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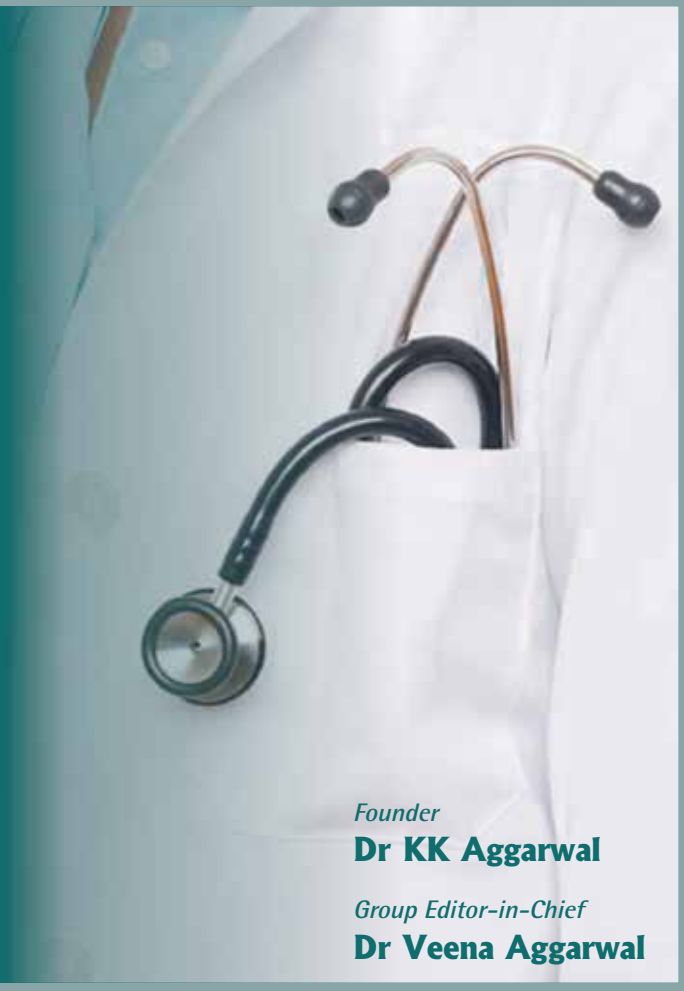

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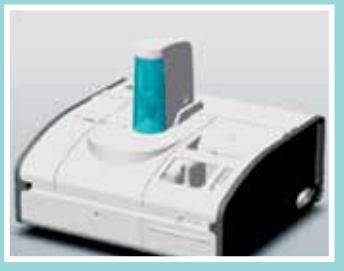

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IMA DMA NDB Meet on "COVID Update, Immune Signature of COVID-19, Treatment Strategies"

COVID UPDATE

- Cases in India are rising but hospitalizations are low. In the UK, 58% of cases were incidentally found cases.
- Coronavirus disease 2019 (COVID-19) *per se* is now behaving like any other virus and humans too are behaving immunologically as they would to any other virus.
- Singapore, Israel and UK, highly vaccinated countries, had the highest daily new confirmed cases per million people as of April 21, 2022. France had the highest number of COVID-19 patients in hospital with 24,894 admissions, followed by UK (17,748), Italy (10,289), US (9,964) as of April 16, 2022.
- In Delhi, the hospital bed occupancy is <1% and ICU admissions are <0.1%.
- Omicron has given robust natural immunity.
- We have to now start moving from infection to disease. The virus is going to find ways to evade immunity and the body will continue to find ways to deal with the virus.
- The daily new confirmed deaths per million people are quite low at 0.04.
- India is doing around 6,000 tests for every confirmed case. Whereas, the US is doing around 20 tests per one confirmed case, UK (13.4), Singapore (10.10), Israel (9.80) and Japan (2.60).
- The effective reproduction rate in the UK has been consistently going down to <1%. But in India, RR is steadily rising and has increased from 0.35 in February this year to 1.32 as of April 19, 2022.
- In the last week, Germany, South Korea, France, Italy and the US were reporting the maximum new infections each day, but they are now showing a decline.
- Europe is the lead driver of infection followed by Asia, US and Canada.
- Transparency in data reporting is important.
- In the UK, which is currently 12% of its peak and falling, even a nationwide lockdown did not prevent the Omicron surge. Despite opening up now, the numbers have not gone up.
- India is <1% of its peak. Despite no lockdown, the Omicron wave did not cross the Delta wave. The rising cases however merit a close watch.
- The US, which is at 5% of its peak, had a partial lockdown (local and in sectors, not nationwide) till very recently, yet made no difference to the waves.
- South Korea had nearly 90% of population vaccinated. India has vaccinated around 75% of its population, but in terms of number of people vaccinated, India is at the top.
- In India, the new cases and recoveries are following very close to each other. Currently the infected cases are less than 15k.

- The 7-day average in India showed a decline from mid-March to mid-April but is again showing a rising trend near the end of April.
- However, the numbers are still low considering the huge population, so no cause for panic yet. There is no indication of a sharp rise.

ABOUT VIRUSES

- Viruses are not always harmful; about 8% of our genome is viral in origin. They are obligate intracellular parasites as they need the host cell machinery to multiply.
- The immune response to any intracellular parasite is either Th1, Th2 or Th17 response. If the body does not recognize the pathogen, the response can be delayed, skewed, hyperinflammatory in terms of magnitude or persistence.
- The Th1 response is largely for intracellular bacteria or viruses and can result in organ specific autoimmunity such as Crohn's disease, *Helicobacter pylori* gastritis and acute renal transplant rejection. It is a phagocyte-mediated immune response.
- The Th2 response is for intestinal nematodes and results in strong antibody production, marked activation of eosinophils and inhibition of several functions of macrophages. It is a phagocyte independent immune response.
- Interleukin (IL)-12 and interferon (IFN)-alpha and gamma from macrophages and natural killer (NK) cells favor Th1 response.
- Early production of IL-4 by a still unidentified cell type favors Th2 response.
- Interferons are the key drivers to immune response to virus. They have several actions. They induce arginine vasopressin (AVP) production by host cells and degrade viral RNA leading to inhibition of viral protein synthesis. They activate NK cells leading to enhanced killing of infected cells by NK cells and enhance MHC expression by host cells leading to enhanced killing of infected cells by cytotoxic T cells (CTLs).
- In COVID, Th17 and Treg cell function is significantly altered.
- Immune response is an interplay of various T cells. There is significant increase in Th17 leading to increased expression of cytokines (IL-17, IL-23, retinoic acid receptor [RAR]-related orphan gamma) and decrease in T regs and also reduced expression of P3-FoxP3, IL-17 and transforming growth factor (TGF)-beta.
- The Th17/Treg and IL-17/IL-10 ratios are strongly predictive of pathology and decreased survival in COVID patients.
- Control inflammation by Day 3 and thrombo-inflammation definitely by Day 10.
- The immune signature of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) includes lymphopenia driven by decrease in T CD4 and CD8, immune imbalance, increased inflammatory cytokines, hyperinflammation, thrombosis. The disease can resolve or persist; the pathology can be local or systemic as seen in long COVID.
- Monitor C-reactive protein (CRP); if rising then act to reduce it. Early and aggressive treatment will improve outcomes.
- IL-6 is the main regulator molecule for all intracellular viruses and bacteria. It activates CTLs, Th1, Th17 cells which secrete perforins, granzyme and trigger release of cytokines leading to pro-inflammatory response.
- Cytokine-mediated hyperinflammation has been strongly correlated with reduced survival.
- IL-6 increases Th17 activity and reduces Treg activity. IL-6 is elevated in autoimmune diseases like rheumatoid arthritis.
- The increased number and function of Th17 cells drive hyperinflammation. They reduce the number and function of Tregs hampering the ability for anti-inflammation.
- Tregs are marked by increase in CD3, CD4, CD25 and low CD127 and Fox P3. Tregs induce immune tolerance and prevent autoimmune disease.
- Tregs are of two types: n (natural) and i (inducible).
- The nTregs develop in the thymus and protect against autoimmunity, while the iTregs develop outside the thymus and their differentiation depends upon contact with non-self antigen, IL-2 and TGF.
- Tregs inhibit activation of both innate and adaptive immune cells; they also inhibit maturation of antigen presenting cells (APCs), decrease available IL-62 and create a pool of memory cells for response at secondary challenge.
- The immune response to SARS-CoV-2 and mechanism of immunopathological changes in COVID-19 are thus driven by a balance between

IL-2, 6 and 17 and between T cells populations with Tregs.

- If the Th1 response can be controlled in 3 days and definitely within 10 days, the cytokine storm can be controlled.
- Early treatment prevents inflammation and progression to thromboinflammation.
- Control measures at population level are personal protection, risk stratification, isolation, vaccination and early detection.
- Fever can be managed with mefenamic acid, respiratory/nasal secretions by H1 block, bronchodilator; inflammation by nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, doxycycline, azithromycin; hyperinflammation by steroids, colchicine; thromboinflammation by aspirin, non-vitamin K antagonist oral anti-coagulants (NOACs) and antiplatelets; monoclonal antibodies by IL-2 and 6 and antivirals.
- Prevention is better than cure. If you want to dodge the bullet, control metabolic dysfunction, treat chronic diseases adequately, fortify mitochondrial health, get adequate good quality sleep, follow anti-inflammatory and vagal lifestyle and create health and wellness.

(*Excerpts from a presentation by Dr Nidhi Dhawan, April 24, 2022, Sunday*)

■■■■

FSSAI Faces Opposition Against its New Star Rating System

When the world is moving towards a healthy lifestyle, Food Safety and Standards Authority of India (FSSAI) has also decided to join in with their new star rating system for packaged food and beverages rather than warning the companies to label products based on ingredients.

Consumer Voice, People's Vigilance Committee, Consumer Unity & Trust Society (CUTS) and several other associations have decided to oppose this move stating that nutritional warnings on food packets are an "urgently required intervention" to protect public health. CUTS chief states that these new regulations are in favor of large food companies, not consumers. Also, the rating models are misleading as the healthier nutrients will cover up the unhealthy ingredient in the rating algorithm.

AIIMS briefed that the consumers prefer direct labeling to warn them about excess salt, sugar, and fats in the packaged food based on a study. Also, the consumers are ready to make healthier choices but star ratings will be difficult to comprehend. (*Source: https://health.economictimes.indiatimes.com/news/policy/fssais-new-star-rating-system-for-packaged-food-faces-a-revolt/90789563*)

Chronic Kidney Disease: A Burden on Public Healthcare Sector

The large disparity stills existing in our nation with our healthcare sector lauded globally along with a severe shortage in the number of healthcare professionals in rural areas, a fact that was brought to light during the emergency of the pandemic. Lifestyle changes and migration has led to a hike in noncommunicable disease with 50% of spending on in-patients which has increased the demand for specialized care.

As per a WHO report, 1 out of every 4 Indians is at the risk of dying from noncommunicable disease before reaching the age of 70. CKD is the sixth fastest-growing cause of death globally with expensive treatment options such as dialysis, and renal replacement being the major setback. The deaths reported due to kidney failure were greater in lower and middle socioeconomic groups in India.

According to a study, more than 60% of the patients had to travel more than 50 km to receive dialysis. The government has eased the situation by introducing the "National Dialysis Program" and setting up dialysis facilities in 688 districts to support the low socioeconomic groups. While fighting COVID-19, our healthcare sector is also building back by providing accessibility and availability to all and actively working to meet the UN's sustainable development goal to reduce premature mortality for noncommunicable diseases.

(*Source: https://health.economictimes.indiatimes.com/news/industry/public-health-challenge-of-chronic-kidney-disease/90789819*)

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Adrenal Advocacy: Focus on Addison's Disease

The adrenals are a pair of tiny glands, weighing just about 3 grams apiece. Yet these glands pack a powerful punch and are essential for life. Adrenal disorders encompass a wide spectrum of causative factors, clinical presentations, complications, comorbid conditions and concerns related to health. Adrenal medicine is not only relevant to clinical practice, but to public health[1] as well.

In this editorial, we discuss the various aspects of adrenal advocacy, with a focus on Addison's disease.

THE BURDEN OF DISEASE

Addison's disease or primary adrenal insufficiency, is an important, but often under diagnosed, disease. The reported prevalence varies up to 117 cases per million population.[2] This figure seems higher than what is experienced in Indian settings. Prof Kochupillai had calculated over 3 decades ago, a burden of 4 per million of primary adrenal disease related to tuberculosis (TB) in India.[3] Currently, we do not have any definitive estimates of nontubercular Addison's disease in our country. Secondary adrenal insufficiency because of the use of exogenous steroids and disorders of the pituitary is much more common in India. A survey of rural households in North Bihar suggested that 1 out of 3 people had been inappropriately prescribed steroids over a period of 6 months for minor ailments.[4] Studies from Kashmir have suggested a large burden of undiagnosed Sheehan's syndrome (postpartum pituitary dysfunction) among adult women.[5] A more recent study suggested that 14% of patients presenting to the hospital with euvolemic hyponatremia had undiagnosed adrenal insufficiency.[6]

CLINICAL IMPACT

Adrenal insufficiency is an important cause of morbidity (Table 1). Because of its subtle and myriad presentation, the condition often goes unrecognized. This is unfortunate, because this abnormality can be easily managed, in a cost-effective manner.

Adrenal insufficiency should be suspected in conditions such as TB, histoplasmosis, existing autoimmune disease and malignancy. It may coexist with other autoimmune

Table 1. Red Flags Raising Suspicious Adrenal Insufficiency

Symptoms
• Weakness, lack of energy
• Vomiting, nausea
• Darkening of skin, mucous membranes
• Weight loss
• Amenorrhea
Signs
• Hypotension
• Postural hypotension
• Hyperpigmentation of skin
Syndromes
• Tuberculosis, e.g., histoplasmosis, cryptococcosis
• Polyglandular, multiple endocrine neoplasia
• Hypopituitarism
Surrogate laboratory abnormalities
• Hypoglycemia
• Hyponatremia

endocrine diseases, and with other endocrine neoplasia. Sudden cessation of exogenous corticosteroid therapy, whether taken on prescription, or as part of so called "alternative" or over-the-counter medication, can also precipitate adrenal insufficiency.[4] Use of high-dose inhaled steroids or use of steroid-containing creams over large areas of diseased skin can also induce secondary adrenal insufficiency.

Electrolyte and metabolic conditions, such as unexplained euvolemic hyponatremia, recurrent hypoglycemia, hyperkalemia and hypotension, should prompt an evaluation of adrenal function.[5] Physicians must be aware of the common symptoms of adrenal insufficiency, including lethargy, anergy, weight loss and darkening of the skin and mucous membranes.

Sudden change in metabolic and endocrine status (for example, an unexplained reduction in dose requirement of glucose-lowering or blood pressure-lowering therapy) is a red flag that calls for adrenal health assessment. Refractory hypotension and/or hypoglycemia, with greater than- anticipated requirement of inotropes and/or glucose support is another sign of adrenal insufficiency.[6]

PUBLIC HEALTH IMPACT

Adrenal insufficiency is a condition, which deserves attention from a public health perspective as well. Misuse of steroids leading to Cushing's syndrome and sudden cessation of these drugs can precipitate adrenal insufficiency. This calls for steroid stewardship, which is defined as the systematic effort to prescribe and monitor glucocorticoids in a rational manner, while balancing benefit and potential risk in patients who require this therapy. Steroid stewardship includes pre-prescription screening, rational prescription, medical care during corticosteroid use and appropriate monitoring after corticosteroid use has been discontinued.[7]

Adrenal insufficiency is also part of congenital adrenal hyperplasia, which can present in various ways. Some individuals present with ambiguous genitalia and may overlap with "transgender" presentations. Transgender healthcare providers should be aware of the anatomic and physiologic impact of adrenal disorders.[8]

ADDISON'S DAY

29th May is observed as International Addison's Day every year. This event has been initiated by the Addison's Disease Self-Help Group, United Kingdom.[9] This is an effort to raise awareness about adrenal disease. The date has been chosen as it is the birthday of John F Kennedy, former US President who self-managed his adrenal insufficiency. This is a suitable platform to come together to support the cause of persons living with adrenal insufficiency.

ADVOCACY AND ACTION

There is a great need to advocate for adrenal health and to take action towards improving suspicion, screening, confirmation and clinical management of adrenal disorders.

Physicians and paramedical professionals should be made aware of the red flags that should prompt evaluation for adrenal insufficiency. Pharmacists must dispense corticosteroids with responsibility, and all cadres of healthcare professionals should own responsibility for steroid stewardship. Sick day rules should be explained and reinforced at each interaction with patients. Persons living with adrenal insufficiency must have continuous access to an emergency kit and their caregivers should be trained in its usage.

