chronic coronary syndromes. In the present cases, BBs were contraindicated because of bronchospasm. For controlling the HR, nondihydropyridine CCBs like verapamil were found ineffective owing to the risk of reduction in systemic arterial pressure, negative inotropic effect and negative impact on gas exchange.

IST is a rare form of atrial tachycardia due to improper rapid depolarization in the sinus node. Clinically, the resting HR is usually high (90-100 beats/min), which would increase abnormally on physical activity. It manifests with symptoms of presyncope, syncope, dizziness, weakness, palpitation and exercise intolerance. Management chiefly includes BBs, CCBs or antiarrhythmic

drugs. But in nearly one-third cases, these drugs fail to relieve the symptoms and are associated with side effects. Ivabradine, due to its role in controlling HR, has shown promising results as its extended indication in IST.⁹

The correction of the IST occurs without measurable bradycardia since ivabradine acts as an open channel blocker. Even when used in combination with BB, it is safe and reduces the risk of hypotension that occurs with BB since the dosage of BB is less in combination therapy. Data from a large case series in patients affected with IST have shown a mean HR reduction of 22 beats/min at 3 months and 34 beats/min after 6 months with ivabradine.¹⁰

Even the quality of life score, short-form 36 items (SF-36) showed significant improvement ($p = 0.001$) and was well-tolerated.¹¹ Even in renal transplant cases with IST, where BB was not helpful and CCB were contraindicated due to drug interactions with immunosuppressants, ivabradine was noted to be effective in controlling HR.¹² The ESC guidelines have recommended BBs as first-line therapy for IST. Ivabradine, alone or with BBs, can be considered in symptomatic patients with IST as a Class IIa recommendation.¹³

Other drugs, like nondihydropyridine CCBs such as verapamil, diltiazem and catheter ablation for refractory cases, are no longer recommended for IST.

Ivabradine has been approved as a second-line drug for chronic stable angina in BB intolerant patients or in whom BBs are contraindicated. Ivabradine, though an off-label indication, can be considered to control HR in HFpEF and IST in clinical practice as there are no adverse effects in these cases.¹⁴

CONCLUSIONS

In patients with HFpEF and IST, lowering HR is beneficial to reduce myocardial oxygen requirement and cardioprotection. Selective action of lowering HR without altering the BP shows promising results for ivabradine in such cases. It also improves exercise capacity and improves the quality of life.

Ivabradine has been proven to be effective for HFrEF and angina, but it has also shown potential benefit in HFpEF and IST. With the increased use of ivabradine in off-label indications, we hope additional clinical studies will be conducted for consideration in future guidelines.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: None.

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Study Links Gabapentinoid Use to Increased Risk of COPD Exacerbation

A recent population-based cohort study published in the *Annals of Internal Medicine* has raised concerns about the use of gabapentinoids, anticonvulsant drugs prescribed for epilepsy and neuropathic pain.

The research involved over 10,000 individuals and found an association between gabapentinoid use and an elevated risk of chronic obstructive pulmonary disease (COPD) exacerbation. These drugs have been reported to cause central nervous system depression, leading to sedation and respiratory depression, particularly in individuals with respiratory diseases like COPD.

The study analyzed insurance data for 356 gabapentinoid users with epilepsy, 9,411 with neuropathic pain and 3,737 with other chronic pain. The researchers matched gabapentinoid users with nonusers based on COPD duration, drug indication, age, sex, calendar year and time-conditional propensity score.

The findings revealed that gabapentinoid use was associated with an increased risk of severe COPD exacerbation, with the peak risk occurring after approximately 6 months of continuous use. The elevated risk was observed across users with epilepsy, neuropathic pain and chronic pain.

Notably, the risk remained consistent regardless of factors such as age, sex, prior COPD exacerbations, use of inhaled corticosteroids, respiratory medication history, or concurrent opioid or benzodiazepine use.

(Source: <https://medicalxpress.com/news/2024-01-gabapentinoids-severe-exacerbation-copd.html>)

Sports-Statin Interaction: Ensuring Safe and Smart Synergy

SANJAY KALRA*, SUNEET VERMA†, KAMAL KISHOR‡

ABSTRACT

Both sports (physical activity) and statins are recommended for the prevention and management of atherosclerotic cardiovascular disease. The synergy that they create in risk reduction, however, may turn dysfunctional at times. Statin usage is associated with a risk of muscle-related conditions including myalgia, myositis and rhabdomyolysis. This risk is exacerbated by unaccustomed physical activity, exercise or sports. The communication shares practical and pragmatic suggestions regarding the prevention and management of the potential sports-statin interactions that may occur. It also highlights the need to consider drug-lifestyle interactions, apart from conventional drug-drug interactions.

Keywords: Atherosclerosis, cardiovascular risk, coenzyme Q, diabetes, physical activity, sports medicine, statins, vitamin D

Physical exercise is the basis of a healthy lifestyle, and is recommended as part of strategies to minimize cardiovascular risk. Statins, too are a part of the comprehensive strategies to prevent and manage atherosclerotic cardiovascular disease (ASCVD). This sports-statin synergy, however, may turn dysfunctional at times.

SPORTS-STATIN INTERACTIONS

Current guidelines¹⁻³ mention the need for caution while co-prescribing exercise and statins. Building upon these expert recommendations, we share pragmatic suggestions for health care professionals regarding potential sports-statin interactions.

We discuss how to prevent, identify and manage these interactions in the course of clinical practice. Awareness about these issues will help maximize the benefits of both sports (and physical activity/exercise) as well as statins in persons who need them.

INDICATIONS

- Sports and statins are essential pillars of cardiovascular disease prevention and treatment.
- Statins should be prescribed, as indicated, in persons with established ASCVD, and those at high risk of ASCVD, to reduce cholesterol and minimize cardiovascular risk.
- Sports, physical activity, dance and exercise (SPADE) should be encouraged in all persons, especially those with high cholesterol and established ASCVD/high cardiovascular risk.
- Health care professionals must be aware that unaccustomed exercise is a risk factor for statin-induced muscle dysfunction.

STATIN VIGILANCE

- Persons on statins should inform their treating physician while starting or intensifying a structured physical activity/sports/exercise/dance (SPASED) regimen.
- Persons recovering from acute coronary syndromes must follow their treating physician's advice regarding graded and gradual cardiac rehabilitation.
- Persons on statins who develop muscle aches, muscle pains, limited range of movement or high-colored urine should inform their treating physician immediately.
- A serum CPK (creatinine phosphokinase) and urine heme should be ordered if clinically indicated.

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SAFE SEQUENTIAL USAGE

- Optimize their metabolic and nutritional parameters including hemoglobin, electrolytes, calcium, magnesium and vitamin D, prior to initiating SPASED regimens and/or statin therapy.
- Avoid up-titrating statin dose and initiating/intensifying SPASED regimens simultaneously.
- Persons pursuing SPASED should inform their treating physician about their current SPASED regimens when statin therapy is initiated.
- Athletes planning endurance exercise like marathons may consider a 2- to 3-day statin holiday prior to the date of the event.

MANAGEMENT OF MYOPATHY

- Persons who develop statin-induced myopathy should temporarily discontinue or de-intensify their SPASED workout. Persons with statin-induced myopathy will benefit from rest, hydration and adequate nutrition.
- Vitamin D and coenzyme Q may be used to prevent and alleviate symptoms.
- Persons with statin-induced myopathy should be monitored regularly, till symptoms and biochemical abnormalities resolve.
- Supportive treatment will be required for persons who develop rhabdomyolysis.

STATIN RECHALLENGE

- Statin rechallenge, with a lower dose or a different statin, should be attempted in persons with a history of statin-induced myopathy, once they have stabilized.

- Pitavastatin, 2 mg or 4 mg daily, may be considered in persons who are unable to tolerate atorvastatin or rosuvastatin.
- Persons who develop myopathy-related symptoms upon rechallenge- may be offered alternative lipid-lowering medication such as ezetimibe, icosapent ethyl or PCSK9 inhibitors.
- Clinical prudence should prevail while deciding whether to offer a statin rechallenge to persons with a history of statin-induced rhabdomyolysis.