The pharmaceutical sector can contribute to adrenal advocacy by providing hydrocortisone, fludrocortisone and adrenocorticotropic hormone at economical rates. We note with pride that the Indian pharmaceutical industry has lived up to this responsibility and Indians have access to economical quality brands of adrenal hormones.[10]

THE WAY AHEAD

Adrenal advocacy is an integral part of health advocacy, and must be propagated at all possible platforms. All stakeholders involved in the diagnosis and care of persons with adrenal disorders should take up this responsibility. Endocrinologists and physicians should take leadership of this campaign, in equal partnership with persons living with adrenal disease, paramedical professionals and policymakers. Adrenal advocacy should be a concerted and continual process, with comprehensive coverage of the entire healthcare community.

Adrenal advocacy should address health policy makers and insurance payers, highlighting the essential nature of treatment for adrenal disease. It is heartening to note that adrenal hormone preparations are part of the World Health Organization Model List of Essential Medicines and the Indian National List of Essential Medicines.[11,12]

The Indian Journal of Clinical Practice hopes to contribute to this cause, through this and other communications. We invite readers to join us in our endeavor to enhance adrenal awareness in our country.

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Children's Development may be Affected by Parental Autoimmune Diseases

A meta-analytical study conducted by a French team links paternal/maternal autoimmune disease with a child's risk of developing a neurodevelopmental disorder such as autism and ADHD. According to the researchers, these connections may be initiated due to exposure to environmental factors such as exposure to pollutants, passive smoking, genetic predisposition, etc. They also proposed that a shared mechanism could be present between the parents and a child, though the maternal route seemed to be riskier.

The neurodevelopmental disorder is caused by a correlation of genes and environmental factors while autoimmune and anti-inflammatory disorders are caused due to activation of the immune system, the circulation of antibodies, cytokines, etc. Several studies have advocated the link between autoimmune disorders and maternal health. However, no data has been provided to indicate the influence of both the parents in a direct way, i.e., during pregnancy.

In the meta-analysis, 14 cases were included with 8.45 lakh mothers and 6 lakh fathers with an autoimmune disorder. Also, 4.98 lakh control mothers and 4.99 lakh control fathers were subjectively recruited. There were 1,82,927 children with neurodevelopmental disorders and 14,168,474 with no such diagnosis or disorder. The results showed that autoimmune diseases in mother and father were associated with a diagnosis of ASD and ADHD in children. Similarly, mothers diagnosed with type 1 diabetes, psoriasis and rheumatoid arthritis increased the risk of ASD and ADHD by the ratio of 1.6, 1.45, 1.38 and 1.36, 1.41, 1.32, respectively. On the other hand, fathers with type 1 diabetes had an increased ratio of ASD and ADHD by 1.42, 1.19 while psoriasis was linked to ADHD at a ratio of 1.18. (*Source: https://www.medscape.com/viewarticle/972960?src=*)

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ORIGINAL RESEARCH

A Study of Erectile Dysfunction in Male Diabetes Patients and its Correlation with Platelet-Lymphocyte Ratio

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ABSTRACT

Introduction: Erectile dysfunction (ED) constitutes a large burden on society given its high prevalence and impact on quality of life. Diabetes is a common cause of organic ED. Prevalence of ED in diabetes ranges from 35% to 85% depending on the study, versus 26% in general population. Platelet-lymphocyte ratio (PLR) has been detected as an important marker for inflammation. Some studies have identified its role in ED but more research is needed. **Material and methods:** It was a hospital-based prospective observational study. According to International Index of Erectile Function (IIEF)-5 questionnaire, patients were divided into 4 categories: mild ED with score 17 to 21, mild-to-moderate ED with score 12 to 16, moderate ED with score 8 to 11 and severe ED with score 1 to 7. Presence of ED and its severity was correlated with age, residence, duration of diabetes, glycemic status, lipid profile, PLR, complications, body mass index (BMI), etc. **Results:** Prevalence of ED in male diabetes patients was found to be 72.4%. Among 110 cases with ED, 8 had mild ED (7.2%), 27 had mild-to-moderate (24.5%), 27 had moderate ED (24.5%) and 48 had severe ED (43.6%). Prevalence of ED was found to be proportional to age. Majority of cases in ED group were those with long-standing diabetes. Correlation of ED with complication of diabetes, like nephropathy and retinopathy, was significant, whereas it was not significant with neuropathy. Significant correlation of ED was found with BMI and PLR. **Conclusion:** ED prevalence was high among the diabetes patients and it increased with age and duration of the disease. Presence of diabetic complications was significantly associated with ED. BMI was significantly associated with development of ED. PLR was significantly higher in ED group and closely related to severity of ED.

Keywords: Erectile dysfunction, diabetes, platelet-lymphocytic ratio

Erectile dysfunction (ED) is a medical problem characterized by getting or keeping an erection hard enough for satisfactory sexual performance.[1] The global prevalence of ED is estimated as 3% to 76.5%.[2] The screening tools used for ED in population-based studies are associated with discrepancies. Owing to its high prevalence and impact on quality of life, ED is a huge burden on the society. It is a risk factor for cardiovascular disease (CVD), dementia and all-cause mortality as well.[2]

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Age is a major determinant of occurrence of ED. It is estimated that men aged between 50 and 59 years have a 3.6-fold higher risk of developing ED in comparison with 18- to 29-year-olds. However, when it comes to men above 70 years of age, the risk escalates to be 6 to 7 times higher.[3]

Diabetes is a common cause of organic ED. The pathophysiology of diabetes-induced ED is multi-factorial. Both vascular and neurological mechanisms usually contribute in people with diabetes. Autonomic neuropathy has a key role to play in the high incidence of ED in diabetes patients.[4] Psychological factors also contribute to ED in diabetes. Some drugs that are frequently used in diabetes patients, such as psychotropic drugs (especially antidepressants), antihypertensive treatment (particularly β-adrenergic-blocker, thiazide diuretics and spironolactone) and certain fibrates have all been associated with drug-related ED.[5]

Prevalence of ED in diabetes ranges from 35% to 85% depending on the various studies, versus 26% in general

population. Onset of ED is usually seen 10 to 15 years earlier in men with diabetes compared to sex-matched counterparts without diabetes.[4,6]

In diabetes, ED is approximately 3.5-times more prevalent,[7] has greater severity and is less responsive to phosphodiesterase-5 (PDE5) inhibitors[8] than in men without diabetes.

In men with diabetes, the severity of ED increases with age, diabetes duration, poor glycemic control and the presence of micro- or macrovascular complications.[9]

Erectile dysfunction is now regarded as a major health problem for the increasingly healthy aging population. Despite ample evidence that ED is among the major complications in diabetes mellitus in men, its presence remains poorly evaluated in routine clinical practice.

The emergence and severity of ED are associated with inflammatory mediators and endothelial dysfunction.[10] No specific marker has been identified so far that could identifythis.

Platelet-lymphocyte ratio (PLR) has been detected as an important marker for inflammation. The normal PLR range in males is 36.63 to 149.[11] Some studies have identified its role in ED but it needs more research. PLR calculated from complete blood count is a simple, cheap and easily obtainable test.

India is a country where conversations about ED are often a taboo and left unspoken. ED is a problem that can impact the patient's quality of life and adversely affect his relationship with his partner. So, more and more research is needed in this area. India being considered the diabetes and impotence capital of the world, and due to lack of any blood parameter showing ED, this study was conducted to evaluate ED in male diabetes patients and its correlation with PLR. This will help us understand the importance of diabetes as a cause of ED and we can have a blood-based marker to detect ED.

MATERIAL AND METHODS

Study Design

Hospital-based prospective observational study.

Study Population

Male diabetes patients attending medical and endocrinology OPD as well as those admitted in these wards were enrolled in the study after taking informed consent.

Study Period

January 2021 to October 2021.

Inclusion Criteria

All male diabetes patients of age >18 years who were sexually active.

Exclusion Criteria

All patients suffering from ischemic heart disease, chronic kidney disease, any endocrine disorder, spinal cord injury, chronic debilitating disease, any inflammatory or hematologic disease to rule out other causes of leukocytosis and thrombocytopenia.

The prevalence period was 10 months and sampling took place over 4 days, randomly selected per month. Detailed history, general physical examination and systemic examination were done.

Patients were divided using International Index of Erectile Function (IIEF)-5 questionnaire into 4 categories: mild ED with score 17 to 21, mild-to-moderate ED with score 12 to 16, moderate ED with score 8 to 11 and severe ED with score 1 to 7. After this, blood investigations were done. Then, the presence of ED and its severity was correlated with age, duration of diabetes, glycemic status, lipid profile, PLR, complications, body mass index (BMI), etc.

OBSERVATIONS AND RESULTS

This study was done in Maharana Bhupal Hospital, Udaipur, Rajasthan, from January 2021 to October 2021. A total of 450 patients were screened, and 184 of them were eligible for the study after applying the exclusion criteria. Out of them, 152 were screened for ED as 32 of them either didn't give consent or didn't complete the questionnaire.

Out of 152 cases, 110 were found to have ED, whereas 42 had no ED. Therefore, prevalence of ED in male diabetes patients was found to be 72.4%. Among 110 cases with ED, 8 had mild ED (7.2%), 27 cases had mild-to-moderate (24.5%), 27 cases had moderate ED (24.5%) and 48 had severe ED (43.6%).

Table 1 depicts that in the ED group, maximum patients were in the elderly age group, i.e., >60 years (43.6%) and in the non-ED group, maximum patients were in the younger age group, i.e., ≤40 years (45.2%). Prevalence of ED in <40 years group was 40.6%, whereas in 51 to 60 years age group, it was 86.4% and in >60 years age group, it was 81.4%. P value was found to be significant. As age increased, risk of having ED increased.

Table 2 depicts that a majority of cases in ED group were those with long-standing diabetes, i.e., >10 years (40.9%), whereas non-ED group was formed mainly by cases with short history of diabetes, i.e., <5 years (54.8%). This correlation was found to be statistically significant (p = 0.018).

Table 3 depicts that 24 out of 110 ED (21.8%) cases had nephropathy as a complication, whereas in non-ED group only 3 out of 42 cases had nephropathy (7.1%). This correlation was found to be statistically significant (p = 0.034). Thirty-six out of 110 ED (32.7%) cases had neuropathy as a complication, whereas in non-ED group 9 out of 42 cases had neuropathy (21.4%). This correlation was not found to be statistically significant (p = 0.172). Fourteen out of 110 ED (12.7%) cases had retinopathy as a complication, whereas in non-ED group no case was found to have retinopathy (0.0%). This correlation was found to be statistically significant (p = 0.015). ED group had more cases with hypertension, i.e., 8.2%, while 7.1% in non-ED group had hypertension, but this correlation was not found to be significant (p = 0.832). ED group had more proportion of cases who were smokers, i.e., 25.5%, as opposed to non-ED group which had 21.4% of smokers, but this correlation was not found to be statistically significant (p = 0.605).

The proportion of patients who consumed alcohol was more in the ED group (20.9%), as opposed to non-ED group which had 9.5% of alcohol consumers, but this correlation was not found to be statistically significant (p = 0.101).

Table 4 shows the comparison of mean values of different biochemical and hematological parameters among ED and non-ED group. Correlation for absolute lymphocyte count (ALC), platelet count (PC), PLR and BMI was found to be statistically significant.

Table 5 shows the correlation of PLR and severity of ED. This correlation was found to be statistically significant (p = 0.003). As the severity increased, PLR values also increased.

Table 1. Distribution of ED with Respect to Age

Age (Years)	Non-ED N (%)	ED N (%)	Total N (%)	Prevalence (%)
≤40	19 (45.2)	13 (11.8)	32 (21.1)	40.6
41-50	7 (16.7)	17 (15.5)	24 (15.8)	70.8
51-60	5 (11.9)	32 (29.1)	37 (24.3)	86.4
>60	11 (26.2)	48 (43.6)	59 (38.8)	81.4
Total	**42 (100.0)**	**110 (100.0)**	**152 (100.0)**	**72.4**
P value				0.00

Table 2. Distribution of Groups According to Duration of Diabetes

Duration of diabetes (Years)	Non-ED N (%)	ED N (%)	Total N (%)
<5	23 (54.8)	34 (30.9)	57 (37.5)
5-10	10 (23.8)	31 (28.2)	41 (27.0)
>10	9 (21.4)	45 (40.9)	54 (35.5)
Total	**42 (100.0)**	**110 (100.0)**	**152 (100.0)**
P value			0.018

Table 3. Comparison on the Basis of Diabetic Complications, Hypertension and Substance Abuse

Variables	Non-ED (n = 42) N (%)	ED (n = 110) N (%)	Total (n = 152) N (%)	P value
Nephropathy				
Present	3 (7.1)	24 (21.8)	27 (17.8)	0.034
Absent	39 (92.9)	86 (78.2)	125 (82.2)	
Neuropathy				
Present	9 (21.4)	36 (32.7)	45 (29.6)	0.172
Absent	33 (78.6)	74 (67.3)	107 (70.4)	
Retinopathy				
Present	0 (0.0)	14 (12.7)	14 (9.2)	0.015
Absent	42 (100.0)	96 (87.3)	138 (90.8)	
Hypertension				
Present	3 (7.1)	9 (8.2)	12 (7.9)	0.832
Absent	39 (92.9)	101 (91.8)	140 (92.1)	
Smoking				
Present	9 (21.4)	28 (25.5)	37 (24.3)	0.605
Absent	33 (78.6)	82 (74.5)	115 (75.7)	
Alcohol intake				
Present	4 (9.5)	23 (20.9)	27 (17.8)	0.101
Absent	38 (90.5)	87 (79.1)	125 (82.2)	

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Table 4. Comparison on the Basis of Biochemical and Hematological Parameters

Parameter	Groups	Mean	SD	P value
TLC	Non-ED	8.6	2.6	0.131
	ED	9.4	3.0	
ALC	Non-ED	2.3	0.8	0.020
	ED	2.0	0.8	
PC	Non-ED	2.4	1.0	0.006
	ED	3.1	1.3	
PLR	Non-ED	122.1	68.2	0.003
	ED	166.9	87.4	
FBS	Non-ED	133.0	27.0	0.196
	ED	141.1	36.8	
PPBS	Non-ED	193.3	53.5	0.674
	ED	197.2	51.2	
HbA1c	Non-ED	8.5	2.5	0.057
	ED	9.6	3.2	
BMI	Non-ED	21.4	2.1	0.021
	ED	22.6	2.9	
TG	Non-ED	143.7	44.8	0.379
	ED	153.6	67.6	
LDL	Non-ED	105.3	41.9	0.560
	ED	110.7	53.2	
HDL	Non-ED	42.7	10.3	0.492
	ED	41.2	11.8	
TC	Non-ED	176.7	48.7	0.637
	ED	181.9	63.7	

TLC = Total leukocyte count; SD = Standard deviation; ALC = Absolute lymphocyte count; PC = Platelet count; PLR = Platelet-lymphocyte ratio; FBS = Fasting blood sugar; PPBS = Postprandial blood sugar; HbA1c = Glycated hemoglobin; BMI = Body mass index; TG = Triglyceride; LDL = Low-density lipoprotein; HDL = High-density lipoprotein; TC = Total cholesterol.

Table 5. Correlation of PLR and Severity of ED

Severity of ED	Mean PLR
Mild	124.6
Mild-to-moderate	144.1
Moderate	162.4
Severe	189.2
P value	0.003

DISCUSSION

In our study, we evaluated 152 male diabetes patients who satisfied inclusion and exclusion criteria. The prevalence of ED in these patients was found to be 72.4%. Garg et al[12] in their study of 50 male diabetes patients noted that ED was present in 39 (78%) patients. Sasayama et al[13] studied 6,112 Japanese male patients from 447 outpatient clinics and found that 81% had some degree of ED.

The differences in prevalence in different studies could be due to cultural differences in the perception and attitude towards ED among the studied populations. Variations in the methodology used in the studies could also account for the differences.

In our study, among 110 cases with ED, 7.2% had mild ED, 24.5% had mild-to-moderate ED, 24.5% cases had moderate ED and 43.6% had severe ED. Maximum cases had severe ED. Similar proportion of severity of ED was detected by Garg et al[12] in their study. They classified ED into 3 categories. Three patients (6%) had mild ED, 18 (36%) patients had moderate and another 18 (36%) patients had severe ED.

Among the socio-demographic variables, age was found to be statistically significant in our study. As age increased, risk of having ED increased.

Similar results were found by Garg et al[12] in their study, in which prevalence increased from 20% in age group of <40 years to 100% in 60 years age group. The effect of age on prevalence and severity of disease might be due to age-related changes occurring in the body and also various other complications that may coexist in diabetes patients.

Wing et al[14] documented that duration of diabetes increases the risk of ED, which was confirmed by the results of our study.

In our study, presence of complications in the form of nephropathy and retinopathy were significantly associated with ED but no such significance was found between neuropathy and ED.

These results were similar to those reported by Garg et al[12] as they found that retinopathy and neuropathy was significantly associated with ED but no such significance was found between nephropathy and ED.