SUMMARY

This brief communication encapsulates and reinforces the concept of sports-statin interaction, and shares ways of mitigating the risk.

All health care and sports professionals should be aware of this information.

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New Study Reveals Cost-effectiveness of Tafenoquine in Treating Vivax Malaria

According to a study published in *PLOS Medicine*, researchers found that tafenoquine, a promising medication for treating vivax malaria, is a cost-effective alternative to the conventional 7-day primaquine treatment, despite the mandatory glucose-6-phosphate dehydrogenase (G6PD) deficiency testing before prescription. Vivax malaria, caused by the *Plasmodium vivax* parasite, is known for its persistent liver-stage infection.

The researchers compared the results of G6PD screening followed by a single dose of tafenoquine against the traditional 7-day low-dose primaquine regimen without G6PD screening. Additionally, merely 62% to 86% of vivax malaria patients complete the full 7-day primaquine treatment, prompting a closer examination of cost-effectiveness in varying completion scenarios. Utilizing an economic evaluation model and a disease transmission model, the researchers explored three primaquine treatment scenarios: patients completing 30%, 67% or 90% of the 7-day course. Remarkably, the results consistently demonstrated that tafenoquine stood out as the most cost-effective treatment across all completion rates compared to primaquine.

Are Advance Medical Directives Legal in India?

Yes, in the landmark judgment titled as “**Common Cause versus Union of India, 2018 (5) SCC 1** passed by the Hon’ble Constitution Bench of 4 Judges of the Supreme Court of India”, it has duly held that the advance medical directives are legal in India. Further in the said judgment, the Hon’ble Apex Court has laid down certain guidelines and directions w.r.t. advance medical directives which shall remain in force till the Parliament makes legislation on this subject.

The Hon’ble Supreme Court has held that:

191. In our considered opinion, Advance Medical Directive would serve as a fruitful means to facilitate the fructification of the sacrosanct right to life with dignity. The said directive, we think, will dispel many a doubt at the relevant time of need during the course of treatment of the patient. That apart, it will strengthen the mind of the treating doctors as they will be in a position to ensure, after being satisfied, that they are acting in a lawful manner. We may hasten to add that Advance Medical Directive cannot operate in abstraction. There has to be safeguards. They need to be spelt out. We enumerate them as follows:

(a) Who can execute the Advance Directive and how?

- (i) The Advance Directive can be executed only by an adult who is of a sound and healthy state of mind and in a position to communicate, relate and comprehend the purpose and consequences of executing the document.
- (ii) It must be voluntarily executed and without any coercion or inducement or compulsion and after having full knowledge or information.
- (iii) It should have characteristics of an informed consent given without any undue influence or constraint.
- (iv) It shall be in writing clearly stating as to when medical treatment may be withdrawn or no specific medical treatment shall be given which will only have the effect of delaying the process of death that may otherwise cause him/her pain, anguish and suffering and further put him/her in a state of indignity.

(b) What should it contain?

- (i) It should clearly indicate the decision relating to the circumstances in which withholding or

withdrawal of medical treatment can be resorted to.

- (ii) It should be in specific terms and the instructions must be absolutely clear and unambiguous.
- (iii) It should mention that the executor may revoke the instructions/authority at any time.
- (iv) It should disclose that the executor has understood the consequences of executing such a document.
- (v) It should specify the name of a guardian or close relative who, in the event of the executor becoming incapable of taking decision at the relevant time, will be authorized to give consent to refuse or withdraw medical treatment in a manner consistent with the Advance Directive.
- (vi) In the event that there is more than one valid Advance Directive, none of which have been revoked, the most recently signed Advance Directive will be considered as the last expression of the patient’s wishes and will be given effect to.

(c) How should it be recorded and preserved?

- (i) The document should be signed by the executor in the presence of two attesting witnesses, preferably independent, and countersigned by the jurisdictional Judicial Magistrate of First Class (JMFC) so designated by the concerned District Judge.
- (ii) The witnesses and the jurisdictional JMFC shall record their satisfaction that the document has been executed voluntarily and without any coercion or inducement or compulsion and with full understanding of all the relevant information and consequences.
- (iii) The JMFC shall preserve one copy of the document in his office, in addition to keeping it in digital format.
- (iv) The JMFC shall forward one copy of the document to the Registry of the jurisdictional District Court for being preserved. Additionally, the Registry of the District Judge shall retain the document in digital format.
- (v) The JMFC shall cause to inform the immediate family members of the executor, if not present at the time of execution, and make them aware about the execution of the document.

- (vi) A copy shall be handed over to the competent officer of the local Government or the Municipal Corporation or Municipality or Panchayat, as the case may be. The aforesaid authorities shall nominate a competent official in that regard who shall be the custodian of the said document.
- (vii) The JMFC shall cause to handover copy of the Advance Directive to the family physician, if any.

(d) When and by whom can it be given effect to?

- (i) In the event, the executor becomes terminally ill and is undergoing prolonged medical treatment with no hope of recovery and cure of the ailment, the treating physician, when made aware about the Advance Directive, shall ascertain the genuineness and authenticity thereof from the jurisdictional JMFC before acting upon the same.
- (ii) The instructions in the document must be given due weight by the doctors. However, it should be given effect to only after being fully satisfied that the executor is terminally ill and is undergoing prolonged treatment or is surviving on life support and that the illness of the executor is incurable or there is no hope of him/her being cured.
- (iii) If the physician treating the patient (executor of the document) is satisfied that the instructions given in the document need to be acted upon, he shall inform the executor or his guardian/close relative, as the case may be, about the nature of illness, the availability of medical care and consequences of alternative forms of treatment and the consequences of remaining untreated. He must also ensure that he believes on reasonable grounds that the person in question understands the information provided, has cogitated over the options and has come to a firm view that the option of withdrawal or refusal of medical treatment is the best choice.
- (iv) The physician/hospital where the executor has been admitted for medical treatment shall then constitute a Medical Board consisting of the Head of the treating Department and at least three experts from the fields of general medicine, cardiology, neurology, nephrology, psychiatry or oncology with experience in critical care and with overall standing in the medical profession of at least 20 years who, in turn, shall visit the patient in the presence of his guardian/close relative and form an opinion whether to certify or not to certify carrying out the instructions of withdrawal or

refusal of further medical treatment. This decision shall be regarded as a preliminary opinion.

- (v) In the event, the Hospital Medical Board certifies that the instructions contained in the Advance Directive ought to be carried out, the physician/hospital shall forthwith inform the jurisdictional Collector about the proposal. The jurisdictional Collector shall then immediately constitute a Medical Board comprising the Chief District Medical Officer of the concerned district as the Chairman and three expert doctors from the fields of general medicine, cardiology, neurology, nephrology, psychiatry or oncology with experience in critical care and with overall standing in the medical profession of at least 20 years (who were not members of the previous Medical Board of the Hospital). They shall jointly visit the hospital where the patient is admitted and if they concur with the initial decision of the Medical Board of the Hospital, they may endorse the certificate to carry out the instructions given in the Advance Directive.
- (vi) The Board constituted by the Collector must beforehand ascertain the wishes of the executor if he is in a position to communicate and is capable of understanding the consequences of withdrawal of medical treatment. In the event, the executor is incapable of taking decision or develops impaired decision-making capacity, then the consent of the guardian nominated by the executor in the Advance Directive should be obtained regarding refusal or withdrawal of medical treatment to the executor to the extent of and consistent with the clear instructions given in the Advance Directive.
- (vii) The Chairman of the Medical Board nominated by the Collector, that is, the Chief District Medical Officer, shall convey the decision of the Board to the jurisdictional JMFC before giving effect to the decision to withdraw the medical treatment administered to the executor. The JMFC shall visit the patient at the earliest and, after examining all aspects, authorize the implementation of the decision of the Board.
- (viii) It will be open to the executor to revoke the document at any stage before it is acted upon and implemented.

(e) What if permission is refused by the Medical Board?