Hypertension was found to be associated with ED in the present study but results were not statistically significant. In contrast, statistically significant results were reported by Al-Hunayan et al.[15]

For smoking and alcohol intake, no statistical significance was found in the present study. However, statistically significant results were reported by Al-Hunayan et al for smoking.[15] This study also showed that glycemic control, as assessed by fasting blood sugar (FBS), postprandial blood sugar (PPBS) and glycated hemoglobin (HbA1c)

level, was not significantly associated with ED in men with diabetes. In contrast, glycemic control was reported to be significantly associated with ED severity in a study by Cho et al.[16]

In our study, no significant correlation was found between dyslipidemia and ED. In contrast, Garg et al[12] reported in their study that mean lipid values (triglyceride [TG], low-density lipoprotein [LDL], high-density lipoprotein [HDL]) were significantly higher in patients with ED as compared to those without ED.

In our study, mean BMI in non-ED group was significantly associated with ED. This was supported by the study by Pizzol et al,[17] but this was not in line with the finding of the study by Garg et al[12] in which BMI was not significantly associated with ED.

Among biochemical parameters, statistically significant correlation was found for absolute lymphocyte count, platelet count and PLR. Mean PLR value was high in ED group. As the severity increased, PLR values also increased. This was confirmed in a study by Akbas et al[18] in which PLR values increased basedon the severity of ED.

CONCLUSION

ED prevalence was high among men with diabetes and it increased with age and duration of the disease. Presence of diabetic complications was significantly associated with ED.

BMI was significantly associated with the development of ED; therefore, lifestyle modification should be recommended to all patients.

This study shows that PLR is higher in patients with ED than men without ED and is also associated with severity of ED. It appears that PLR and other inflammatory markers might play a role in the identification of patients with ED and developing a treatment approach.

ED in men with diabetes is likely to become a more serious problem in the future with the rapidly increasing prevalence and earlier onset of diabetes. We recommend screening of all men with diabetes for ED since it is a neglected medical problem and also a culturally sensitive matter.

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1. Kalra S, et al. Indian Journal of Clinical Practice. 2022; 32 (12): 2 - 6. **HCTZ** = Hydrochlorothiazide.

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REVIEW ARTICLE

Losartan: Benefits Beyond Hypertension

SANJAY KALRA*, PRABHU KASTURE†, VIKAS MAKKAR‡

ABSTRACT

Losartan was the first angiotensin AT1 receptor blocker (ARB) approved by US Food and Drug Administration (FDA) for the treatment of hypertension. In addition to its established antihypertensive and end organ effects, several benefits of losartan beyond its antihypertensive effect have been demonstrated in clinical trials. Apart from its class effects of ARBs, losartan has pharmacokinetic and pharmacodynamic properties that are unique to it. It has shown considerable benefits as uricosuric agent, in erectile dysfunction and in prevention of stroke in hypertension patients with left ventricular hypertrophy. This review presents the benefits of losartan beyond being a hypertensive agent and associated clinical outcomes.

Keywords: Losartan, ARB, erectile dysfunction, uricosuric agent, hypertensive

The first angiotensin receptor blocker (ARB) approved by Food and Drug Administration (FDA) in 1995 as an antihypertensive drug was losartan. It is one of the most studied ARBs supported by over 1,000 clinical trials. It was the first clinically used drug and has made significant contributions to the understanding of angiotensin II in the kidney and the advantages of inhibiting angiotensin II at the AT1 receptor. Current evidence support its usage beyond the class effects of losartan, which are unique including its effect on uricosuria, thrombosis and erectile dysfunction (ED).[1]

This review will present an overview of these benefits of losartan and its place in hypertension therapy.

PHARMACOKINETICS

Losartan is a nonpeptide molecule, a competitive antagonist with selective binding to AT1 receptors. With an oral bioavailability of 33%, it has significant first-pass metabolism using the cytochrome P450 enzymes. The active metabolites are 10 to 40 times more potent by weight than the parent molecule and are reversible, noncompetitive inhibitors of the AT1 receptor. Forty percent of losartan is eliminated in urine and 60% in feces. The half-life of losartan is 2 hours, while the terminal half-life of the metabolites is longer, 6 to 9 hours.[1] Losartan is primarily metabolized by P450 in the liver. Few side effects of losartan have been reported in clinical trials, and it has a low risk of interaction with other drugs.[2-5]

MECHANISM OF ACTION

Losartan is a selective and competitive angiotensin II receptor inhibitor at the AT1 receptor site, leading to a compensatory rise of renin and angiotensin I levels. It binds with high affinity to the AT1 receptor and is more than 10,000 times more selective for the AT1 receptor than the AT2 receptor.[6]

It blocks angiotensin II-induced vasopressin release (reduces the excretion and absorption process of the kidney), adrenal catecholamine release (reduces the response to physical and emotional stress) and in turn, affects the rapid and slow-pressor response (reflex for a hike or dropping of blood pressure [BP]) by vasodilation or vasoconstriction, thirst, cell growth and multiplication (cellular hypertrophy and hyperplasia), reduces reaction time in case of stimuli (noradrenergic neurotransmission) and decrease the pumping speed of heart muscles (sympathetic tone increase) further lowering BP and reducing supply of oxygenated blood to different parts of the body.[6]

It also blocks the angiotensin II-induced vasoconstriction and action of aldosterone, which eventually reduces BP.

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Compared to angiotensin-converting enzyme (ACE) inhibitors, angiotensin II-receptor inhibitors effectively inhibit the renin-angiotensin system, not affecting the response to bradykinin.[6]

LOSARTAN INDICATIONS

Losartan received FDA approval for hypertension treatment either as monotherapy or in combination with other antihypertensive agents. Patients, who had both hypertension and left ventricular hypertrophy (LVH), are given losartan to reduce the risk of stroke. It is also indicated in patient with hypertension and coexisting type 2 diabetes with diabetic nephropathy and increased serum creatinine and proteinuria to reduce the occurrence of doubling of serum creatinine or end-stage renal disease (ESRD). However, losartan has shown a multitude of benefits beyond these FDA-approved indications.[1]

The LOAT (LOsartan vs ATenolol) study conducted on patients with Marfan syndrome demonstrated losartan to be a useful, low-risk alternative to beta-blockers in the long-term management of these patients.[7] The PREVER-treatment study showed that treatment with losartan as a first-drug regimen was equivalent to diuretics in reducing BP and resulted in a favorable left ventricular (LV) remodeling.[8] The COMPAS-BPV study showed that the BP-lowering effect of the office visit-to-visit standard deviation of systolic BP was similar between losartan and amlodipine.[9]

Results of Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial showed that when compared with atenolol, losartan is superior to atenolol for treatment of patients with isolated systolic hypertension and electrocardiographically documented left ventricular hypertrophy (ECG-LVH).[10] Losartan prevents more cardiovascular (CV) morbidity and death for a similar reduction in BP and is better tolerated. Losartan also confers benefits beyond reduction in BP.[11] Losartan was more effective than atenolol in reducing CV morbidity and mortality from all causes in patients with hypertension, diabetes and LVH.[12]

In the LIFE study, it was seen that losartan-based therapy led to significant cerebrovascular benefit compared with conventional therapy among hypertensive patients with LVH across the spectrum of CV risk. There were fewer strokes in the losartan groups for almost all levels of stroke severity and the effect was consistently seen in all clinical subgroups except for those delineated by age and ethnicity.[13,14]

Losartan along with valsartan and candesartan are indicated for the second-line treatment of heart failure in those cases where ACE inhibitors are not tolerated. The results of the Evaluation of Losartan In The Elderly (ELITE) I and II trials have demonstrated that treatment with losartan was similar to that with captopril in terms of all-cause mortality, sudden death or resuscitated arrests as well as New York Heart Association (NYHA) class improvement.[15]

BENEFITS BEYOND HYPERTENSION

Uricosuric Benefits of Losartan

High serum uric acid levels and chronic kidney disease (CKD) are risk factors for CV events.[16] Hypertension and proteinuria have been constant factors in progressive CKD and the use of drugs such as ACE inhibitors and/or ARBs with or without diuretics or low-sodium diets lead to an improvement in kidney outcome in adults and children, and adolescents with CKD. In this context, the uricosuric effects of losartan in adults and children, and adolescents with CKD become important. Studies have shown that losartan is the only drug amongst other ARBs and ACE inhibitors that lowers serum uric acid in adults.[17,18]

Uric acid has demonstrated a critical role in the pathogenesis of hypertension and kidney disease progression. The pathophysiological mechanisms involved in the pathogenesis include renin-angiotensin-aldosterone system (RAAS) upregulation, kidney afferent arteriopathy, endothelial dysfunction, oxidative stress and systemic inflammation. It has been seen in several cross-sectional studies that hyperuricemia is present in many individuals with untreated essential hypertension, and serum uric acid are associated with prehypertension.[19]

Uricosuric agents increase the urinary excretion of uric acid, thus reducing serum uric acid levels. ARBs have been studied for their potential to inhibit urate transporter 1 (URAT1) and residual uricosuric effects.[20,21] However, there is lack of inhibitory effect of candesartan, olmesartan and valsartan on URAT1. Telmisartan has no clinically evident uricosuric effect.[15]

Whereas in a double-blind study comparing losartan with placebo, it was shown that losartan conferred significant renal benefits in patients with type 2 diabetes and nephropathy and it was generally well-tolerated. It reduced the occurrence of a doubling of the serum creatinine concentration and ESRD but did not affect the rate of death. These benefits exceeded those attributable to changes in BP.[22]

The results of the Japan Hypertension Evaluation with Angiotensin II Antagonist Losartan Therapy (J-HEALTH)

study have shown that losartan-based antihypertensive treatment increases the estimated glomerular filtration rate (eGFR) and decreases BP, proteinuria and serum uric acid. It is known that hyperuricemia is a major contributor to increased CV risks in early-stage CKD. Thus, an early reduction of proteinuria and serum uric acid is predictive of future improvement of renal function which in turn has a considerable effect on the occurrence of CV events, especially in CKD patients.[16] Losartan has been known to increase the excretion of uric acid and reduce the serum uric acid levels in both healthy and hypertensive individuals an effect not seen by other ARBs.[15]

Studies have shown that losartan exhibits statistically significant lowering of serum uric acid levels or increase in fractional excretion of uric acid; however, no other ARB showed statistical benefit. Losartan is the only ARB that has consistently demonstrated a significant reduction in serum uric acid levels, and appears to be a safe and efficacious agent to reduce serum uric acid levels in patients with hyperuricemia.[21] Compared with irbesartan and candesartan, losartan significantly reduced serum uric acid levels in hypertensive patients with hyperuricemia and gout.[21,23] Another study comparing candesartan with losartan showed that while both the drugs reduced BP, only losartan showed an effect in reducing uric acid.[24]

Combination therapy of losartan with antihyperuricemic agents significantly decreased serum uric acid and increased uric acid clearance and 24-hour urinary uric acid excretion.[25]

It is shown that increased serum uric acid concentration is an independent risk factor for ESRD. Treatment with losartan reduces serum uric acid compared with placebo treatment in patients with type 2 diabetes mellitus and nephropathy. In a post hoc analysis of 1,342 patients with type 2 diabetes mellitus and nephropathy, it was seen that the degree of reduction in serum uric acid is eventually associated with the degree in long-term renal risk reduction and explains part of losartan's renoprotective effect.[26]

In a post hoc analysis of a prospective study conducted in children with proteinuria, it was seen that losartan provided long-term beneficial effects on serum uric acid and eGFR.[17]

In a double-blind randomized placebo-controlled trial in anuric or oliguric patients with calcular obstruction of a solitary kidney, losartan treatment contributed to renal function recoverability after relief of calcular obstruction of the solitary kidney.[27]

Losartan in CKD

Hyperuricemia has been related to hypertension, diabetes, CV and kidney disease in adults. Increased serum uric acid is commonly seen in patients with CKD due to declining GFR and resultant uric acid retention. Recent years have demonstrated that hyperuricemia is also a contributing factor for both the development and progression of CKD in adults.[17]

The results of Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study showed that losartan was more effective compared to placebo in protecting against the progression of nephropathy due to type 2 diabetes, despite the presence of hypertension in the study participants. The study showed that losartan conferred significant renal benefits in patients with type 2 diabetes and nephropathy and was well-tolerated in the patients. When compared with a placebo, losartan given as adjunct to conventional antihypertensive treatment reduced the risk of the ESRD by 28% and reduced the level of urinary protein excretion by 35% in patients with coexistent diabetic nephropathy in RENAAL study.[22]

Effect on Erectile Dysfunction

Impaired erectile function in men occurs as a part of metabolic disturbance and as a sequela of chronic use of few antihypertensive therapies. Results of a prospective interventional study have shown that in men with uncontrolled hypertension (BP ≥140/90 mmHg), losartan improved erectile function and both satisfaction and frequency of sexual activity. Since side effects impact the management of hypertension, an additional benefit of losartan therapy is its positive influence on the quality of life.[28]

A clinical trial conducted on diabetic patients with ED showed that losartan is effective and well-tolerated in diabetic ED, particularly in mild-to-moderate ones. Losartan use led to a significant improvement in the mean International Index of Erectile Function (IIEF-5) score, the percentage of successful penetration, and the successful intercourse completions. Treatment with losartan is related to improved erectile function, sexual satisfaction and frequency of sexual activity in hypertensive patients.[29]

Another study showed that angiotensin II activation may be the causative link in apoptosis and fibrosis of the corpus cavernosum through Smad and non-Smad pathways, leading to corporal fibrosis and corporal veno-occlusive dysfunction (CVOD) and ED. Losartan treatment greatly improved the histological and

molecular changes and CVOD compared with sildenafil with a modest effect on ED.[30]

However, telmisartan did not show any improvement or worsening of ED as seen in the ONTARGET/TRANSCENDT studies.[31]

Effect on Sleep

It is known that sleep disturbance is a common issue at high altitudes, caused due to abnormal ventilatory responses whilst sleeping. The results of a study suggested that peripheral chemoreceptor hypersensitivity is mostly driven by AT1 receptors. It was observed that angiotensin II blockade by losartan reduced the impact of high-altitude exposure on sleep physiology measured by actigraphy. Losartan can thus offer additional benefits in providing protection for high-altitude sleep disturbance.[32]

PLACE OF THERAPY OF LOSARTAN IN HYPERTENSION

- **Hypertension:** First-line therapy with thiazide diuretics.
- **Diabetic nephropathy:** First-line therapy in patients with type 2 diabetes mellitus and hypertension.
- **Patients with higher uric acid levels:** ARB of choice.
- **Hypertension with LVH:** Losartan reduces the risk of stroke.
- **Hypertension in patients with ED:** First choice drug.

CONCLUSION

Losartan is the first ARB to be approved by FDA for use in several conditions including hypertension and diabetic nephropathy. It is renoprotective, reduces increased serum uric acid and improves ED. It is the first-line of therapy in hypertension and has renoprotective benefits in patients with diabetic nephropathy.

As seen in the results of several trials, losartan has been indicated for the treatment of diabetic nephropathy and should be considered as the ARB of choice in these patients. Losartan also has an additional benefit of reducing the risk of ESRD when given with traditional antihypertensive treatment. In patients with higher uric acid levels, losartan should be considered as the ARB of choice. Owing to its exclusive action on uric acid as compared with other ARBs, it can be the choice of therapy in patients with high uric acid levels.

Losartan is one of the most investigated ARBs in patients with ED along with valsartan and irbesartan. Treatment with losartan has established effects on improving ED, sexual satisfaction and frequency of sexual activity in hypertensive patients. Losartan given alone or in combination with tadalafil is known to have a significant improvement in ED in diabetic patients, those with mild-to-moderate ED benefiting the most from losartan use. On the other hand, telmisartan did not have any significant effect on ED. Based on the existing clinical evidence, losartan is preferred as the first-choice antihypertensive agent in hypertension patients with ED, hyperuricemia, CKD and LVH.

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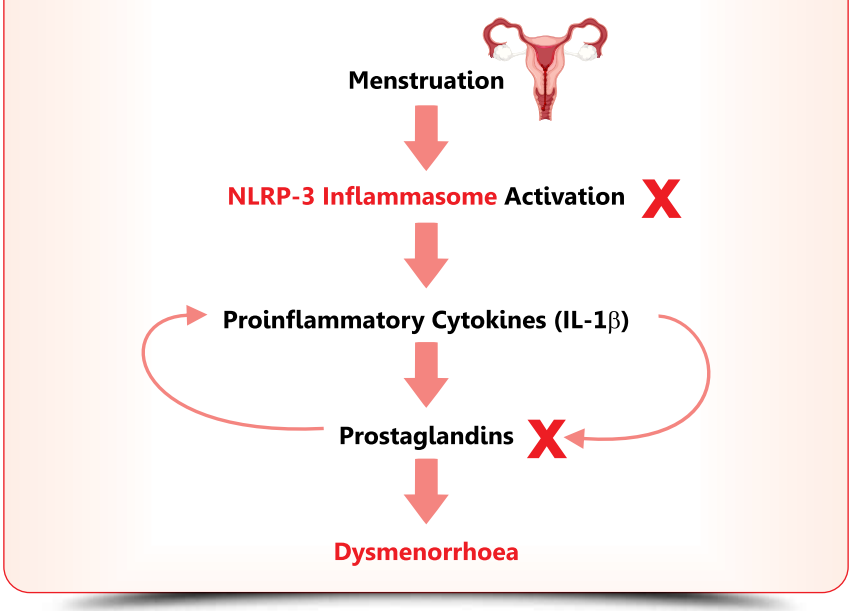

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REVIEW ARTICLE

NLRP3 Inflammasome in the Pathogenesis of Dysmenorrhea and Role of Mefenamic Acid as its Inhibitor

JAYAM KANNAN*, SUNITA CHANDRA†, KAMINI RAO‡, PRABHU KASTURE#

ABSTRACT

While the role of prostaglandin as a trigger in dysmenorrhea is well known, not many are aware that inflammation and nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome are also implicated in primary dysmenorrhea (PD). Inhibition of NLRP3 inflammasome and inflammation pathways is an important approach to treating dysmenorrhea and also the symptoms of premenstrual syndrome. Mefenamic acid is an effective and selective inhibitor of the NLRP3 inflammasome, which can be considered the most important option for PD treatment owing to its action via various pathways. In this article, the authors have reviewed the role of inflammation and NLRP3 inflammasome in causing PD, how inhibitors of NLRP3 inflammasome can treat dysmenorrhea and the mechanism of action of mefenamic acid as NLRP3 inflammasome inhibitor and its role in PD.

Keywords: NLRP3 inflammasome, primary dysmenorrhea, inflammation, mefenamic acid

Primary dysmenorrhea (PD) is a common gynecological problem among young women of reproductive age group. It constitutes functional dysmenorrhea without a specific gynecological pathological origin and has a severe effect on all aspects of the lives, work and study of female patients. Currently, prostaglandin secretion is proposed to be the trigger for PD.[1] It has also been reported that inflammation has a potent effect on the pathological process of PD. As a core part of inflammation, the nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome is involved in several acute and chronic diseases including dysmenorrhea.[2]

In this article, the role of NLRP3 inflammasome in causing primary dysmenorrheic pain and its inhibition as a potential target for treating dysmenorrhea is explored. Mefenamic acid is known to have the NLRP3 inflammasome inhibitory action in addition to its prostaglandin inhibitory action and this may help further augment its anti-inflammatory action.

THE NLRP3 INFLAMMASOME

Excess of inflammation is known to worsen many diseases and is often linked to the aberrant activation of the NLRP3 inflammasome. NLRP3 is usually found in cells of the innate immune system such as macrophages where it responds to danger in the form of pathogen or damage-associated molecular patterns (PAMPs or DAMPs), respectively. In response to external unfavorable stimulus, NLRP3 interacts with an adaptor protein leading to an activating platform for the protease caspase-1. Caspase-1 cleaves pro-inflammatory cytokine precursors pro-interleukin (IL)-18 and pro-IL-1β into active forms secreted from the cell. It also cleaves the pore-forming protein gasdermin D which eventually forms membrane pores causing pyroptotic cell death.[3]

MENSTRUATION AS AN INFLAMMATORY EVENT AND NLRP3 INFLAMMASOME INVOLVEMENT

Menstruation is a self-inflammatory process leading to the shedding of the functional layer of the endometrium

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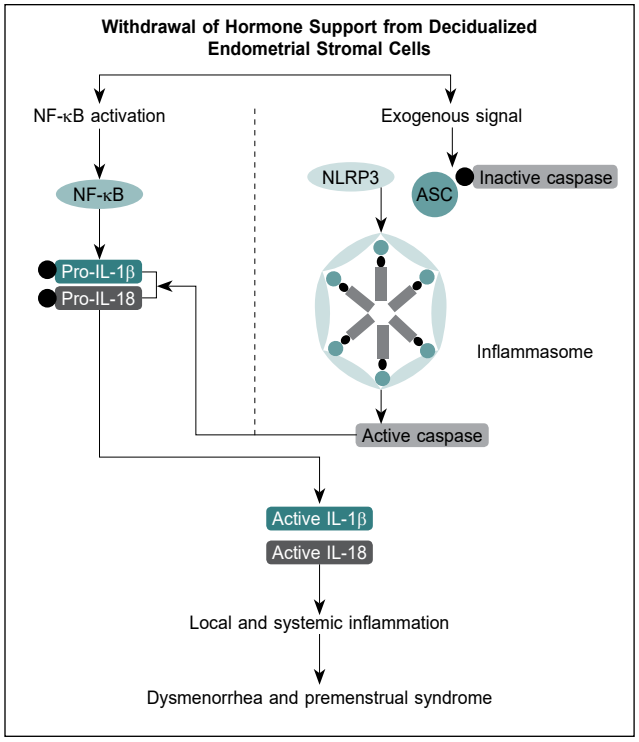

Figure 1. Pathways involving NLRP3 inflammasome leading to PD.

at the end of a nonconception cycle. Several significant changes in endometrial function occur through the entire menstrual cycle including spontaneous hormone-mediated terminal differentiation of endometrial stromal cells and decidualization. The shedding of these cells is critical for the preparation of new conception cycle. Hence, these decidualized cells play a key role in detecting hormone withdrawal at the end of a non-conception cycle, intervening local inflammation within the endometrium.[4] Figure 1 shows the pathways involvig NLRP3 inflammasome leading to PD.

Menstruation event is related to the activation of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), local release of chemokines and cytokines and inflammatory leukocyte influx. Systemically, chemokines and cytokines fluctuate across the menstrual cycle.[4]

It has been noted that NLRP3 inflammasome components immunolocalize to decidualized endometrial stromal cells immediately before menstruation. *In vitro* model of menstruation has also given evidence of the activation of NLRP3 inflammasome.[4]

Besides, there is evidence suggesting that the NLRP3 inflammasome plays a regulatory role in the expression of cyclooxygenase-2 (COX-2) via the NF-κB pathway. Studies have shown that NLRP3 inflammasome can be activated and expressed in PD.[2]

In addition, serum C-reactive protein (CRP) is an important marker of inflammation. With the resolution of inflammation or tissue damage, the CRP concentration reduces. It has been seen that IL-6 acts as the primary inducer of CRP gene expression, with IL-1β further augmenting the effect.[5]

Prostaglandins are a major factor causing the increased abnormal uterine activity. During menstruation, prostaglandin F2α (PGF2α) and prostaglandin E2 (PGE2) stimulate prolonged uterine contractions that reduce blood flow resulting in uterine ischemia.[1] Additionally, prostaglandins also modulate various steps of inflammation thereby coordinating the entire process in both pro-inflammatory and anti-inflammatory directions. PGE2 and its receptors regulate the production of inflammatory cytokines such as IL-1β, IL-6 and monocyte chemotactic protein-1.[6]

Prior to menstruation, endometrial tissue acquires the features of inflammation, red and edematous. Endometrial edema results from the high localized production of chemokines IL-8, pro-inflammatory cytokines such as IL-1, IL-6, tumor necrosis factor (TNF)-α and leukocyte inflow. These pro-inflammatory cytokines are responsible for upregulating inflammatory responses. These mediators also trigger the synthesis or release of prostaglandins causing excessive contraction of the uterine muscle, which leads to ischemic pain of PD. It has been reported that the level of IL-6 and TNF-α is higher in the plasma of women with dysmenorrhea compared to those without menstrual disorders.[7]

INHIBITOR OF THE NLRP3 INFLAMMASOME

As we have seen that inflammation underpins menstrual disorders such as dysmenorrhea; thus, targeting inflammatory pathways is a potential approach to ameliorate or reduce menstrual associated pain and general consequences of inflammation including the cluster of symptoms referred to as 'premenstrual syndrome'.[4]

In animal model study, that a molecule inhibiting NLRP3 activation led to a marked alleviation of the pain and pathological damage in PD. It was seen that the molecule inhibited the activation of NLRP3 inflammasome in uterine tissues of mice with PD and also inhibited production of prostaglandin in uterine tissues of mice with PD.[2]

MEFENAMIC ACID AS NRLP3 INFLAMMASOME INHIBITORS AND ITS ROLE IN PD

Current evidence suggests that mefenamic acid, a fenamate, is an effective and selective inhibitor of

the NLRP3 inflammasome by inhibiting the volume-regulated anion channel, an action independent of the COX inhibition.[8] Besides, the transient receptor potential melastatin 2 (TRPM2) is a plasma membrane cation channel through which the influx of extracellular calcium occurs. Activation of TRPM2 channel increases the activity of NLRP3 and IL secretions, aggravating the inflammation and cytokine release. Mefenamic acid inhibits the TRPM2 channels and reduces the calcium influx, which in turn blocks the NLRP3 inflammasome.[9]

It is known that NLRP3 mediates IL-1β secretion responsible for several inflammatory responses. The NLRP3 inhibitory action of mefenamic acid thus attenuates the pro-inflammatory cytokine (IL-1β) levels.[9]

The mainstay of treatment for dysmenorrhea, mefenamic acid offers complete relief of all the symptoms of dysmenorrhea in patients by exhibiting its actions via various pathways including COX-2 inhibition, bradykinin antagonism, inhibition of uterine contractility triggered by, prostaglandin-endoperoxide analogs, reduction of the high uterine resting tone and the frequency of contractions.[1,10] With its additional activity in inhibiting NLRP3, mefenamic acid is an ideal treatment in conditions with dysregulated NLRP3 inflammasome such as PD.

Mefenamic acid provides significant protection against increased levels of TNF-α and IL-1β. The use of mefenamic acid has previously been shown to reduce the CRP levels reflecting its significant anti-inflammatory activity.[5]

CONCLUSION

It is a well-established fact that menstruation is a self-inflammatory process. Apart from prostaglandins and other mediators like bradykinin, histamine and acetylcholine, etc. NLRP3 activation leads to expression of pro-inflammatory cytokines like IL-1β, which play prominent role in the underlying inflammatory process in dysmenorrhea. The inhibition of NLRP3 will help in easing the excess inflammation in PD and associated premenstrual symptoms. Mefenamic acid is an effective and selective inhibitor of NLRP3 inflammasome that acts by blocking the volume-regulated anion channel and TRPM2, a pathway acting independently of COX inhibition. By inhibiting NLRP3 inflammasome, mefenamic acid minimizes the formation of pro-inflammatory cytokine, IL-1β levels. Well-established safety and efficacy, and its action through multiple pathways including COX inhibition, bradykinin antagonism, inhibition of uterine contractility, reduction of CRP levels and NLRP3 inhibition makes mefenamic acid an ideal option to treat dysmenorrhea.

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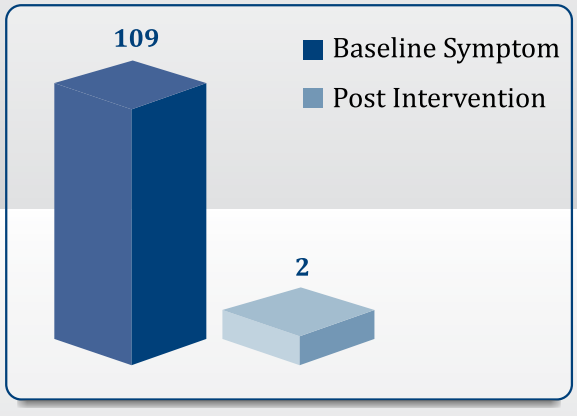

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CLINICAL STUDY

Safety and Efficacy of Paracetamol + Lignocaine Injection in Patients with High-grade Fever: A Prospective Analysis

ABHIJIT NEOG*, DEEPAK BHANDARI†, PIYUSH A PATEL‡, PARVEZ HASHMI#, JITENDRA MORE¥, ARUN MISHRA£, ILIAS ALI§, POOJA S BANERJEE^

ABSTRACT

Paracetamol is frequently used as an analgesic and antipyretic across the world. However, there is no data on Indian patients regarding the safety and efficacy of paracetamol + lignocaine injection in patients with high-grade fever. Hence, a prospective analysis was conducted to assess the safety and efficacy of paracetamol and lignocaine injection in patients with high-grade fever and mild-to-moderate body pain. The study is a real-world prospective study. The results showed that following intervention with paracetamol and lignocaine injection, 98% patients showed resolution of fever and 58% patients showed improvement in pain symptoms. The authors suggest that clinicians should consider paracetamol and lignocaine injection in patients with high-grade fever and associated pain and discomfort.

Keywords: Paracetamol, paracetamol + lignocaine injection, high-grade fever

The febrile response is a complicated event involving several immunologic and physiologic pathways. It is the most frequently observed physical sign in critically ill patients related to systematic inflammatory response syndrome or infections.[1] Antipyretics are commonly employed in patients with fever. Among the antipyretics, paracetamol is one of the most commonly used synthetic, nonopioid and centrally acting drug. It acts by inhibiting the cyclooxygenase-3 and the prostaglandin synthesis, within the central nervous system, leading to resetting of the hypothalamic heat-regulation center.[2]

Paracetamol is used to lower temperature in patients with fever as untreated fever places additional physiological stress on patients who are already ill.[3] While paracetamol is approved for the treatment of pain and fever in several countries worldwide, there is not enough real-world data on Indian patients regarding the effect of intravenous (IV) paracetamol given in combination with lignocaine in patients with high-grade fever. Such data would help clinicians in making informed decisions about the use of paracetamol-lignocaine combination in their patients. Hence, a prospective study was conducted among patients suffering from high-grade fever and mild-to-moderate body pain to assess and establish the safety and efficacy of IV paracetamol + lignocaine combination in high-grade fever patients.

METHODS

The study is a real-world prospective study to assess the efficacy of IV paracetamol + lignocaine combination and the occurrence of adverse events in patients with high-grade fever and pain. All patients with high-grade fever (>102°F) and mild-to-moderate body pain, aged 18 years or above, and those willing to give feedback were included in the study. Any patient with other serious ailments such as acquired immunodeficiency syndrome (AIDS), cancer, renal or hepatic dysfunction were excluded from the study. After the patients were enrolled for the study, preliminary body temperature reading was taken, and associated symptoms, if

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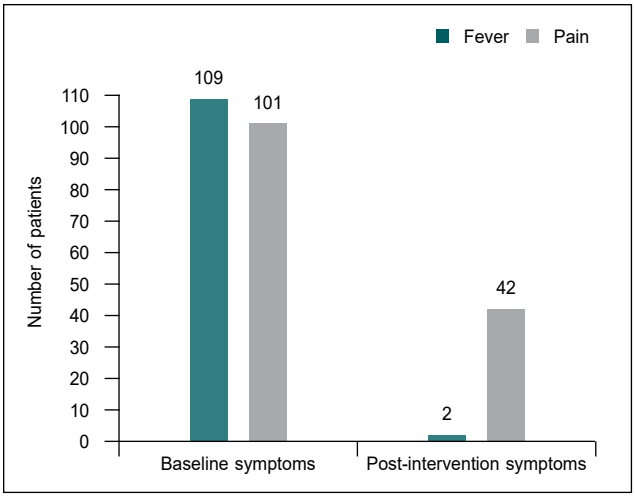

Figure 1. Baseline and post-intervention symptoms in the study participants.

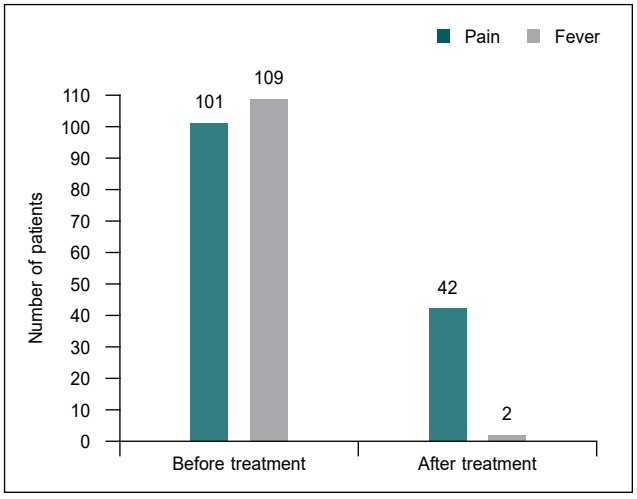

Figure 2. Patient response after paracetamol + lignocaine injection (58% patients showed relief in pain, while 98% patients showed resolution of fever).

any, were also noted. Patients were administered paracetamol + lignocaine IV or IM and patient feedback of pain score on a visual analog scale (VAS) were recorded after administration. The temperature reading was taken after 15 to 30 minutes of administration and any change in associated symptoms was also captured. The patients were checked for the appearance of any side effects such as skin rashes, nausea, vomiting, etc.

Written consent was taken formally from the study participants after informing them about the study, use of the medicine in their condition, and any related side effects that may occur. The data was collected anonymously. Analysis of the responses was carried out by calculation of simple percentages.

RESULTS

The study included 109 patients (31 females and 78 males). All patients had baseline fever (>102°F) and 101 patients reported pain as one of the associated symptoms. Thirteen patients were diagnosed with dengue, while there were 1 patient each with diabetes, urinary tract infection, compound fracture and lower rib pain.

Within 30 minutes of using parenteral paracetamol + lignocaine, only 2 patients reported low-grade fever, while 42 patients (38.5%) reported low-grade pain (based on VAS score). Figure 1 depicts the baseline and post-intervention data of the patients.