- (i) If permission to withdraw medical treatment is refused by the Medical Board, it would be open to the executor of the Advance Directive or his

family members or even the treating doctor or the hospital staff to approach the High Court by way of writ petition under Article 226 of the Constitution. If such application is filed before the High Court, the Chief Justice of the said High Court shall constitute a Division Bench to decide upon grant of approval or to refuse the same. The High Court will be free to constitute an independent Committee consisting of three doctors from the fields of general medicine, cardiology, neurology, nephrology, psychiatry or oncology with experience in critical care and with overall standing in the medical profession of at least 20 years.

- (ii) The High Court shall hear the application expeditiously after affording opportunity to the State counsel. It would be open to the High Court to constitute Medical Board in terms of its order to examine the patient and submit report about the feasibility of acting upon the instructions contained in the Advance Directive.
- (iii) Needless to say that the High Court shall render its decision at the earliest as such matters cannot brook any delay and it shall ascribe reasons specifically keeping in mind the principles of "best interests of the patient".

(f) Revocation or inapplicability of Advance Directive

- (i) An individual may withdraw or alter the Advance Directive at any time when he/she has the capacity to do so and by following the same procedure as provided for recording of Advance Directive. Withdrawal or revocation of an Advance Directive must be in writing.
- (ii) An Advance Directive shall not be applicable to the treatment in question if there are reasonable grounds for believing that circumstances exist, which the person making the directive did not anticipate at the time of the Advance Directive and which would have affected his decision had he anticipated them.
- (iii) If the Advance Directive is not clear and ambiguous, the concerned Medical Boards shall not give effect to the same and, in that event, the guidelines meant for patients without Advance Directive shall be made applicable.
- (iv) Where the Hospital Medical Board takes a decision not to follow an Advance Directive while treating a person, then it shall make an application to the Medical Board constituted by the Collector for consideration and appropriate direction on the Advance Directive.



Stress Linked to Metabolic Syndrome: Study Highlights Importance of Stress Management

A recent study published in *Brain, Behaviour, and Immunity-Health* revealed a connection between stress and metabolic syndrome, prompting researchers to advocate for simple, cost-effective stress-management strategies to improve biological health outcomes.

Using data from a national survey, the study involved 648 participants with an average age of 52. The research focused on how inflammation, triggered by stress, contributes to the relationship between stress and metabolic syndrome. Biomarkers for inflammation, physical exam results and perceived stress reports were analyzed to build a statistical model.

The findings revealed that stress is associated with metabolic syndrome, and inflammation explains more than half of this connection, precisely 61.5%. This emphasizes the impact of stress on health markers, highlighting its role in initiating biological changes.

While various factors contribute to metabolic syndrome, including lifestyle choices, socioeconomic status, age and gender, stress management emerges as a crucial strategy in preventing or mitigating the risk of metabolic syndrome.

(Source: <https://www.hindustantimes.com/lifestyle/health/stress-management-could-reduce-biological-risk-study-101705330434554.html>)

31st Annual Scientific Meeting of Indian National Association for Study of the Liver (INASL 2023)

ENDOSCOPIC BARIATRIC AND METABOLIC THERAPY. WHERE ARE WE AND WHERE ARE WE GOING?

Dr D Nageshwar Reddy, Hyderabad

Obese patients with nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH) require an endoscopy balloon or gastropasty with/without duodenal mucosal resurfacing (DMR), while lean patients with NAFLD/NASH require endoscopic DMR. Duodenum is at the center of metabolic control; a sustained glycemic improvement is seen even after 12 months after a single DMR. Duodenal nutrient passage strongly influences insulin sensitivity, independent of weight change. DMR is safe and yields beneficial disease-modifying metabolic effects, especially in patients with high fasting plasma glucose levels. The newer DMR therapies include Laser, radiofrequency ablation (RFA) and electroporation.

RECET™ is the first nonthermal endoscopic ablative therapy and, thus, the only therapy to ablate cells selectively. It is feasible with the technical success achieved in 100% of subjects. It is safe and well-tolerated, with a few mild to moderate and transient adverse events. No serious adverse events have been reported with RECET™. Duodenal RECET™ results in durable and clinically meaningful improvement in glycemic control. A dose response has been observed, with higher energy doses being more effective without any increased risk of adverse events.

ENDOSCOPIC/RADIOLOGIC MANAGEMENT OF NONVARICEAL PORTAL HYPERTENSIVE BLEEDING

Dr Vikram Bhatia, New Delhi

Nonvariceal portal hypertensive bleeding is bleeding in the gastrointestinal tract caused by portal hypertension (PHT), but not from esophageal or gastric varices. Instead, it involves bleeding from other sources within the digestive system due to increased pressure in the portal vein system. The four most common types of nonvariceal portal hypertensive bleeding include:

- **Portal hypertensive gastropathy (PHG):** It is attributed as the cause of 4% of all acute bleeding in chronic liver diseases (CLD). A study has shown that transjugular intrahepatic portosystemic shunt (TIPS)

can improve the endoscopic appearance of PHG lesions in 6 to 12 weeks, with reduced transfusion requirements.

- **Gastric antral vascular ectasia (GAVE):** In argon plasma coagulation (APC) treatment of GAVE, more profound mucosal injuries must be avoided. Additionally, studies have shown that the recurrence-free rate following this treatment is 50% for 1 year and 35% for 3 years. In the case of APC-refractory GAVE, the RFA treatment method can be used as it yields comparable results to APC. Endoscopic variceal ligation (EVL) is superior to APC and RFA treatment of GAVE with a success rate of 81% to 87.8%. TIPS is not effective for treating GAVE
- **Portal hypertensive duodenopathy (PHD):** The frequency of PHD among cirrhosis patients with esophageal varices is 14%. This condition can be treated with TIPS and APC.
- **Portal hypertensive colopathy (PHC):** This chronic condition has a 3% to 71% prevalence in cirrhosis patients. Although bleeding from PHC is uncommon, it is seen in 0% to 9% of cases.

Some of the additional key points to remember are:

- PHG, PHD and PHC are poorly defined entities with an unclear clinical correlation.
- There is a dearth of data on the frequency and significance of bleeding from PHT-related non-variceal sources.
- Treatment for bleeding from PHG, PHD and PHC should be individualized.

ROUTE OF LIVER BIOPSY – PERCUTANEOUS, EUS, TJLB, LAPAROSCOPIC: HOW TO CHOOSE?

Dr Manas Panigrahi, Bhubaneswar

A liver biopsy is usually the most specific test to assess the nature and severity of liver diseases, such as multiple parenchymal liver disease, abnormal liver tests of unknown etiology and fever of unknown origin. In addition, it can be helpful in monitoring and detecting focal or diffuse abnormalities in imaging studies.

Several methods are currently available for obtaining liver tissue: percutaneous biopsy, transjugular biopsy,

endoscopic ultrasound (EUS) and laparoscopic biopsy. Each of these methods has its advantages and disadvantages.

Plugged liver biopsy (PLB), a modification of percutaneous liver biopsy, is performed in patients with impaired coagulation where transjugular liver biopsy (TJLB) is unavailable. It also provides greater access to both hepatic lobes, thereby increasing the adequacy and yield of tissue.

Additionally, this method is cost-effective, requires less technical skills, is suitable for patients who are obese, and results in lower post-procedure discomfort. Hence, it can be used in various clinical settings.

On the other hand, TJLB is known to reduce the overall risk of complications associated with PLB. This method can also be used in a patient with coagulopathy and acute liver failure.

However, noninvasive methods are gaining acceptance at present. They are also considered reliable and applicable tools for predicting the course of liver cirrhosis, such as EUS-guided liver biopsy (EUS-LB). This method can diagnose the presence of liver disease that progresses in a zonal fashion, such as primary sclerosing cholangitis, viral hepatitis and nodular regeneration. In contrast, some of the disadvantages associated with this are the complexity and expensive nature of the procedure.

The laparoscopic method can be used to visualize the peritoneum and to decide between operation and conservative treatment strategies in cases of peritoneal carcinomatosis. Also, this is used to biopsy hepatic masses when vascular structures limit the transcutaneous approach.

Remember, "*One size does not fit all*", so an individualized approach is the key to finding an appropriate modality. Furthermore, the choice of one technique over the other depends on the following:

- Availability
- Personal preference
- Clinical situation.

TRANSJUGULAR LIVER BIOPSY AND HEPATIC VEIN PRESSURE GRADIENT

Dr Sreedhara B Chaluvasetty, Chandigarh

- TJLB is an alternative to a percutaneous liver biopsy.

- Specimens obtained from TJLB have a reduced risk of hemorrhage compared to those obtained with the percutaneous technique.
- Its clinical role has expanded due to the possibility of performing hemodynamic evaluation.
- TJLB is indicated in failed percutaneous liver biopsy or in a patient with a contraindication to percutaneous biopsy, in coagulopathy (a most common indication), massive ascites, patients requiring hemodynamic evaluation as part of their diagnostic workup, morbid obesity, liver transplant or with serum bilirubin >6, in patients undergoing a TIPS procedure.
- There are no real contraindications for a TJLB. However, relative contraindications include a lack of suitable venous access and a biopsy of a focal lesion.
- An international normalized ratio (INR) of >2 and a platelet count of <30 should be corrected before a patient is taken up for the TJLB procedure. The Society of Interventional Radiology (SIR) guidelines establish that additional blood products should be administered if the INR is >2.5 times the control and the platelet count is <30,000.
- Overall, TJLB is a highly efficacious, well-tolerated and safe procedure. Adequate liver samples of good quality for diagnostic and staging purposes can be obtained with minimal risks.
- Hepatic vein pressure gradient (HVPG) is the safest and most reproducible method to measure portal pressure.
- HVPG is the pressure difference between the wedge hepatic vein pressure (WHVP) and the free hepatic vein pressure (FHVP).
- HVPG >10 mmHg indicates clinically significant portal hypertension (CSPH). Patients with CSPH are at high risk of developing clinical complications, including variceal bleeding, ascites and encephalopathy.
- While a biopsy sample represents only a small liver area, serial HVPG measurements characterize the overall degree of fibrosis or cirrhosis, reflecting an underlying heterogeneous disease process.
- HVPG is the gold standard for PHT measurement, and its safety and reproducibility are well-proven. It has become an important diagnostic and prognostic tool and can be adopted in routine practices as per the Baveno VII consensus.

HCFI Dr KK Aggarwal Research Fund

Round Table Environment Expert Zoom Meeting on “Environmental Challenges in 2024 and Scope of Public participation”

December 31, 2023 (Sunday, 12 noon-1 pm)

- The choices made and action taken in the next few years will play a very critical role in deciding our future and of generations to come.
- Greenhouse gas (GHG) emissions reached a new high in 2022. In September 2023, global average temperatures were 1.8°C higher above the pre-industrial times.
- To avoid breaching the upper limit of 2°C, the GHG emissions will have to be 28% lower than the current by 2030.
- To keep the temperature below the target of 1.5°C, as per the Paris Agreement, GHG emissions need to be 42% lower by 2030.
- Decisions taken in COP 28, particularly the accelerated short-term actions and an orderly transmission away from fossil fuel will help in achieving the targets of GHG reductions.
- Our environmental concerns in 2024 will be mainly dominated by climate change. Global warming and climate change can cause other serious issues besides increase in temperature, such as rising ocean levels impacting coastal cities, dramatic climate events such as long droughts and massive flooding, extinction of certain species, etc.
- Other challenges include the increasing air pollution, especially in the Indo-Gangetic plain; waste management, especially in the urban areas; deforestation, because of land acquirement for building and other developments and depleting ground water table in many cities leading to an imminent water crisis.
- Pollution by electric vehicles is going to be another challenge because of environmental concerns around lithium mining along with issues regarding proper disposal and recycling of lithium batteries.
- The impact of electric vehicles on the grid needs to be considered.
- It needs to be explored if the electricity required for electric vehicles can be generated from renewable energy sources.
- There are gaps in public transport system with issues of time and reliability.
- Unless drastic measures are taken, vehicular pollution will not reduce.
- Although the use of electric vehicles is increasing, the shift is gradual. People are apprehensive about taking these vehicles for long distances. Infrastructure is needed for electric vehicles to become the preferred mode of travel.
- CRRRI (Central Road Research Institute) is engaged in research in converting parali (stubble) to bitumen. Research is ongoing for use of plastic waste in road construction.
- India's first steel slag (industrial waste) road came up in Surat in 2022. Such roads have also been built in Arunachal Pradesh.
- Road dust is a huge problem. Proper cleaning of drains before monsoons is a must.
- The health of the river has not been given importance. It should be treated as a living being and should be provided care in a similar manner. Doing so will take care of water pollution and river pollution.
- We have to find out reasons as to why our taps do not provide safe drinking water. There are several reasons for this. Intermittent supply of water is one reason for this. Sewage flow should be channel flow; this prevents entry of dirty water in fresh water even if the supply is intermittent.
- The general public should know how to test for clean water. Orthotolidine (OT) solution water testing kit can be used. Add 2 drops in tap water, if the water turns yellow, this means that the water has chlorine and one can drink.
- Awareness will increase the confidence of public in tap water. Lot of funds are needed and not in a piecemeal manner. Rivers cannot be cleaned unless action is taken in a holistic way.
- There are lot of upcoming challenges in water supply and sewerage in the coming years. For example, the population of Delhi has grown to over 2.5 crores, while the amount of water produced has not increased beyond 900 MGD (million gallons per day). The pressure of increase population leads to exploitation of ground water.

- Government has the potential to do rain water harvesting in district parks, ridge areas, on roof tops of schools and colleges. Storm water drains can be isolated for rain water harvesting.
- Action needs to be taken against illegal industries discharging their chemical effluents in the ground, because of which the ground water becomes toxic.
- Sewerage water is another area that needs to be tackled. Delhi generates 800 MGD sewerage water and around 550 MGD is treated.
- The rest goes into ponds and lakes and thence to the river.
- There should be increase in the use of nonconventional water sources. Treated water can be used for horticulture, irrigation.
- Urban planning focuses mainly on cars. There is no effort to encourage nonmotorized traffic.
- Use of hydrogen cars will mean less environmental pollution.
- Car fitness should be emphasized rather than phasing out of cars after a certain set period of time. If the vehicle is nonpolluting, it should be allowed to run, even after the time limit. This will also reduce financial burden.
- Noise pollution has largely been ignored.
- We should move in the direction of providing solar panels on car roofs.
- The developing planning should change and become more preventive.
- Public participation is a must to tackle these challenges. Every citizen should think how many carbon credits to save and change their lifestyle.
- Public can mainly be involved in waste reduction or recycling.
- A political will to tackle these problems appears to be missing.
- The public and the government should work together to clean the rivers.
- All things have to start at the micro level, which will then grow.
- Adopting the Mission LiFE (Lifestyle For Environment) program of the Government of India can help meet most of these challenges with the help of the public.

Participants: Mr Paritosh Tyagi, Mr RS Tyagi, Mr Neeraj Tyagi, Mr Pradeep Khandelwal, Mr Rajeev Sharma, Dr Ravindra Kumar, Dr Anil Kumar

Minutes of an International Weekly Meeting on “Reversible Diabetes”

Speaker: Dr KP Chandra MD (*Internal Medicine*), DFiD (CMC), FICP, FiSH, FUPDA, FRTDI, FISCN, FISMN, Director, Dept. of Internal Medicine & Diabetes Care, Health City Vistaar Hospital, Lucknow; Director, Chandra Diabetes & Obesity Clinic, Lucknow

January 13, 2024 (Saturday, 9.30-10.30 am)

- The concept of reversal of diabetes is very important at this point of time because 100 million people in India already have diabetes and ~150 million are on the verge of getting diabetes.
- Type 2 diabetes has always been thought as an inevitably life-long disease with irreversible and progressive beta-cell damage.
- However, restoration of normal glucose metabolism within days after bariatric surgery in most people with type 2 diabetes disproves this concept. Changes in gut hormones and profound decrease in calorie intake are mechanisms that lead to this effect.
- When the disease process itself has reversed and there is no pathophysiology, this is reversal.
- Remission is defined as disappearance of signs and symptoms of a disease, but pathophysiology may still remain.
- Partial remission is having blood sugar that does not meet the classification for type 2 diabetes (fasting blood glucose [FBG] 126, postprandial plasma glucose [PPG] <200, A1c >6.5) for at least 1 year while not taking any medications to lower blood glucose.
- Complete remission is a return to normal glucose values (FBG <100, PPG <140, A1c <5.7) for at least 1 year while not taking any medications to lower blood glucose.
- Prolong remission is a return to normal glucose for at least 5 years while not taking any medications to lower blood glucose.
- When we talk of reversal of diabetes, it is important to know the pathophysiology of type 2 diabetes and how decline in beta-cell function occurs.
- There is progressive beta-cell dysfunction in type 2 diabetes and as the dysfunction continues, we keep on optimizing/intensifying treatment beginning with lifestyle modifications + oral antidiabetic drugs (OADs), then basal insulin + OADs are added. The change has to be done in typical therapeutic progression so reversal can be obtained.