None of the patients reported any adverse effects following the use of parenteral paracetamol + lignocaine. Figure 2 shows the patient responses in terms of efficacy of paracetamol + lignocaine combination on fever and pain before and after the treatment.

DISCUSSION

Paracetamol is recommended for use around the world as the most popular agent for the treatment of mild-to-moderate pain due to its analgesic and antipyretic activity.[4]

Injectable paracetamol was approved in 2002; its onset of action is within 5 to 10 minutes of administration, peak effect occurs in 1 hour and the duration of action lasts for 6 hours. It does not have any major adverse effects, has no sedative effect and does not interfere with platelet or kidney functions.[5]

A double-blind placebo-controlled randomized trial showed that parenteral paracetamol-lignocaine combination led to significantly higher and longer analgesic effects compared with the same dosage of plain paracetamol administered in oral form.[6] Patients' response to pain as per VAS score was found to be 0 in the majority of cases, while a few reported grade 1 and 2 pain (6.9% and 23.7%, respectively).

Our study also showed that paracetamol + lignocaine injection led to a significant reduction in fever within 15 to 30 minutes of administration, which lasted for at least 6 hours. None of the patients reported any side effects. These results are in sync with an earlier study where Jarde and Boccard had demonstrated that parenteral paracetamol has a quicker onset of action (at 15- and 30-minutes post-dose) and was also more efficacious with significantly fewer patients who required remedication.[6] In the present study, the paracetamol + lignocaine injection also showed a longer duration of action.

It has also been shown in an earlier study that the combination of paracetamol and a local anesthetic also reduce the pain caused by injections.[7]

CONCLUSION

The clinical implication of our study is that the onset of action of paracetamol in combination with lignocaine administered intravenously, can occur within 15 to 30 minutes. There are no adverse effects, there is an effective reduction of associated signs and the duration of action is much longer. Paracetamol + lignocaine injection can be effective when given to patients with high-grade fever and leads to an effective reduction in VAS pain score. Due to the combination of paracetamol and lignocaine, there is no pain at the site of injection; hence, it can be easily administered to the patient. The results of this study establish that short-term treatment of moderate pain and fever with paracetamol + lignocaine given via IV route is clinically justified. Physicians should consider using IV paracetamol in combination with lignocaine in patients with fever and associated discomfort or pain to relieve patient suffering and reduce pain, which may help provide optimal patient care.

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■■■■

CASE REPORT

Gas Under Right Hemidiaphragm: A Rare Presentation of Unruptured Liver Abscess

OP MEENA*, ATUL KUMAR MEENA†, ARUN KUMAR MEENA†, HEMLATA MEGHWAL‡, RAJESH MEENA#, SANJEEV KUMAR GOYAL†, MASARA RAM PATEL†

ABSTRACT

A perforated liver abscess mimics hollow viscus perforations. It may be accompanied by pneumoperitoneum and peritonitis. A hollow viscus perforation appears to be the most common cause of gas under diaphragm. In about 10% of the cases, it can be due to rare abdominal and extra-abdominal causes. One of the causes could be intra-abdominal infection caused by gas-forming organisms. We are reporting a rare case of pneumoperitoneum resulting from an unruptured liver abscess in an old male with no comorbidity. An unruptured pyogenic right lobe liver abscess in a 70-year-old male was accompanied by X-ray flat plate abdomen features suggestive of free gas under the right hemidiaphragm. Culture of the pus drained from liver abscess grew Klebsiella sensitive to piperacillin and tazobactam, and antibiotic treatment was administered.

Keywords: Liver abscess, gas under hemidiaphragm, intra-abdominal infection, gas-forming pyogenic liver abscess

Pyogenic liver abscess (PLA) is a key reason behind hospital admissions and life-threatening disease in low-middle income countries. Spontaneous gas-forming pyogenic liver abscess (GFPLA) is a rare nonsurgical cause of gas under right hemidiaphragm. The spectrum of GFPLA may mimic hollow viscus perforation because it is often associated with pneumoperitoneum and peritonitis. *Escherichia coli* and *Klebsiella pneumoniae* are among the most common pathogens causing pyogenic liver abscess.

In 85% to 90% of cases, pneumoperitoneum is due to perforation of a hollow viscus. In about 10% of the cases, it can be due to rare abdominal and extra-abdominal causes. One of the causes could be intra-abdominal infection caused by gas-forming organisms.

We report a rare case of pneumoperitoneum resulting from an unruptured liver abscess in an old male with no comorbidity.

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CASE REPORT

A 70-year-old male, nonsmoker, nonalcoholic, presented with complaints of pain abdomen and fever for 15 days. He had history of open cholecystectomy 2 years back.

On examination, patient was febrile and abdominal tenderness was present over right hypochondrium; bowel sounds were present. His pulse rate was 110/min, blood pressure was 110/70 mmHg and respiratory rate was 20/min. Investigations done were as follows: Hemoglobin - 7.3 g/dL, total white blood cell count - 6900/cc, neutrophil - 50% and lymphocytes - 19.2%. His total bilirubin and direct bilirubin were normal. Serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and alkaline phosphatase (ALP) were increased around 10 times. His total protein and albumin were below normal. Chest X-ray and X-ray flat plate abdomen (FPA) in erect posture showed gas shadow under right hemidiaphragm (Figs. 1 and 2).

Abdominal ultrasound was done to look for possible cause of gas under right hemidiaphragm. Ultrasound abdomen showed moderate hepatomegaly with altered echotexture and abscess in right lobe of liver. After that, contrast-enhanced computed tomography (CECT) abdomen was performed which showed unruptured liver abscess as evident by intact capsule in right lobe and moderate hepatomegaly (Fig. 3 a and b).

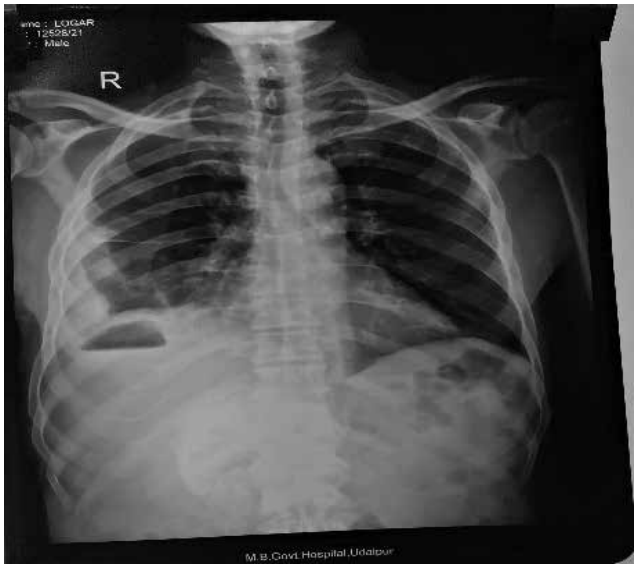


Figure 1. Chest X-ray PA view shows gas under right hemidiaphragm.

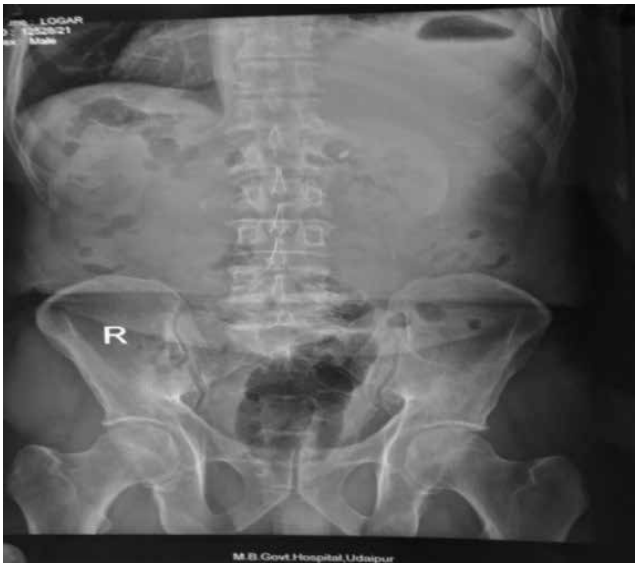
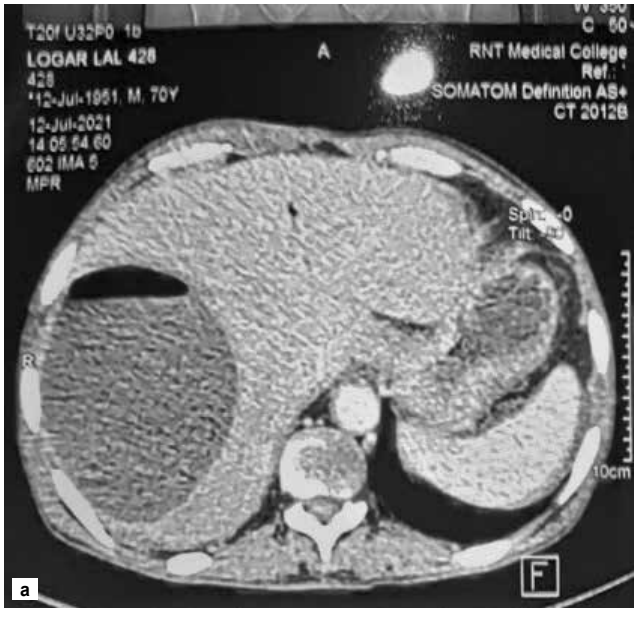


Figure 2. X-ray abdomen erect shows gas under right hemidiaphragm.



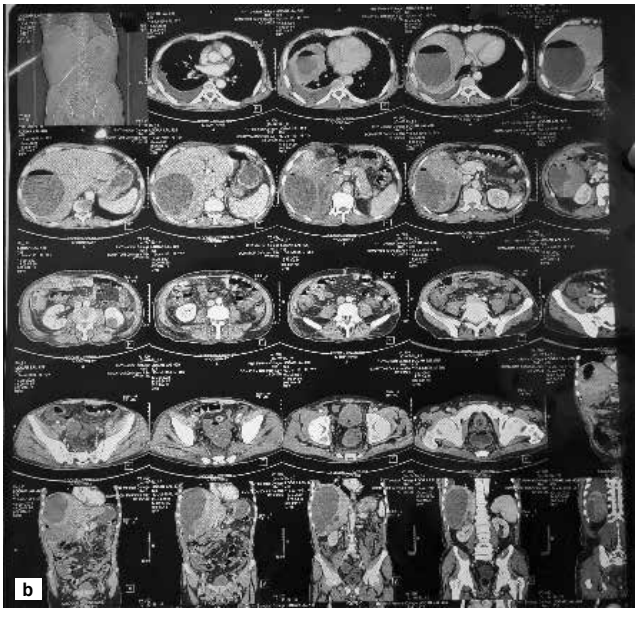


Figure 3 a and b. CECT abdomen shows a large well defined peripherally enhancing hypodense lesion with air fluid level in segment VII of right lobe of liver extending into segment VI also.

A clear air fluid level was visible on CT film inside the liver abscess. Liver abscess was drained (approximately 2 lt.) after confirmation of diagnosis. Pus was light yellow with greenish hue and was sent for culture and sensitivity which showed the growth of *K. pneumoniae*, sensitive to piperacillin and tazobactam. Treatment with antibiotic therapy was started.

DISCUSSION

Pyogenic liver abscess (PLA) is a pus filled pocket of fluid within the liver and it is a common infectious disease worldwide relating to a mortality rate ranging between 15% and 19%. GFPLA remains one of the most dangerous complications with a high fatality rate, in spite of aggressive management.

There are many possible causes of liver abscess, including diseases of the biliary system, a portal venous source arising from intestinal pathology, embolization of bacteria during hepatic surgery, abdominal infection, infection in blood, infection of the bile draining tubes and trauma that damage the liver, but in 15% to 45% of cases, it is cryptogenic where no cause is identifiable.

Most are single and insidious in onset, as the case reported here. In approximately 40% of cases, hepatic abscesses are polymicrobial. Anaerobic organisms are involved in approximately 40% to 60% of the cultures, the most common organisms being *E. coli* and *K. pneumoniae*.

In this particular case, the patient showed signs and symptoms of acute abdomen and radiological evidence of gas under right hemidiaphragm. A provisional diagnosis of gastrointestinal perforation was made. Bowel perforation and recent surgical procedure are commonest causes of pneumoperitoneum.

The chest X-ray and X-ray FPA are abnormal in approximately 50% of the cases, with findings reflecting subdiaphragmatic pathology, such as an elevated right hemidiaphragm, right pleural effusion or atelectasis. Occasionally, there may be left-sided findings in the case of an abscess in the left lobe of the liver.

Pneumoperitoneum is a rare radiological finding in liver abscess. It usually results from the perforation of an intraperitoneal hollow organ, in which case, it is considered a surgical emergency (in 85% to 90% of cases). Only about 10% of pneumoperitoneum cases have nonsurgical causes, for which surgical intervention is usually not required.

In this case, liver abscess filled with pus and having air fluid level visible in CECT abdomen, was responsible for gas under right dome of diaphragm in chest X-ray and X-ray FPA in erect posture.

CONCLUSION

Liver abscess with intact capsule, having air fluid level, imparting the radiological finding of gas under right dome of diaphragm on X-ray FPA in erect posture, is a rare nonsurgical finding. Every case of pneumoperitoneum is not due to a perforated hollow viscus. In this case, the air fluid level inside the cavity of liver abscess was attributed to the gas-forming organism *K. pneumoniae*.

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Heart Inflammation after COVID Jab is a Common Scenario

There was always an existing doubt about the side effects COVID vaccine with several cases of people developing myopericarditis. While the numbers were small, the inflammation of the heart was a serious concern. Now, researchers have claimed that myopericarditis after a COVID jab is not a risk greater than the same posed by any other vaccination. In a study conducted in Singapore, the researchers revealed that the chances of developing myopericarditis are about 18 cases per million dosages. When grouped, non-COVID vaccinations have an average of 56 cases of myopericarditis per million doses. They also noted that myocarditis was more common in individuals who have taken mRNA jabs, with a 10-fold increase in the risk of developing heart conditions in males after the second dose.

The researcher added that the risk of such adverse events overweighted the benefits of vaccination in terms of hospitalization, infection and mortality rates. The study results can be used to frame policies regarding the administration of mRNA vaccine to the young male population. (*Source: https://www.theguardian.com/society/2022/apr/11/heart-inflammation-after-covid-vaccine-no-more-common-than-after-other-jabs*)

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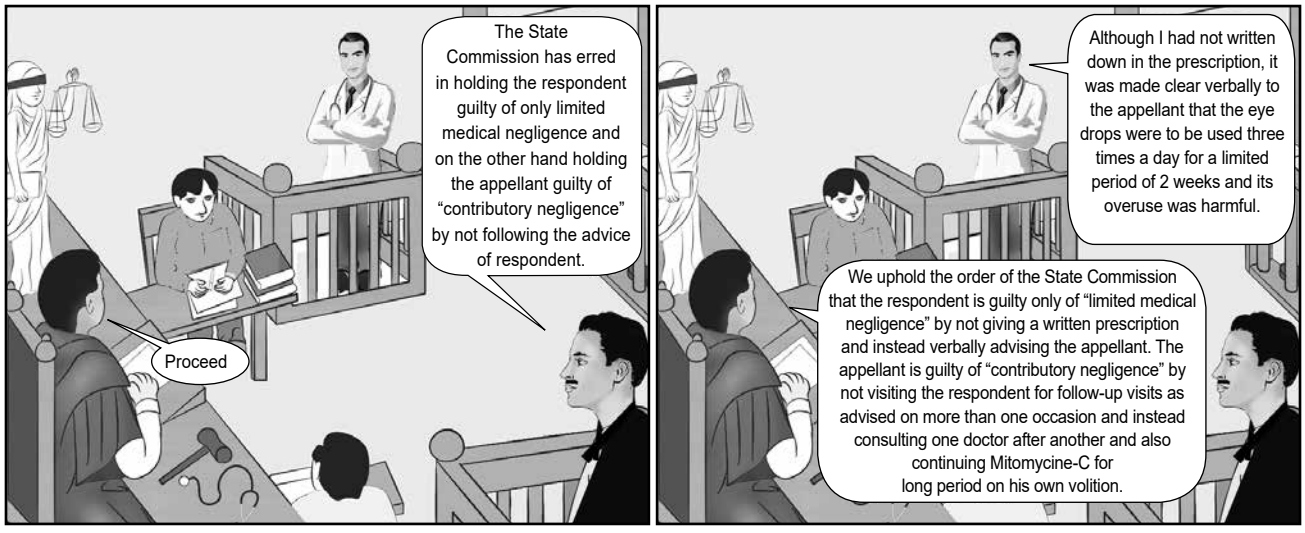
Case of Limited Negligence on Part of the Doctor and Contributory Negligence by the Patient



Lesson: The order dated 31.08.2006 in Complaint Case No. C-21/95 of the State Consumer Disputes Redressal Commission Delhi stated "By not prescribing in writing in the prescription that medicine Mitomycine-C should be used, at first instance, only for 2 weeks, OP has committed an offence of limited medical negligence as complainant also cannot be excused for contributory negligence by not approaching the treating doctor after few days and hopping from one doctor to another and continued using the medicine for long resulting in dry-eye syndrome causing loss of vision in the eye."