- The glycemic control deteriorates over time in type 2 diabetes with progressive decline in beta-cell function regardless of the intensity of the treatment.
- Beta-cell dysfunction occurs because of several factors such as chronic hyperglycemia, glucotoxicity, hyperinsulinemia and lipotoxicity. Acting together, these factors lead to beta-cell dysfunction.
- The 6-year Da Qing Diabetes Prevention Study showed that lifestyle interventions led to 49% lower incidence of type 2 diabetes, when the intervention was done at the time of prediabetes stage.
- Another study examined the cumulative incidence of type 2 diabetes in over 3,000 patients with prediabetes for more than 4 years. The risk reduction was 58% with lifestyle intervention and 31% with metformin.
- These data question the concept that the disease is progressive. By certain interventions, the disease process can be halted.
- Metabolic dysfunction and insulin resistance leads to hyperinsulinemia, which causes increased hunger and increased chronic calorie intake. To reverse disease activity, this vicious cycle has to be stopped.
- The Twin Cycle hypothesis was given by Roy Taylor. Chronic calorie excess leads to accumulation of fat in the liver with eventual spill over into the pancreas, eventually causing metabolic inhibition of insulin secretion after meals and onset of hyperglycemia. To reverse this, fat accumulation in the liver and triglycerides have to be decreased.
- Reversing the twin cycle can effectively improve the beta-cell function.
- With weight loss, the liver fat becomes normal and there is normal insulin sensitivity.
- Fat accumulation therefore seems to be a pathway where if intervention is done, reversal can be possible.
- The DiRECT study (Diabetes Remission Clinical Trial) was an open-label trial conducted at 49 primary care practices in Scotland and England. It included patients with recently diagnosed type 2 diabetes (<6 years) and not receiving insulin.
- Results showed weight loss of ≥ 15 kg in 24% participants in the intervention group and none in the control group at 12 months. Diabetes remission was seen in 46% in the intervention group and just 4% in the control group. In the group with <5 kg weight loss, the remission was 7%; in 5-10 kg group, it was 34%; in 10-15 kg group, it was 57% and in >15 kg weight loss, it was 86%. Intervention at the right time with diagnosis of diabetes within 6 years with good weight loss led to remission in this study.
- The study concluded that almost half of the participants achieved remission to a non-diabetic state and were off antidiabetic drugs at 12 months. Remission of type 2 diabetes is a practical target for primary care.
- Glucagon-like peptide-1 (GLP-1) analogs have multiple positive effects on beta cells. They increase beta-cell function (homeostasis model assessment or HOMA), beta-cell glucose sensitivity (insulin secretion rate or ISR), secretory capacity and first phase insulin secretion. They reduce proinsulin:insulin ratio.
- Liraglutide has been shown to improve beta-cell function in patients with type 2 diabetes.
- In a post hoc analysis of STEP 2 trial, semaglutide 2.4 mg was seen to improve beta-cell function in patients with type 2 diabetes.
- There is published data for early intensive insulin therapy for remission of type 2 diabetes.
- If diabetes is treated intensively in the beginning itself, it helps in beta-cell preservation and insulin secretion.
- Intensive diabetes therapy helped preserve beta-cell function and insulin secretion at 3.5 years after diagnosis of type 2 diabetes.
- In a meta-analysis of 7 trials, short-term intensive insulin therapy for type 2 diabetes resulted in improvement in HOMA-B (beta-cell function) and decrease in HOMA-IR (insulin resistance). Hence, short-term intensive insulin therapy improves beta-cell function and insulin resistance and helps to achieve long-term drug-free glycemic remission.
- A study analyzing predictors of sustained drug-free diabetes remission over 48 weeks following short-term intensive insulin therapy in early type 2 diabetes found that the remission group had lower baseline A1c, better baseline beta-cell function and shorter duration of diabetes (<2 years).
- People who had diabetes for <2 years had 56% higher chances of having drug-free remission of type 2 diabetes after 48 weeks of intensive insulin therapy.
- The least probability of reversal is seen in severe insulin deficiency, while mild obesity-related diabetes and mild age-related diabetes have excellent probability of reversal.

- Very low calorie diets have emerged as a way to remission of diabetes.
- Evidence shows that early intensive insulin therapy helps in re-differentiation of beta cells and attain sustained drug-free diabetes remission.
- Early intensive insulin therapy has led to partial remission of diabetes as seen in many studies.
- Visceral fat is responsible for insulin resistance leading to hyperinsulinemia and beta-cell exhaustion resulting in progression of type 2 diabetes.
- When visceral fat is reduced, lipotoxicity in liver and pancreas decreases and there is less gluconeogenesis in the liver leading to remission of diabetes.
- In insulin resistance, the GLUT receptors do not respond appropriately and adequately to insulin. When insulin sensitivity improves, they respond better to insulin and thus inward movement of glucose in the muscle becomes more effective.
- Muscle mass is critical in absorbing the glucose we eat. With age, muscle mass is lost.
- Intermittent fasting not only reduces fat, it also increases sensitivity of glucose.
- The concept of chronomedicine is becoming very important now. When there is dyssynchrony between diurnal variation and sleep, the synchrony between various hormones gets deranged and there is

increase in counter-regulatory hormones leading to diabetes. Frequent snacking among those who sleep late increases calorie intake and then to diabetes. Night owls have a higher incidence of obesity, hypertension and diabetes compared to early birds.

- Remission of type 2 diabetes seems a possible option in appropriate populations. Type 1 diabetes is not reversible.
- Appropriate lifestyle modification with early intensive treatment in obesity-related diabetes and duration of diabetes <6 years, may reverse beta-cell dysfunction.
- Even reversal of diabetes is possible, if prolonged remission is seen in such cases.

Participants: Dr Yeh Woei Chong, Singapore, Chair of Council-CMAAO; Dr Wasiq Qazi, Pakistan, Immediate Past President-CMAAO; Dr Akhtar Hussain, South Africa; Dr Prakash Budhathoki, Nepal

Invitees: Dr Monica Vasudev, USA; Dr Mulazim Hussain Bukhari, Pakistan; Dr Azizan Abdul Aziz; Dr P Lata Anand; Dr Shashi Khanna; Dr Ashok Nathwani; Dr Tejveer Singh Chauhan; Dr Upendra Mehta; Dr Arun Kapoor; Dr Meena Bajaj; Dr Vishwanathan S Iyer; Dr Anurag Mathur; Dr KiranVinayek; Dr Poonam Chablani; Dr Abhay Jain; Dr Vishnu Bhutia; Adv Sonia Madan; Dr Sanchita Sharma, Editor-IJCP Group

Moderator: Mr Saurabh Aggarwal

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Overuse of Antifungal Creams Linked to Rise in Drug-resistant Infections

Excessive prescription of antifungal creams is contributing to the emergence of drug-resistant infections, warned a study led by Dr Jeremy Gold, US Centers for Disease Control and Prevention (CDC). Published in the CDC's *Morbidity and Mortality Weekly Report*, the research highlighted a concerning increase in severe antimicrobial-resistant superficial fungal infections, particularly drug-resistant forms of ringworm. Significant outbreaks of drug-resistant ringworms in Southeast Asia, unresponsive to standard treatments, have raised alarm. He noted that patients are experiencing extensive lesions and delayed diagnoses, emphasizing the need for caution in prescribing these medications.

The study revealed primary care doctors as major contributors to the overprescription issue, with dermatologists and podiatrists showing higher rates of prescriptions per doctor. Misdiagnosis based solely on visual inspection is identified as a significant problem, with confirmatory diagnostic testing seldom conducted.

A small percentage of physicians are responsible for a substantial proportion of antifungal prescriptions, with 10% of prescribers accounting for nearly half of these medications in 2021. The study may need to pay more attention to the problem, as many antifungals are available over the counter without a prescription. Of particular concern is the extensive use of clotrimazole-betamethasone, a combination of a steroid and an antifungal, linked to drug-resistant ringworm and potential skin damage.

(Source: <https://www.punjabnewsexpress.com/health/news/overuse-of-antifungal-skin-meds-driving-drug-resistant-disease-study-236388>)

News and Views

Treatment Outcomes of Drug-resistant TB with Comorbid Diabetes

Patients with drug-resistant (DR-TB) or multidrug-resistant tuberculosis (MDR-TB), who had concomitant diabetes mellitus have higher probability of unsuccessful treatment and treatment failure, while those without diabetes were more likely to be cured, according to a new study published in *BMC Infectious Diseases*.¹

This study was a systematic review and meta-analysis, which included 25 studies following a comprehensive search of the PubMed, Excerpta Medica Database (EMBASE), Web of Science, ScienceDirect and Cochrane Library databases for papers published in English until July 2022. The focus of the search was on studies that reported the association between diabetes mellitus and treatment outcomes among patients with DR-TB and MDR-TB. Together these studies involved a total of 16,905 participants with DR-TB, of which nearly 60% had MDR-TB and 11.5% had a history of diabetes mellitus.

Among all patients with DR-TB, the pooled odds ratio (OR) for unsuccessful treatment outcomes was 1.56. The pooled OR for cured treatment outcomes was 0.64. The pooled OR for completed treatment outcomes was 0.63 and for treatment failure, it was 1.28.

In the group of patients with MDR-TB, the pooled OR for unsuccessful treatment outcomes was 1.57, for cured treatment outcomes it was 0.55 indicative of lower likelihood of successful treatment. For completed treatment outcomes, the OR was 0.66 indicating a decreased likelihood of treatment completion. Lastly, the pooled OR for treatment failure was 1.37 suggesting an increased risk of treatment failure.

The pooled OR for risk of death among patients with either DR- or MDR-TB who also had diabetes was 1.32; it was 1.33 for those without diabetes.

The findings suggest that diabetes mellitus is a risk factor for adverse outcomes in patients with DR-TB or MDR-TB, which may be due to the higher bacterial burden and reduced effectiveness of the anti-TB drugs. Controlling the high blood glucose levels therefore may result in a more favorable prognosis for these patients. This study underscores the significance of diagnosing diabetes mellitus in individuals with DR-TB/MDR-TB as coexisting diabetes complicates the control and

management of TB, making it more challenging to combat the disease effectively.

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High FSH Linked to Lower Prevalence of NAFLD in Older Women with Type 2 Diabetes

Postmenopausal women with type 2 diabetes with lower follicle-stimulating hormone (FSH) levels are at a higher risk of developing nonalcoholic fatty liver disease (NAFLD), suggests a recent study published in the *Journal of Diabetes*.¹

In this cross-sectional study, 583 postmenopausal Chinese women diagnosed with type 2 diabetes mellitus were enrolled from January 2017 to May 2021. The average age of the participants was 60.2 years. Data pertaining to anthropological characteristics, biochemical indexes and abdominal ultrasound findings were collected retrospectively. NAFLD was diagnosed with the help of abdominal ultrasound. FSH levels were quantified via enzymatic immunochemiluminescence and then categorized into tertiles for further analysis. Logistic regression was performed to evaluate the relationship between FSH levels and the prevalence of NAFLD.

Out of the 583 women who were recruited, 332, accounting for 56.94% of the sample, were found to have NAFLD. When postmenopausal women in the lowest tertile of FSH were compared with those in the highest tertile, it was observed that the latter group had a significantly lower prevalence of NAFLD ($p < 0.01$). After controlling for variables such as age, duration of diabetes, metabolism-related indicators and other sex-related hormones, a negative association between FSH and NAFLD was detected with OR of 0.411 ($p < 0.001$). Subgroup analysis revealed no significant interactions between FSH and metabolic factors in relation to the presence of NAFLD.

This study has demonstrated a negative correlation between FSH levels and NAFLD in postmenopausal women with type 2 diabetes. These findings propose that FSH may potentially serve as a valuable biomarker or risk factor for the screening and identification

of postmenopausal women at a heightened risk of developing NAFLD.

Reference

1. Ge S, et al. Association between follicle-stimulating hormone and nonalcoholic fatty liver disease in postmenopausal women with type 2 diabetes mellitus. *J Diabetes*. 2023;15(8):640-8.

Benefits of Semaglutide in Patients with Severe Obesity and History of Bariatric Surgery

Adults who had previously undergone bariatric surgery for severe obesity and did not respond to the surgery achieved comparable weight loss results to those who had no history of the surgery when they started taking once-weekly semaglutide, according to a new study published in the journal *Obesity*.¹

This retrospective cohort study was conducted by researchers from the University Hospital of Montpellier and University of Montpellier in France to evaluate the efficacy of semaglutide 2.4 mg in patients with severe obesity with body mass index (BMI) 40 kg/m² or higher. These patients had undergone bariatric surgery, either sleeve gastrectomy or gastric bypass, but had been either unsuccessful in achieving satisfactory weight loss or had regained weight. They were compared to patients without a previous history of bariatric surgery but had BMI within the similar range.

Between April 2022 and October 2022, a total of 111 participants were included for the analysis; of these, 36 had a history of bariatric surgery and were categorized as BS+ group, while the remaining 75 did not and were clubbed as the BS- group. In the BS+ group, majority (n = 28) had a sleeve gastrectomy, while 8 had undergone gastric bypass surgery. All of the patients were given semaglutide treatment for a period of 24 weeks with an initial dose of 0.25 mg per week subcutaneously, which was gradually increased until reaching a final dosage of 2.4 mg per week. The effectiveness of the treatment was evaluated by measuring the difference in percentage of weight loss at 24 weeks, changes in BMI and waist circumference between the two groups.

The overall weight loss at 24 weeks was significant amounting to 9.1%. In the BS+ group, treatment with semaglutide led to a significant weight loss of 9.8%, with no notable difference in weight loss compared to the BS- group, which experienced weight loss of 8.7%.

After 24 weeks, 72% of the bariatric surgery group lost minimum of 5% of their body weight, with 36% achieving a weight loss of at least 10% and 8% losing 15% or more of their weight. The BS- group showed

comparable results, with 62% losing at least 5% of body weight, 31% achieving a weight loss of at least 10%, and 8% experiencing a 15% or greater weight loss after 24 weeks. The waist circumference reduced by 9.2 cm in the BS+ group and 7.8 cm in the BS- group.

Both groups showed similar reductions in glycated hemoglobin (HbA1c), low-density lipoprotein (LDL) cholesterol, triglycerides and serum glutamic-oxaloacetic transaminase (SGOT). Adults who had previously undergone bariatric surgery experienced a decrease in Fibrosis-4 score, while those who had never had surgery did not. The patients in BS+ group did not encounter any additional side effects when compared to those in the BS- group. Semaglutide is FDA approved for chronic weight management in adults with obesity or overweight with at least one weight-related condition, e.g., high blood pressure, type 2 diabetes or high cholesterol as adjunct to lifestyle modifications.