COURSE OF EVENTS

- June 1993: Following a minor complaint of a cosmetic nature in his left eye, the appellant consulted respondent, who is an eye surgeon, in his clinic in Daryaganj, who after examining him informed that he was suffering from an innocuous growth known as pterygium and since there was likelihood that the growth may increase, excision was advised through a minor surgery, which would ensure that the appellant's eye would become normal within 5 days. Appellant, therefore, agreed to undergo this surgery.
- October 1993: The respondent conducted the surgery on the appellant at his clinic and the appellant was thereafter prescribed medicines for both local application, which included Mitomycine-C, as also oral medication. However, soon after, the appellant's left eye became red and there was acute pain and irritation, which persisted, and therefore he consulted the respondent, who assured him that if he continues to regularly use Mitomycine-C, his eye would become normal. However, during the course of using this medicine, appellant's eye further deteriorated and became very dry and there was loss of vision in that eye. Appellant complained about this to the respondent, who changed the medicine, which only further aggravated the condition.
- The appellant consulted another ophthalmologist Dr G, who informed him that his left eye had become very dry due to wrong prescription of Mitomycine-C and he was advised to consult Dr P at Hospital A, New Delhi.
- Dr P confirmed that the eye had got damaged due to prolonged use of Mitomycine-C.
- The appellant thereafter went to hospital B where this diagnosis was confirmed by a cornea specialist, Dr A. He was advised to stop using all the medicines, including Mitomycine-C.
- Being aggrieved because of the medical negligence and deficiency in service on the part of respondent, because of which the appellant's eye became dry,

he issued a legal notice to respondent to pay him Rs. 10 Lakhs as compensation but received no response.

- Appellant, therefore, approached the State Commission with a complaint of medical negligence and deficiency in service against respondent and requested that he be directed to pay Rs. 10 lakhs as damages and compensation since there was total loss of vision in appellant's left eye, which had adversely affected both his professional and personal life, as also any other relief as deemed appropriate.
- Respondent on being served filed a written rejoinder denying the above allegations, which he termed as false, frivolous and vexatious. It was contended that appellant approached him with a condition known as pterygium, which is a growth of extra skin and if it reached the pupil area of the eye, it could permanently hamper the appellant's vision. Surgery was, therefore, necessary, which was satisfactorily conducted. The appellant thereafter advised both oral medication as also medicine through local application.
- After a week, when the healing of the appellant's eye was completed, respondent advised the respondent to use Mitomycine-C for 2 weeks since this was necessary to prevent recurrence of pterygium. This medicine, which comes in the form of injection, was converted into eye drops for use three times a day and appellant was verbally told that over use of this medicine for more than 2 weeks is harmful.
- Unfortunately, the appellant did not heed this advice and instead of coming back for a further check up appears to have continued using Mitomycine-C and taking treatment from various other doctors as per his own whim and fancy.
- It was only on 03.03.1994 i.e. after over 4 months that appellant visited the respondent and told him that he was still continuing the use of Mitomycine-C. Respondent immediately asked him to discontinue the same and to come back after 15 days.
- The appellant again did not heed this advice and consulted the respondent after 3 months i.e. on 22.06.1994 when he was prescribed natural tear drops and lacri-lube ointment.
- A perusal of these facts clearly indicate that it was the appellant who was responsible for the damage caused to his left eye by prolonged use of Mitomycine-C on his own volition and against medical advice given by respondent. There was, therefore, no deficiency in service or medical negligence of respondent.
- The State Commission after hearing the parties and on the basis of evidence produced before it held the respondent guilty of "limited negligence" by not advising the appellant in writing to use Mitomycine-C only for a particular limited period. The relevant part of the order of State Commission reads as follows:

"*By not prescribing in writing in the prescription that medicine Mitomycine-C should be used, at first instance, only for 2 weeks to OP has committed an offence of limited medical negligence as complainant also cannot be excused for contributory negligence by not approaching the treating doctor after few days and hopping from one doctor to another and continued using the medicine for long resulting in dry-eye syndrome causing loss of vision in the eye. OP is guilty of this limited medical negligence amounting to deficiency in service due to which the complainant has lost his vision of one eye though he can also be not absolved from contributory negligence which is a mitigating circumstance for awarding compensation.*"

The State Commission, therefore, held that a lump-sum compensation of Rs. 50,000/- to the appellant would meet the ends of justice.

- Being aggrieved by the lesser compensation, the present first appeal has been filed before National Consumer Disputes Redressal Commission (NCDRC).

ALLEGATION OF THE APPELLANT

- Learned counsel for the appellant contended that the State Commission erred in holding the respondent guilty of only limited medical negligence and on the other hand holding the appellant guilty of "contributory negligence" by not following the advice of respondent.
- Following the surgery, the appellant did visit the respondent doctor for further check-up prior to 03.03.1994. According to appellant, respondent had prescribed him Mitomycine-C on 18.10.1993 and the prescription did not indicate either the duration for taking the medicine or its possible harmful side effects.
- The appellant was also not advised when he should come back for a follow-up check. Further, when the appellant visited the respondent on 03.03.1994 with a serious complaint regarding his operated

eye, respondent again sought to hide the correct facts by recording that the condition of appellant's eye as also the vision was normal.

- Since the appellant had already started losing his eyesight and he was having acute pain in his eye, he was constrained to approach other doctors, who advised the appellant to immediately stop the use of Mitomycine-C. It was these doctors who informed him that the problem in his left eye had occurred due to over use of Mitomycine-C, which should not have been used for more than 2 weeks.
- Counsel for the appellant further stated that the conduct of the respondent was suspect before the State Commission as is evident from the fact that he did not produce the necessary documents on the ground that these had been destroyed in a fire. Because of the medical negligence and callousness on the part of respondent, appellant lost the vision in his left eye causing him a great deal of mental agony and adversely affecting his work as a senior clerk in the Supreme Court of India.

REJOINDER OF THE RESPONDENT

- Learned counsel for respondent denied the above allegations and stated that it is not factually correct that respondent had prescribed Mitomycine-C to the appellant on 18.10.1993 i.e. immediately following the surgery. In fact, he was prescribed other medicines and ointments after the surgery and it was only after a week when the eye had healed that Mitomycine-C was prescribed to the appellant.
- It is a proven fact in ophthalmology medical literature that Mitomycine-C is successful in checking the recurrence of pterygium, which has a very high incidence of recurrence and is routinely prescribed for limited periods following such surgeries. It was under these circumstances that respondent rightly prescribed this medicine to the appellant. Although not written down in the prescription, it was made clear verbally to the appellant that the eye drops were to be used three times a day for a limited period of 2 weeks and its over use was harmful.
- This is further confirmed by the fact that respondent converted only one vial of Mitomycine-C injection into eye drops, which would have lasted at the most for a little over 2 weeks. From this fact alone, it is clear that the Appellant had been procuring this medicine and getting it converted into eye drops from some other doctor(s) and in this way using it for several weeks i.e. till 03.03.1994 when he next visited the respondent, who immediately directed him to discontinue the use of this medicine.
- Learned counsel for respondent pointed out that a senior ophthalmologist of hospital A, Dr M, has confirmed to him in writing that appellant had consulted him and also informed him that he was continuing to use Mitomycine "on his own".
- Appellant continued to disregard medical advice of Respondent even after 03.03.1994 by not coming for follow-up visits, which he was advised to do by respondent, who had prescribed him some other medicines and wanted to assess their effect.
- From the above facts, it is clear that appellant, who was not an illiterate person and who had been clearly orally advised to use Mitomycine-C eye drops only for a limited duration by respondent, failed to follow this advice and continued to use the medicine on his own, for which respondent cannot be held responsible, particularly since appellant did not even come for the follow-up visit after 2 weeks. There was no medical negligence or deficiency in service on the part of respondent, who had prescribed the right medicine and given correct advice regarding its limited period of use. The present first appeal, therefore, having no merit deserves to be dismissed.

OBSERVATIONS OF NCDRC

- The appellant visited the respondent's clinic with a complaint in his left eye and was detected with pterygium, for which a minor surgery was conducted is not in dispute.
- It is also a fact that appellant was prescribed Mitomycine-C by respondent, which is a drug of choice, to ensure that pterygium does not recur since it has a high degree of recurrence.
- While it is a fact (as also observed by the State Commission) that no directions were given by respondent in writing to appellant regarding the duration for which the drug should be used or any written precaution against its prolonged use, we find force in the contention of respondent that since he had converted only one vial of Mitomycine injection into eye drops, this itself indicates that the intention was clearly for its limited use for about 2 weeks and not for several months.
- When specifically asked by us, learned counsel for the appellant also fairly conceded that respondent had converted only one vial of Mitomycine injection into eye drops, thus confirming the respondent's clear intention regarding its use for a limited period. It is, thus, apparent that appellant

had been using this medicine for several weeks by getting the Mitomycine injection converted into eye drops through some other source and not by the respondent, for which respondent cannot be held responsible.

- It was under these circumstances that the State Commission had held the respondent guilty of only "limited medical negligence" for not having put down in writing the dosage and duration of the medicine in the prescription slip.

ORDER OF THE NCDRC

We agree with this finding. We further agree that the appellant is guilty of "contributory negligence" by not visiting the respondent for follow-up visits as advised on more than one occasion and instead consulting one doctor after another and also continuing Mitomycine-C for long period on his own volition, which resulted in the dry eye syndrome and consequent loss of vision in the left eye. To sum up, we uphold the order of the State Commission that respondent is guilty only of "limited medical negligence" by not giving a written prescription and instead verbally advising the appellant, for which a compensation of Rs. 50,000/- is reasonable and we, therefore, confirm the same. The present first appeal is dismissed. Respondent is directed to pay a sum of Rs. 50,000/- to the appellant within 6 weeks, failing which it will carry interest @ 6% per annum for the period of default. No costs.

REFERENCE

1. Case no. 692 of 2006, NCDRC; Order date 16.01.2013.

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Study Suggests Three Symptoms Indicating the Risk of Self-Injury in Cancer

According to a Canadian study published in *JAMA Oncology*, moderate-to-severe anxiety, depression and shortness of breath symbolize nonfatal self-injury (NFSI) among cancer patients. In a population-based control study for 180 days after a fresh diagnosis, each symptom was linked with a 60% hike in the risk of NFSI. Julie Hallet, MD, an Associate Scientist at Sunnybrook Health Sciences Centre in Toronto stated that the physicians should be aware that self-injury is a problem after a cancer diagnosis. She added that attempted suicide doesn't necessarily indicate self-injury. Self-injury can also represent a means to cope with a cancer diagnosis psychologically. The study included adults diagnosed between 2007 to 2019 who have completed the Edmonton Symptom Assessment System (ESAS) evaluation within 36 months following their diagnosis. The assessment has nine common symptoms such as pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being and shortness of breath to be rated on a scale of 0 to 10 with 0 being no symptom and 10 representing the worst symptom. The study included 406 diagnosed patients with NFSI and 1,624 diagnosed controls without NFSI.

The results showed that the adjusted ratio for moderate-to-severe anxiety, depression and shortness of breath were 1.61, 1.66 and 1.65, respectively. Each 10-point score was linked with higher risk at a ratio of 1.51. Based on the result, the author stated that the ESAS scores are important in identifying the pattern and providing better support to the patients. Madeline Li, MD, PhD, a psychiatrist and clinician-scientist at Toronto's Princess Margaret Cancer Centre commented on the study that NFSI is linked with distress while cancer is the stressor. She added that the studies' identification of three symptoms is significant as it intimates a clinician to identify the reason behind it. (*Source: https://www.medscape.com/viewarticle/972935?src=*)

Experts Suggests Lifestyle Changes in Teens can Lead to Kidney Stone

Kidney stones are deposition of calcium usually observed in the middle age. However, lifestyle changes and obesity have led to kidney stones at younger ages, suggested experts at 5th advancements in Endourology 2022, a 3-day event held in Ahmedabad. Experts from various countries such as Turkey, France, Switzerland, etc. were present at the event. Dr Kandarp Parikh, Organizing Chairman of the event stated that the conference aimed to bring together the experts in the field to discuss the evolution of technology, benefits and disadvantages including related case studies. He stated that in the last few years, physicians have witnessed a fast-paced change in the different aspects of minimal access surgery, RIRS, bipolar TURP, HOLEP, etc. Many of which are now used in the Indian medical sector. Earlier, pricing used to be a deterrent, however, now such procedures have become cost-effective and easily accessible. (*Source: https://health.economictimes.indiatimes.com/news/industry/kidney-stones-in-teens-caused-by-lifestyle-changes-experts/91194139*)

HCFI Dr KK Aggarwal Research Fund

HCFI Round Table Environment Expert Zoom Meeting on "World Air Quality Report 2021: What Concrete Steps are Needed to Improve the Air Quality for Better Health - Part 1"

3rd April, 2022 (Sunday, 12 noon to 1 pm)

- The World Air Quality Report 2021 was released by the World Health Organization (WHO) on 22nd March, 2022.
- Air pollution is considered to be the world's largest threat to health and accounts for 7 million premature deaths every year.
- Air pollution aggravates many diseases ranging from asthma, lung cancer and heart disease.
- According to the report, 40,000 deaths in children under the age of 5 years are directly linked to particulate matter (PM2.5).
- This report is based only on one parameter, which is PM2.5 and includes data from 6,475 cities in 117 countries around the world.
- The annual PM2.5 concentration of 5 μg as defined by the WHO in its latest air quality guidelines is very difficult to achieve. Countries in South East Asia, South Asia and the Far East suffer from the highest annual PM2.5. Out of the 107 capital cities listed, only 4 meet the WHO guideline of 5 μg for PM2.5.
- PM2.5 is more than 10 times the WHO limit in almost 50% of the cities in India.
- Avoidable sources of air pollution should be completely eliminated e.g., diesel gen sets are used in situation of power breakdown. If there is no power breakdown, gen sets will not be needed. Another example is resuspension of dust.
- Green belt can be used as a wall against the entry of fine dust, odor and sound. Instead of just increasing the quantity of greenery, green belts should be created at appropriate places keeping in view the meteorological conditions.
- To control roadside dusts, the area should either be paved or should be green.
- The method of measuring air quality needs to be reviewed. Benzene and other volatile organic compounds (VOCs) which are now known to be present in urban air are not measured or controlled.
- Research is still needed so that we do not continue with the old parameters.
- According to the new report, New Delhi is the most polluted capital city in the world and Bhiwadi in Rajasthan is the most polluted city.
- Delhi should instead be called the most "dusty" capital. We are measuring mass in μg, but we don't know how toxic it is. So, its not correct to label one city as the most polluted. Delhi is in the Indo-Gangetic plain. There is windblown dust and mainly PM10 (60-70%); PM2.5 increases only in winters because of burning, etc.
- Now Gen sets up to 800 kv have to include a system which can collect 70% of PM2.5 emissions, according to a directive of the Commission for Air Quality Management.
- There is 20% reduction in PM2.5 from 2018 vs. 2021; PM10 also shows 12% to 15% reduction.
- The report does not mention geogenic, climate and geography aspects of pollution.
- Emission data among different cities in the same country or even different places in the same city is not comparable. This is neither realistic or logical.
- We cannot control the geogenic sources of air pollution.
- The validity of low-cost sensors is questionable. Temperature and humidity make a major difference to the low-cost sensors. These sensors have to be calibrated thoroughly for 3 to 4 seasonal cycles.
- It may give indicative measurement only in case of particulate matter and not any other parameter.
- If it cannot be calibrated, then it should not be used as there is no sanctity of data. It may vary from 50% to 300%.
- Low-cost sensors are just sensors, they are not analyzers.
- They can give a qualitative indication of air pollution, but whether the same can be taken for quantitative analysis needs to be questioned.
- Without correction factors, with normalization, without understanding the anthropogenic or geogenic sources, the scientific veracity of this report is questionable.

- The Central Pollution Control Board (CPCB) has come out with directions to not include low-cost sensor data in any national network on Air Quality Index (AQI) or any other national regulatory purpose.
- India has calibration facility in the National Physical Laboratory (NPL), but cost of this may be more than the cost of the sensor.
- Disposal of dust collected during mechanical sweeping of roads is most important. Unless this is done, the dust will resuspend in the ambient air.
- Pollution more than 50% cannot be controlled. The year 2020 was the cleanest year in the last decade. Data showed that PM2.5 was 28-30 and PM10 was more than 40. This data was when all activities had been shut down due to the lockdown.
- Greenery should not be less than 20-30% of the area of the development. There are no guidelines on how much greenery should be developed in new townships.
- A change in approach to city planning is required.
- We have to be careful about greenery and water sprinkling as ozone levels increase with greenery and bigger particulates are formed with water sprinkling.
- In Delhi, biomass is freely available because of pruning.
- Water sprinkling is not a proven mitigation method. It has to be tested and the quantity also has to be optimized. Its an emergency measure and can be done once in a week/month, but should not be a regular option to control air pollution.
- Natural VOCs contribute to the formation of ozone.
- Its important to distinguish between survival emissions and luxury emissions.