According to the authors, this is the first study to showcase the effectiveness of semaglutide treatment in patients with a history of bariatric surgery versus those without. Both groups had comparable weight loss outcomes. The improvement in cardiometabolic parameters and fibrosis was also similar to those without a history of bariatric surgery. The study specifically focuses on individuals with severe obesity, who also had comorbid conditions such as dyslipidemia, hypertension, heart disease or obstructive sleep apnea. This group of patients, especially those who regained significant amount of weight, has hitherto been excluded from clinical trials thinking that pharmacotherapy would be ineffective. The findings of this study debunk this assumption and highlight semaglutide 2.4 mg as a safe potential treatment option for this specific population group, who have not been able to achieve the desired weight loss and still have a BMI in the severely obese category. "These findings have the potential to inform clinical decision-making and guide future research efforts aimed at improving outcomes in this specific patient population", write the authors.

Reference

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Risk Factors for Poor Glycemic Control in Diabetes Patients

Patients who are on oral hypoglycemic drugs and insulin and also have pathological proteinuria double their odds of having poor glycemic control, suggests a

study published January 2, 2024 in the *Journal of Global Health Reports*.¹

This cross-sectional study aimed to assess the long-term management of patients with diabetes and identify the factors that contribute to inadequate glycemic control. The study recruited 226 diabetic patients out of the 268 attending an outpatient clinic at Saint-Nicolas Hospital in Saint-Marc, Haiti from March to May in 2022. The patients were questioned by examiners to evaluate the association between poor glycemic control, as per the American Diabetes Association criteria, and demographic and clinical factors identified from a literature review.

In this study, nearly 85% of the participants were female, with a mean age of 60 years. Almost 60% of the study subjects had diabetes for a minimum of 5 years and 67.26% had poorly controlled diabetes. Based on the Morisky score, 50.88% of the patients demonstrated good adherence to their treatment. Hypertension as a comorbid condition was present in 95% and 59% were overweight or had obesity. The multivariate analysis conducted after logistic regression revealed that patients with pathological proteinuria were twice more likely to have poor glycemic control with OR of 2.20. Patients on oral hypoglycemic drugs and insulin were also at higher risk of having poor control of their diabetes with OR of 2.58.

In order to prevent acute complications and reduce the risk of long-term complications, as well as lower health care utilization and associated costs, it is crucial to maintain adequate glycemic control. Based on these results, the study suggests that enhancing patient education before optimizing pharmacological treatment could potentially improve glycemic control and prevent micro- and macrovascular complications. However, in order to gain a more comprehensive understanding, a larger study that explores additional potential obstacles is needed to supplement the findings of this current research.

Reference

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Vaginal Hysterectomy Vis-à-Vis Laparoscopic Hysterectomy for Benign Gynecologic Disease

Vaginal hysterectomy, performed for a benign gynecologic disease is associated with less operative time,

fewer complications and speedier recovery, even though patients had more postoperative pain on the day of surgery, when compared to laparoscopic hysterectomy, according to a study published in the December 2023 issue of the journal *Obstetrics & Gynecology*.¹

This systematic review and meta-analysis aimed to compare the outcomes in women who underwent laparoscopic hysterectomy and vaginal hysterectomy for a benign gynecologic disease.

A total of 23 randomized controlled trials published between 2000 and February 2023 were included in the study following a search of major databases, including PubMed, Scopus, Web of Science, ClinicalTrials.gov and the Cochrane Library. Out of the 2,408 subjects included in the study; 1,105 had undergone vaginal hysterectomy and 1,303 had undergone laparoscopic hysterectomy.

When the two groups were compared, participants in the vaginal hysterectomy group had fewer postoperative urinary tract infections with OR of 1.73. The blood loss during the surgery was also lower in this group. The mean difference in blood loss was -68. Although the total duration of surgery including the recovery time was shorter with vaginal hysterectomy, patients experienced greater postoperative pain on the day of surgery. Other complications such as need for conversion to laparotomy, visceral organ damage, or wound dehiscence, were rare.

These findings suggest that vaginal hysterectomy could be the preferred surgical approach for a benign gynecologic disease condition such as leiomyoma, adenomyosis, uterine prolapse.

Nevertheless, the decision to opt for a particular surgical approach of hysterectomy, minimally invasive or abdominal, should be based on the individual patient after a careful risk-benefit analysis.

The American College of Obstetricians and Gynecologists (ACOG) also recommends vaginal hysterectomy as “the approach of choice whenever feasible”. It recommends laparoscopic hysterectomy as the preferred approach in patients in whom the vaginal route is not possible.²

References

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Prayer for Inner Happiness

Stress is defined as the physical and mental reaction to the interpretation of a known situation. In absence of a known situation there cannot be a stress. One cannot be stressful for a person who has just died in New York in an accident unless he or she is a known person.

There has to be a right, conscious-based interpretation of the situation as the same situation can bring happiness to one and stress to the other.

The most important consequence of stress, physical or mental, therefore, depends on the right interpretation of the situation.

The interpretation or judgment in the body is governed by chemical reactions and is controlled by the balance of autonomic balance system, which in turn is governed by the interaction of parasympathetic and sympathetic nervous systems.

During the phase of acute stress, when the sympathetic system is predominant, the heart rate and blood pressure increase and a person cannot take correct and decisive decision.

He or she is likely to make mistakes, which can often be detrimental to living. Sympathetic mode is basically the mode of flight or fight reactions of the body.

Right conscious-based decisions can only be taken in a state of relaxed mind when the intention is inserted in the field of consciousness. The relaxed state of the body is the parasympathetic mode, which is healing and is evident by reduction in heart rate, blood pressure and increase in the skin resistance. Most conscious-based decisions will be based on truthfulness, will be necessary and will bring happiness to both the persons and the surroundings.

The yogic lifestyle by which a person learns the dos and don'ts of living, does regular practice of correct postures, daily pranayama and practices regular withdrawal from the outer atmosphere, helps in preparing a state of physical and mental body state, which is more receptive for conscious-based decisions. Yoga Sutras of

Patanajali included them in his Ashtanga yoga as the processes of Yama, Niyama, Asanas, Pranayama and Pratyahara.

Prayers have no value when the mind is not at rest. All of us have participated in hundreds of mourning prayers with 2 minutes of silence. This prayer has no value if the 2 minutes of silence is not observed. If prayer is done without it the mind will remain restless and we will keep on thinking these 2 minutes are not over yet.

The process of silence does shift our awareness towards test and parasympathetic state and temporarily we get to be in contact with the memories of the departed soul and we pay homage to him or her. Today a large number of organizations are teaching the process of meditation but the same cannot be taught unless a person practices procedures by which the mind gets relaxed.

The eight limbs of Patanjali focus in detail about premeditation preparations and once that is learned one can go to the other three limbs which are Dharna, Dhyana and Samadhi.

Yoga asanas are different from exercises. They stimulate and stretch all or one of the seven charkas, autonomic plexuses, and ganglion and there located ductless endocrine glands. Also during a yogasana the mind is in the exercise and not wandering here and there.

While yogic exercises at rest are termed yoga asanas and the same yogic meditative exercises with activity are called traditional Indian dances. Western exercises and dances do not follow the principles of yoga. Many international studies have shown that over one-third of the people during their lifetime pray either for their own illness or for somebody else.

All hospitals should have spirituals areas. The prayer and meditation rooms in a hospital setting invariably will provide an arena which will improve patient-doctor relationship and will reduce the rising disputes amongst them in the country.



What Kind of Employee are You?

Employee "A" in a company walked up to his manager and asked what my job is for the day? The manager took "A" to the bank of a river and asked him to cross the river and reach the other side of the bank. "A" completed this task successfully and reported back to the manager about the completion of the task assigned. The manager smiled and said "GOOD JOB".

Next day Employee "B" reported to the same manager and asked him the job for the day. The manager assigned the same task as above to this person also. The Employee "B" before starting the task saw Employee "C" struggling in the river to reach the other side of the bank. He realized that "C" has the same task.

Now "B" not only crossed the river but also helped "C" to cross the river. "B" reported back to the manager and the manager smiled and said "VERY GOOD JOB".

The following day Employee "Q" reported to the same manager and asked him the job for the day. The manager assigned the same task again. Employee "Q" before starting the work did some home work and realized "A", "B" & "C" had all done this task before. He met them and understood how they performed. He realized that there is a need for a guide and training for doing this task. He first sat and wrote down the procedure for crossing the river; he documented the common mistakes people made, and tricks to do the task efficiently and effortlessly. Using the methodology he had written down, he crossed the river and reported back to the manager along with documented procedure and training material. The manager said "Q" you have done an "EXCELLENT JOB".

The following day Employee "O" reported to the manager and asked him the job for the day. The manager assigned the same task again. "O" studied the procedure written down by "Q" and sat and thought about the whole task. He realized that the company was spending lot of money in getting this task completed. He decided not to cross the river, but sat and designed and implemented a bridge across the river and went back to his manager and said, "You no longer need to

assign this task to any one". The manager smiled and said "Outstanding job 'O'. I am very proud of you."

What is the difference between A, B, Q & O?

Many a times in life we get tasks to be done at home, at office, at play.

Most of us end up doing what is expected out of us. Do we feel happy? Most probably yes. We would be often disappointed when the recognition is not meeting our expectation.

Let us compare ourselves with "B". Helping someone else with the problem often improves our own skills. There is an old proverb (I do not know the author) "learn to teach and teach to learn". From a company point of view "B" has demonstrated much better skills than "A" since one more task for the company is completed.

"Q" created knowledge base for the team. More often than not, we do the task assigned to us without checking history. Learning from other's mistake is the best way to improve efficiency. This knowledge creation for the team is of immense help. Re-usability reduces cost there by increases productivity of the team. "Q" demonstrated good "team-player" skills.

Now to the outstanding person, "O" made the task irrelevant; he created a Permanent Asset to the team.

If you notice B, Q and O all have demonstrated "team performance" over and above individual performance; they have also demonstrated a very invaluable characteristic known as "INITIATIVE".

Initiative pays off everywhere whether at work or at personal life. If you have initiative you will succeed. Initiative is a continual process and it never ends. This is because this year's achievement is next year's task. You cannot use the same success story every year. The story provides an instance of performance, whereas measurement needs to be spread across at least 6 to 12 months. Consequently performance should be consistent and evenly spread. Out-of-Box thinkers are always premium and that is what everyone constantly looks out for. Initiative, Out-of-Box thinking and commitment are the stepping stone to success.





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Lighter Side of Medicine

HUMOR A MATHEMATICIAN, A PHYSICIST AND AN ENGINEER

A mathematician, a physicist and an engineer were traveling through Scotland when they saw a black sheep through the window of the train.

"Aha," says the engineer, "I see that Scottish sheep are black."

"Hmm," says the physicist, "You mean that some Scottish sheep are black."

"No," says the mathematician, "All we know is that there is at least one sheep in Scotland, and that at least one side of that one sheep is black!"

FATHER IS A LAWYER...

While in Atlanta on vacation, Little Johnny's Daddy took one afternoon to see historic sites Downtown.

Two young families were also in line to see the sites. Little Johnny struck up a conversation with one of the boys in line.

"My name is Tommy. What's yours?" asked the first boy.

"Johnny".

"My Daddy's an accountant. What does your Pop do for a living?" asked Tommy.

Little Johnny replied, "My Daddy's a lawyer."

"Honest?" asked Tommy.

Johnny replied, "No, just the regular kind."

CONTACT LENS

The teenager lost a contact lens while playing basketball in his driveway. After a fruitless search, he told his mother the lens was nowhere to be found. Undaunted, she went outside and in a few minutes, returned with the lens in her hand.

"How did you manage to find it, Mom?" the teenager asked. "We weren't looking for the same thing," she replied. "You were looking for a small piece of plastic. I was looking for Rs. 150."

EXPERIMENT ON A DOG

Some scientists decided to do the following experiments on a dog.

For the first experiment, they cut one of the dog's legs off, and then they told the dog to walk. The dog got up and walked, so they learned that a dog could walk with just three legs.

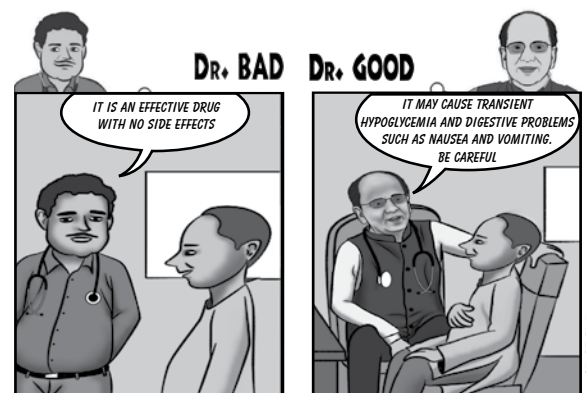
For the second experiment, they cut off a second leg from the dog, and then they told the dog once more to walk. The dog was still able to walk with only two legs.

For the third experiment, they cut off yet another leg from the dog and once more they told the dog to walk. However, the dog wasn't able to walk with only one leg.

As a result of these three experiments, the scientists wrote in their final report that the dog had lost its hearing after having three legs cut off.

Dr. Good and Dr. Bad

SITUATION: An individual with T1DM was prescribed pramlintide in addition to insulin therapy.



LESSON: Although the addition of pramlintide to insulin therapy improves glycemic control and reduces insulin requirement and body weight in patients with T1DM, its use is associated with transient hypoglycemia and digestive disorders.

Oncotarget. 2017;8(39):66504-15.

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Paintal AS. Impulses in vagal afferent fibres from specific pulmonary deflation receptors. The response of those receptors to phenylguanide, potato S-hydroxytryptamine and their role in respiratory and cardiovascular reflexes. Q. J. Expt. Physiol. 1955;40:89-111.

Books

Stansfield AG. Lymph Node Biopsy Interpretation Churchill Livingstone, New York 1985.

Articles in Books

Strong MS. Recurrent respiratory papillomatosis. In: Scott Brown's Otolaryngology. Paediatric Otolaryngology Evans JNG (Ed.), Butterworths, London 1987;6:466-470.

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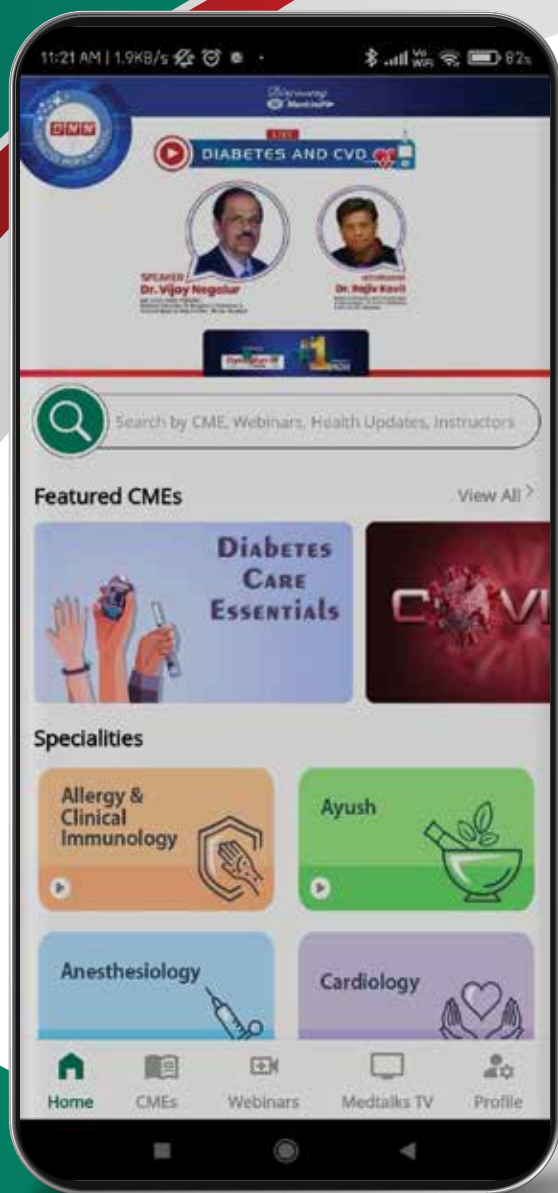
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