Participants: Dr Anil Kumar, Mr Vivek Kumar, Mr Paritosh Tyagi, Dr M George, Dr Dipankar Saha, Dr Rajeev Sharma, Mr Neeraj Tyagi, Mr Ankit Sethi, Mr Vikas Singhal, Mr Pradeep Khandelwal, Ms Ira Gupta, Dr S Sharma

HCFI Round Table Environment Expert Zoom Meeting on "World Air Quality Report 2021: What Concrete Steps are Needed to Improve the Air Quality for Better Health – Part 2"

10th April, 2022 (Sunday, 12 noon to 1 pm)

- The WHO Air Quality Report 2021, released in March is based on PM2.5 only.
- The report has used data of air quality monitoring stations and low-cost sensors.
- Bhiwadi in Rajasthan is the most polluted city in the world with a PM2.5 of 106.2 μg/cu mm. Delhi is the most polluted capital city in the world. No city in India met the latest WHO guidelines.
- Dust suppression methods must be used to control pollution. Graded Response Action Plan (GRAP), national air quality control program and state air quality control programs have also focused on this.
- Proper disposal of the dust collected during mechanical road sweeping is very important.
- The focus should also be on developing green belts to arrest dust. The slogan should be "either pave or green".
- Data of low-cost sensors cannot be compared with air quality monitoring station data.
- Toxic components of PM2.5 are a matter of concern.
- Industries and power plants in developing countries use coal (survival emissions). Hence, data of developing countries should not be compared with data of developed countries.
- Construction and demolition waste contribute significantly to air pollution in the form of PM2.5 and PM10.
- Delhi currently has five construction and demolition waste recycling plants. This not only controls air pollution but also controls excessive use of natural resources. Air pollution can be limited by providing such facilities all over the country.
- The only solution for legacy waste is segregation of waste into wet waste and dry waste.
- Formation of secondary organic aerosols is a big challenge.
- It is very important to stop organic pollution arising due to biomass burning, which forms black carbon and which is difficult to capture. Hydrocarbons are proven carcinogens.
- There is lack of awareness about rule and management plans.
- Failure of knowledge transfer or knowledge gap is also one of the reasons for high levels of air pollution.
- There is system failure when it comes to implementation of the rules. This is an administrative issue and not a technical issue.
- Emergence of secondary pollutants in the atmosphere is governed by local meteorological

conditions and hence, we have no control over these.

- There is a need to study the health impact of the pollutants and find out what mitigation methods can be adopted to prevent the harmful impact. Masks are one such option.
- Air pollution is a multidimensional issue. There are several challenges and many stakeholders. But there is a lack of coordination and consistency among them.

Participants: Dr Anil Kumar, Mr Vivek Kumar, Mr Paritosh Tyagi, Dr M George, Dr Dipankar Saha, Dr Rajeev Sharma, Dr SK Gupta, Dr SK Tyagi, Mr Pradeep Khandelwal, Mr Sanjeev Aggarwal, Mr Neeraj Tyagi, Mr Ankit Sethi, Mr Vikas Singhal, Mr Varun Singh, Ms Ira Gupta, Dr S Sharma,

Minutes of an International Weekly Meeting on COVID-19 Held by HCFI Dr KK Aggarwal Research Fund

Topic: COVID-19 Variants, Recombinants and Way Forward

Speaker: Prof Shashank Joshi, *Endocrinologist, Joshi Clinic, Lilavati Hospital & Bhatia Hospital, Mumbai; Member, COVID-19 Maharashtra State Task Force*

9th April, 2022 (Saturday, 9.30-10.30 am)

- As the Omicron wave is receding, across the world there has been a concern and fear of recombinants.
- The world is divided into two camps: the Inevitability camp and the Avoidance camp.
- The inevitability camp says that the Omicron wave was mild, lung to lung cell virulence is mild and the vaccine and/or infection-induced T cells hold up well and protect from severe disease. Booster shot is immaterial because it will last only up to 3 months. We can't worry about long COVID, we don't need antivirals and probably we can get over all this because we have hybrid immunity.
- But there is the avoidance camp, which says that disease is less severe and mild is not always mild. It is a big concern even now in the US and Europe. Even today we are losing people who are immunocompromised, aged because we do not have an assured layer of defense. The precaution doses are helpful but despite four doses we are getting breakthrough infections and we are getting debilitating long COVID across the world. Medical supplies like antivirals are limited. The highly transmissible newer strains particularly BA.1 and BA.2 are definitely around the corner. They are more contagious and transmissible.
- The Omicron strain (BA1.1.529) was detected in November 2021; it grew out from Alpha, Beta and the Gamma variants, which were totally replaced by the Delta strain. It has the highest transmissibility, lower disease severity and highest immune escape from previous infections.
- This strain was mainly discovered in South Africa and Hong Kong between November 11 and November 23 with more than 30 mutations in the spike protein alone. It has 10 mutations on the ACE2 receptor (the Beta variant has 3 and the Delta variant has 2 mutations). It has S gene target failure, but the initial BA.1 strain was rapidly overtaken by the BA.2 strain, which did not have S gene target failure.
- Omicron is now the dominant strain in the world and has replaced the Delta variant, which was lethal and virulent. It is rapidly transmissible, supermutant strain with more than 50 mutations; it has immune escape; breakthrough infections are common, but the severity and virulence of Omicron are less severe whether it is BA.1, BA.2 or BA.3. The BA.2 is causing havoc around the world.
- The number of mutations in Delta are sparse but they are plenty in Omicron. But the global fear is that if these two strains combine, we will get a deadly recombinant strain, which has been popularly called as Deltacron, which created huge fear.
- Most of the reportages in last 3 to 6 months were predominantly linked to probably contamination they were called recombinants.
- The monoclonal antibodies which work now have moved away from the traditional casirivimab and imdevimab to sotrovimab and tiglivimab and the newer upcoming molecules.
- COVID therapy today is all about immune boosting through vaccines. Neutralizing monoclonal antibodies of different types, immune modulators like steroids, IL-6 blockers and antiviral like molnupiravir, paxlovid or remdesivir. But the focus clearly is on no deaths, less severity of disease and mild-to-moderate disease.
- When two related viruses infect the same cell, i.e., during a coinfection, the viral replicating machinery can accidently switch from genome to other resulting in a mixed genome. This is viral recombination.
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been doing this all through the

pandemic. However, it is easy to see when the two parental viruses are distantly related, e.g., alpha or prevariant. Therefore, the reason we are seeing lots of recombinants is as until recently we had lots of genetically distinct viruses in circulation such as Delta, BA.1 and BA.2. When recombination occurs between these lineages, it is possible to identify, even if the switched part of the genome is small.

- All this was highlighted because UK and Europe do a lot of genome sequencing. When BA.1 took off in Europe and USA, there was a very high Delta wave already circulating. So, when BA.1 Omicron came, there were huge opportunities for coinfection, recombination and transmission going onwards.
- The new recombinant lineages fall in two categories: Delta × BA.1 (referred to as Deltacron in the media) and classical recombination of BA.1 × BA.2, which is now being described in the UK.
- XD is the new recombinant lineage; it the new name for the French Delta × BA.1 lineage sequenced at the Pasteur Institute. It contains the spike protein of BA.1 and the rest of the genome from Delta. It currently comprises of several 10s of sequences; possibly more transmissible, but virulence is unknown.
- The XE is a large UK BA.1 × BA.2 lineage. It was sequenced and verified by the UKHSA and the Wellcome Sanger Institute. It has the spike and structural proteins from BA.2 but the 5′ part of its genome is from BA.1. At present, it comprises several hundred sequences.
- The XF is a UK Delta × BA.1 lineage. It was also sequenced by the UKHSA. It has the spike and structural proteins from BA.1 but the 5′ part of its genome is from Delta. At present, it comprises several tens of sequences.
- The UK currently uploads around 10x more sequences than France. Therefore, 10s of sequences in France are roughly equivalent to 100s of sequences from the UK.
- Recombinants that contain the spike and structural proteins from a single virus (such as XE or XF) are fairly likely to act similarly to their parental virus. So, there is no major fear or concern.
- All these recombinants, including smaller clusters that have not been assigned, should be closely monitored for signs of growth and attempts should be made to isolate and characterize where possible.
- Recombinants are here to stay. They are more transmissible, but may be less virulent. Immune escape is another challenge with recombinants.
- India had a Delta wave from April to May and the Omicron wave from mid-December to end of January. There has been a large exposure to infection naturally. Also, 190 Cr of Indians have been vaccinated. Hence, the Indian population is likely to have hybrid immunity. Therefore, the probability of a fourth wave which may disrupt the country is less likely in the next 3 to 6 months. Hybrid immunity is the best immunity. We need hybrid immunity across the world.
- As of date, COVID is still predictably unpredictable. The only overarching feature in the way forward is to save lives. Behave responsibly, preferably mask if in crowded closed spaces and get your vaccination on schedule.
- The immunocompromised, elderly, those with lot of comorbidities are still at risk. COVID can still kill in this vulnerable group.
- The threat of recombinants is real. But they are not likely to pose a major threat in the near future.
- We need to look into alternative routes of vaccine delivery and vaccine platforms. Nasal vaccines could be effective. In India, one nasal vaccine is under research and trial.
- The m-RNA was a robust platform good for spike protein but it has limitations.
- Hybrid immunity - vaccine-induced as well as natural acquired immunity is going to play a key role in times to come as we live with COVID. But we have to protect our vulnerable population.
- Waves will keep on coming and going. We hope that even if transmissibility goes up, virulence should come down. We need to have incremental innovation on vaccine platforms, vaccine route of delivery and have better neutralization capabilities as new strains and recombinants will come.

Participants – Member National Medical Associations: Dr Marthanda Pillai, India Member World Medical Council, Advisor-CMAAO; Dr Mvuyisi Mzukwa, South Africa; Dr Angelique Coetzee, South Africa; Dr Akhtar Hussain, South Africa

Invitees: Dr Monica Vasudev, USA; Dr Shashank Joshi, India; Dr Patricia La'Brooyi; Dr EC Ng; Dr Blan Lee; Dr Chia Ai Mian; Dr Hamid Ahmad; Dr Kathleen Su Meng Yp; Dr Ng Hwee Hin; Dr S Sharma, Editor-IJCP Group

Moderator: Mr Saurabh Aggarwal

eAPICON 2021

IMPORTANCE OF INFLUENZA VACCINATION IN ADULTS

Dr Leong Hoe Nam, Singapore

- Global annual influenza epidemics affect 5-10% of adults and 20-30% of children. It leads to 3-5 million cases of severe disease and result in up to 6,50,000 deaths.
- Flu viruses come and go; but it will come back.
- Influenza pandemics cause substantial morbidity and mortality. The 1918 Spanish flu (H1N1) saw 50-100 million deaths; 1957 Asian flu (H2N2) saw 2 million deaths; 1968 Hong Kong flu (H3N2) saw 1 million deaths; 2009 (H1N1) flu saw 2,00,000 deaths.
- There are four circulating strains now. Flu B diverged – two strains.
- COVID year – Number of specimens positive for influenza decreased in both Northern and Southern hemispheres, but despite the low numbers of influenza, it will rise again when masks or safe distancing are relaxed. Quadrivalent influenza vaccine is the new standard.
- There is a significant disease burden of influenza B – It represents nearly 25% of circulating influenza strains.
- Circulating B lineage may vary between countries in the same year and in the same region. Influenza B causes epidemics about every 2-4 years. Symptoms of influenza A and B infections are similar. Individual level risk of hospitalization or mortality is also similar between influenza A and B.
- Influenza increases the risk of exacerbation and hospitalization in patients with noncommunicable diseases (NCDs).
- Influenza immunization benefits in NCDs – Prevent infection; protect against NCDs (heart attack, stroke); protect against complications from existing NCDs.
- Influenza vaccination reduces CV events in patients with acute coronary syndrome.

LDL-C LOWERING: CURRENT GUIDELINES – WHAT IS APPLICABLE TO INDIANS?

Dr SN Narasingan, Chennai

- Elevated Lp(a) is an independent risk factor for atherosclerotic cardiovascular disease (ASCVD), calcific aortic valve stenosis, stroke and peripheral artery disease.
- Elevated Lp(a) probably increases the risk of heart failure.
- Is it a missing link in premature and malignant ASCVD in Indians? Lp(a) should form a part of lipid panel.
- PCSK9 inhibitors seem to confer benefit in patients with high baseline Lp(a). Lipid apheresis is effective and expensive.
- Antisense oligonucleotides are promising. Cardiovascular outcome trial (CVOT) results are awaited.

INTERPRETING THE LINK BETWEEN HYPERURICEMIA AND CARDIOMETABOLIC DISORDERS AND MANAGEMENT

Dr Alan Almeida, Mumbai

- About 90% of hyperuremic cases are due to decreased uric acid excretion. The etiology includes: Overproduction of uric acid; Decreased uric acid excretion; Genetic disorders and in-born errors of metabolism; Genetic disorders.
- Comorbidities associated with hyperuricemia include cardiovascular (CV) disorders, hypertension, metabolic disorders, diabetes, chronic kidney disease (CKD) and obesity.
- Guidelines cut-off values of uric acid for hyperuricemia – Women: >6 mg/dL; Men: >7 mg/dL; Children and adolescents: >5.5 mg/dL.
- Uric acid levels 7-9 mg/dL double the risk for incident kidney disease. Levels >9 mg/dL triple the risk of incident kidney disease.
- PERL study – There was no evidence of clinically meaningful benefits of serum urate reduction with allopurinol in kidney outcomes in patients with type 1 diabetes and early to moderate diabetic kidney disease.
- CKD-FIX study – Urate lowering treatment with allopurinol did not halt decline in eGFR in patients with high risk of progression of CKD.
- Management – Serum uric acid level 7-8 mg/dL: Lifestyle modification; 8-9 mg/dL + comorbidities: Lifestyle modification + pharmacotherapy;

>9 mg/dL with or without comorbidities: Lifestyle modification + pharmacotherapy.

- CARES study prompted FDA boxed warning on febuxostat.
- CARES trial on febuxostat vs. allopurinol – In patients with gout and major CV coexisting conditions, febuxostat was noninferior to allopurinol with respect to rates of adverse CV events. All-cause mortality and CV mortality were increased with febuxostat vs. allopurinol.
- FAST trial on febuxostat vs. allopurinol – Febuxostat was noninferior to allopurinol with respect to the primary CV endpoint. Long-term febuxostat use was not associated with an increased risk of death or serious adverse events compared with allopurinol.
- FAST study prompted to reconsider and modify the advice to avoid the use of febuxostat in patients with CV disease.

API-DIAS 2020-21: DIGITAL OUTREACH – REACHING THE UNREACHED

Dr Agam Voram, Mumbai

- Until a decade ago, the entire physician education was highly fragmented without having a common approach with limited impact. API-DIAS was created to have a unified platform for providing high science evidence-based, accurate and unbiased information to healthcare professionals.
- In 2013-14, API started a first of its kind CME initiative called API-DIAS.
- Since its inception, API-DIAS has touched upon numerous therapeutic areas with an aim to share information and best practices for efficient healthcare management.
- COVID-19 completely transformed the delivery of CME initiatives.
- COVID-19 has significantly enhanced the importance of technology in healthcare industry and helped gain a deeper understanding of the state of digital transformation in healthcare.
- API-DIAS 2020-21, A digital outreach program: The fourth edition of the program is focused on 'Digital Outreach'. In 2020, due to an unprecedented challenge presented by the pandemic, API-DIAS transformed into a digital avatar.
- Key achievement of API-DIAS 2020-21:
  - Improving awareness about latest scientific developments – 100+ hours of immersive scientific content delivered
  - Enhancing geographical outreach of the program – 85,000+ HCPs participated from APAC, MCI credit points allocated for each webinar
  - Enhancing access to quality CME content – 100+ top national, international speakers have delivered lectures
  - Enhancing quality of care by dissemination of best practices in healthcare management – Around 90 topics across multiple therapeutic areas covered already.
- API-DIAS 2020-21 – A therapy shaping platform: This version of API-DIAS witnessed the launch of strategic initiatives such as white papers, book launches, guidelines, etc.
  - Launch of white paper on adult immunization by API in collaboration with MoHFW-GoI, RSSDI, GSI, FOGSI in the presence of 2000+ participating delegates
  - Launch of white paper on hyperuricemia by API in collaboration with RSSDI and Indian Society of Nephrology
  - Launch of India's first guidelines on Thyroid and Diabetes by RSSDI
  - Launch of a book titled "Acid Peptic Disease and Beyond" by Dr Nageshwar Reddy.
- API-DIAS webinars received accreditation from Maharashtra Medical Council. Attending each webinar has entitled physicians with 1 credit point each for the first time in India.

MALE HYPOGONADISM: PERSPECTIVES ON DIAGNOSIS, DIALOGUE AND THERAPY

Dr Sanjay Kalra, Karnal

- Hypogonadism or testosterone deficiency (TD) is a clinical and biochemical syndrome characterized by low levels of testosterone (T) with associated signs and symptoms. There is decreased functional activity of the gonads.
- Classification of male hypogonadism – *Hypergonadotropic hypogonadism/primary:* High LH, FSH, low testosterone; *Hypogonadotropic hypogonadism/secondary:* Low LH, FSH, low testosterone. *Organic and functional: Organic* – Any proven pathology affecting the hypothalamic-pituitary-gonadal axis; Should be treated with conventional medications (gonadotropins or testosterone) accordingly; Functional – Absence of any recognized organic alterations in hypothalamic-pituitary-gonadal axis;

Should be treated first by resolving or improving the associated comorbidities.

- Androgen deficiency increases with age in healthy men. In Indian men, there is a 20-48% prevalence in men above 40 years of age. Up to 85% of late onset hypogonadism is due to a functional impairment of the hypothalamus-pituitary-testicular axis, mostly secondary to metabolic conditions. Men with higher total testosterone concentrations had 42% lower risk of type 2 diabetes than those with lower concentrations, in meta-analyses.
- Screening questionnaires – Androgen Deficiency in Aging Males (ADAM); Quantitative ADAM (qADAM); Aging Male Survey (AMS); Massachusetts Male Aging Study (MMAS); Hypogonadism Impact of Symptoms Questionnaire (HIS-Q).
- The sensitivity for the ADAM is about 97%, for the AMS 83% and the MMAS 60%. Specificity was 30% for the ADAM, 59% for MMAS and 39% for AMS.
- Three things which determine signs and symptoms of low testosterone – Age/suddenness of onset; severity of androgen deficiency; underlying cause.
- How to make correct diagnosis – 3 things to remember: Signs and symptoms suggestive of hypogonadism; early morning fasting sample for testosterone; levels below 300 ng/dL on 2 separate days.
- Goals of testosterone therapy in adults – Ensure no untoward side effects are present; maintain normal testosterone levels; symptom improvement.
- Monitoring of therapy – Biochemical: Hematocrit; Prostate-specific antigen; Ultrasound prostate; Clinical – Unexplained aggression and violence; Sexual hyperactivity; Male pattern alopecia, sudden onset or worsening; Darkening of skin; Gynecomastia, sudden onset.
- Most guidelines recommend against TTh in patients with metastatic or locally advanced prostate cancer and in patients at high risk for recurrent prostate cancer.
- Use TTh in stable coronary artery disease (CAD) patients or in stable heart failure; avoid in unstable CAD, decompensated heart failure.

a-HELLO: API INITIATED THERAPY SPECIFIC RECOMMENDATIONS FOR TELECONSULTATION

Dr Mangesh Tiwaskar, Mumbai; Dr Shashank R Joshi, Mumbai

- Telehealth has three aspects: Monitoring of patients, telemedicine and tele-education.
- Medicolegal issues – *Doctor-patient relationship:* The lack of face-to-face contact in some modes of telemedicine is seen as a barrier to adequate development of the doctor-patient relationship. *Informed consent:* Informed consent is an important medicolegal requirement while treating a patient; consent should be obtained for telemedicine interaction, transmission of data, treatment, monitoring and consultation. *Privacy:* The right to privacy has been an integral part of medical ethics and is supported by various codes including the International Code of Medical Ethics; password security should be maintained to avoid unauthorized access to information. *Rights of patients:* Patient has a right to receive one's medical record in the electronic format to know standards and safety guidelines. *Reimbursement:* Currently, there is no provision for reimbursement from medical insurance in telemedicine practice.
- HIPAA Guidelines on Telemedicine: Electronic protected health information (ePHI) – The channel of communication used for communicating ePHI at distance also has to be HIPAA-compliant; You should not use SMS, Skype or email for telemedicine: as copies of communications sent by SMS, Skype or email remain on service providers' servers, and contain individually identifiable healthcare information; Communicating with patients using secure messaging.
- Challenges and the future: Institution of a regulatory authority; Standardized format of information to patients and consent form with option to opt in/out of telemedicine; Mandatory telemedicine courses for all medical students and refresher courses for medical practitioners and technical staff; Responsibility for privacy, confidentiality and security of patient information and treatment; Accreditation/ licensing of doctors using telemedicine; Building confidence of both the patient and distant doctor; Clear guidelines for teleconsulting insurance and on issues of telemedicine across national borders; Standardization of equipment and teleservices; Equipment liability, maintenance and authority; Telemedicine laws for information storage and access; Establishing telemedicine unit at every hospital.
- The pandemic has changed our practice. 'Safety first' has become the dictum. The change is not difficult; doctors have to adapt and adopt new systems.

- Need for therapy specific teleconsultation guidelines: Ever evolving response to combat the pandemic; minimal access to quality healthcare services; telemedicine is the preferred and most accessible channel; Reliability and quality from digital consultation practices continues to be in question; Available guidelines are generic and do not cover indication specific use cases; Ambiguity around application and suitability of digital platforms across different therapeutic areas.
- Pros of teleconsultation: Gives access to healthcare services in remote areas and to those with mobility issues; It has the power to overcome geographical barriers; It may provide an opportunity to reduce healthcare spending; It can save time for the patient and caregiver; a medical practitioner or hospital can consult with different specialists, irrespective of their location; It helps patients to engage with their healthcare providers more frequently, in a convenient way, which may result in a better doctor-patient relationship; The follow-up of patients is likely to be better.
- Cons of telemedicine: Telemedicine requires infrastructure and technical training; It may reduce direct interaction of patients with doctors; There is a lack of standardized format to the interaction and the absence of a consent form for either opting for or refusing the service; Telemedicine is still not included in the medical curriculum; Besides ambiguity regarding responsibilities in case of negligence, there are concerns about privacy, confidentiality, security of patient information and treatment; There is no clarity with respect to medicolegal issues arising out of telemedicine; Currently, no health insurance policy in India factors in telemedicine.

HEART RATE AN INDEPENDENT RISK FACTOR AND THE PROFICIENT STUDY

Dr Jagdish Hiremath, Pune

- Increased heart rate (HR) commonly precedes effort-induced ischemia and the frequency of ischemic episodes is twice as high in patients with a resting HR >80 bpm as compared to those with HR <70 bpm.
- Increased HR is an independent risk factor for ischemia-triggered arrhythmia, infarct size and mortality.
- Both β-blockers and nondihydropyridine calcium antagonists reduce HR, with the degree of angina reduction being directly related to the magnitude of HR reduction.
- In many clinical trials in patients with angina, ivabradine, given as monotherapy or in combination with β-blockers, has been shown to have antianginal and anti-ischemic effects and to improve quality of life (QoL).
- In angina patients with congestive heart failure (CHF) and left ventricular systolic dysfunction (LVSD), the use of ivabradine improves prognosis, reduces recurrent hospitalizations and improves QoL.
- The results of the PROFICIENT study support the use of ivabradine PR, once daily, as an additional option to the conventional formulation of ivabradine, twice daily, used in the management of stable chronic heart failure with systolic dysfunction.
- Use of ivabradine PR will help in building treatment adherence and in return might improve clinical outcomes of the patients.

THE ART AND SCIENCE OF IVT IN ACUTE ISCHEMIC STROKE

Dr MV Padma Srivastava, New Delhi

- Time is brain. Current management of acute ischemic stroke revolves around the concept of core and collaterals.
- Tissue based selection of patients for acute reperfusion therapies is more important than time and clock based inclusion.
- Newer advances in neuroimaging have made it possible to select such cases more optimally.
- Newer thrombolytic agents hold more promise for a better strategy of thrombolysis.

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News and Views

India Expands COVID Booster to All Adults from 10th April, 2022

Strengthening its efforts to curb the COVID pandemic, India will offer booster doses of the COVID-19 vaccine to all adults from 10th April, 2022. However, the free third dose will be restricted to frontline workers and those over the age of 60 years who can get it at government centers.

Those older than 18 who received a second dose 9 months ago will be eligible for the "precautionary" dose, as per the health ministry. The health minister said while flagging the decision that this will be, "adding an extra layer of safety".

The booster program started in January, limited to frontline workers and the elderly. A total of 24 million booster doses have been given in the country. The country has administered 1.85 billion vaccine doses among its population of 1.35 billion, 82% of which are Covishield doses. Other vaccines used in India are the indigenously developed Covaxin and Corbevax, and Russia's Sputnik V. (*Reuters, April 8, 2022*)

New Ayushman Bharat Health Schemes Offer More Procedures, City-specific Pricing

The National Health Authority (NHA) has introduced differential pricing centered on the type of city and level of care and added 365 new procedures, according to their utilization and cost-effectiveness. This was done with the objective of rationalizing the packages offered under the government's Ayushman Bharat health insurance scheme. The new version of the Health Benefit Package, 2022 was launched under the Ayushman Bharat Pradhan Mantri Jan Arogya Yojana with a total of 1949 procedures.

The new procedures included in the scheme include bone marrow transplants and cochlear implant surgery. Additionally, high-end drugs and diagnostics such as magnetic resonance imaging (MRI) and computed tomography (CT) scans have been unbundled from the packages so that their cost is not included in the primary treatment package and if needed can be created as a separate head.

As per the NHA office memorandum, "*the rationalization exercise for revision of HBP 2022 comprised of an extensive review of current scheme performance in terms of its utilization and related issues, consideration of cost evidence to determine the variation in cost and price, an exhaustive consultation with expert committees in different specialties, inputs from state health agencies, hospital associations and other stakeholders.*" (*TNN, Apr 9, 2022*)

India Diabetes Study: High BMI Linked to Raised Risk of CVDs

India Diabetes Study (IDS) has reported that more than 55% of newly diagnosed type 2 diabetes mellitus (T2DM) patients in India have low high-density lipoprotein cholesterol (HDL-C) values, suggesting that they are at higher risk of developing some form of cardiovascular disease (CVD) in their lifetime. The study also said that 42% of all T2DM patients are at a higher risk of hypertension. As per the Indian Consensus Group guidelines, the mean body mass index (BMI) of the patients was recorded to be 27.2.

The study published in the *PLOS* journal was supported by Eris Lifesciences and co-authored by 16 doctors during the period 2020-2021. It was conducted with the involvement of more than 1,900 physicians and had a sample size of 5,080 patients with a mean age of 48 years, from 27 states across the country.

Dr AG Unnikrishnan said, "*India Diabetes Study focused on highlighting the cardiovascular risk factors in newly diagnosed diabetes patients across India. While treatment should focus on dietary changes, physical activity and glucose control, additionally addressing cardiovascular risk by strategies like a blood pressure control and lipid management offer a more holistic way of management- as also suggested in the India Diabetes Study.*"

The study also reported that 92.5% and 83.5% of the total patients did not receive any cholesterol-lowering and antihypertension treatment. Low HDL-C was reported as the most frequent major risk while 82.5% of patients seemed to have at least one cholesterol-related abnormality. (*ET HealthWorld, April 8, 2022*)

Treatment of Mild Hypertension During Pregnancy is Safe and Effective

There were fewer adverse pregnancy outcomes when pregnant women with mild chronic hypertension were treated with an antihypertensive medication before or during the first 20 weeks of pregnancy in the Chronic

Hypertension and Pregnancy (CHAP) trial published in the *New England Journal of Medicine.*[1]

A total of 2,408 pregnant women with mild hypertension were enrolled in this multicenter trial, from 2015 to 2021. Of these, 1208 participants were assigned to treatment with antihypertensive medication to keep their blood pressure (BP) below 140/90 mmHg (intervention group); the remaining 1,200 received an antihypertensive only when the BP increased to 160/105 mmHg and higher (control group). They were followed through delivery and for 6 weeks after delivery.

Results showed that treatment of hypertension to keep the BP below 140/90 mmHg reduced the odds of preterm birth or other pregnancy-related complications. About 70% of women did not have any negative pregnancy outcomes, while 30% developed pre-eclampsia, placental abruption, preterm birth (<35 weeks) or intrauterine or neonatal death. About 37% of the participants in the control group experienced a similar adverse event.

The antihypertensive treatment had no adverse impact on fetal growth as the birth weight of infants was comparable between the two groups. Most of them had normal birth weight; 11% of babies born to participants who received medication and 10% of babies born to those in the control group had impaired fetal growth.

This study from the National Institutes of Health (NIH) shows that hypertension in pregnancy can be safely and effectively treated. Giving antihypertensive therapy to keep BP below 140/90 mmHg in pregnant women with mild chronic hypertension is a feasible strategy rather than waiting to start treatment when hypertension increases to severe levels, according to the study.

Reference: *Tita AT, et al; Chronic Hypertension and Pregnancy (CHAP) Trial Consortium. Treatment for mild chronic hypertension during pregnancy. N Engl J Med. 2022 Apr 2. [Epub ahead of print]*

A Low-salt Diet Improves the Quality of Life in Heart Failure Patients

A recent study published in *The Lancet* reported that while low-sodium diets help in improving the quality of life for people with heart failure, they did not reduce clinical events such as hospitalization or emergency room visits.

Researchers in the study reported that reducing sodium intake in the diet can benefit people with heart failure. However, adverse clinical outcomes such as hospitalization do not get affected by the reduction of sodium in diet. In the study, participants were randomly placed into two groups, the intervention group with a low-sodium diet (<1500 mg of sodium daily) and the control group receiving the standard of care of the region they were located in. The results showed that the hospitalizations, emergency room visits, and all causes of death were not reduced for participants in the low-sodium diet group compared to the control group. However, a moderate benefit on quality of life and in the New York Heart Association (NYHA) scale classification in the intervention group was seen.

The study results were summarized by Dr Paz as, "*Following a low-salt diet did not reduce death or trips to the hospital in people with congestive heart failure. Despite this fact, there still was a signal for benefit in some key endpoints favoring a low-salt diet, including functional assessments.*" (*Do low salt diets improve outcomes in heart failure? [medicalnewstoday.com)]*)

ADHD Patients could Benefit from Caffeine Use

It was suggested in a recent review capturing animal model studies that caffeine may help manage cognitive symptoms, such as deficits in attention, learning and memory, in individuals with attention deficit hyperactivity disorder (ADHD). The results on hyperactivity and impulsiveness were ambiguous suggesting that it may not be suitable for ADHD with these symptoms.

Study researcher, Javier Vazquez said that since there are not too many rugs available for therapy of ADHD, certain medications and stimulants are laced with confusion about being used in childhood adolescence. This study on caffeine becomes valuable for patients with ADHD.

The results suggested that caffeine could be used to treat individuals with ADHD whose symptoms mainly involve attentional deficits, but further studies are needed to validate these results in human studies. (*ADHD: Could caffeine treat some symptoms? [medicalnewstoday.com]*)

Experts Suggest Shortening the Wait Time for Elective Surgery after an Asymptomatic COVID-19 Infection

Some perioperative specialists recommend that wait times for elective surgery after asymptomatic COVID-19 infection should be shortened, in sync with the current state of the pandemic.

The American Society of Anesthesiologists and the Anesthesia Patient Safety Foundation currently recommend that elective surgeries should be delayed for at least 7 weeks after a COVID-19 diagnosis in unvaccinated patients. In a letter to the *British Journal of Anesthesia*, the specialists said that the data being

used for these recommendations are from earlier in the pandemic and since current variants of the virus cause less severe disease, they should be revised to a shorter time duration. (*Specialists Call for Shorter Surgery Delays* after *COVID Infection [medscape.com*])

The First Sublingual Drug Dexmedetomidine Approved for Agitation

The US Food and Drug Administration (FDA) has approved dexmedetomidine sublingual film for the acute treatment of agitation related to schizophrenia or bipolar I or II disorder in adults.

This is the first FDA-approved, orally dissolving, self-administered sublingual treatment for agitation. It is recommended to assess vital signs including orthostatic measurements before administering the drug. In mild-to-moderate cases, 120 μg SL or buccal initially is recommended. However, if agitation persists, dosage may be increased up to 60 μg for up to 2 doses at least at a gap of 2 hours; not to exceed 240 μg/day. In severe cases, the initial dose recommended is 180 μg SL or buccal (BUC). In case the agitation persists, 90 μg for up to 2 doses at least 2 hours apart may be given: to a maximum daily dose of 360 μg/day.

Dexmedetomidine has been continually infused in mechanically ventilated patients before, during and after extubation. It is not necessary to discontinue dexmedetomidine before extubation. (*FDA Okays First Sublingual Med for Agitation in Schizophrenia, BD [medscape.com]*)

Kappa Immunoglobulin Assessment Comes up as a Cheaper and Faster Test for MS

In new research, it was suggested that a test measuring kappa immunoglobulin-free light chains in cerebrospinal fluid (KCSF) is a tested alternative for diagnosing multiple sclerosis (MS).

The results of the study showed that the kappa test was similar in efficacy but much more convenient to run in the laboratory, less expensive and rapid compared with other commonly used tests. The study confirmed the role of kappa free light chains (KFLC) in the diagnostic work-up for MS. Both KFC index (corrected for blood-CSF barrier permeability) and KFLC/IgG ratio (assessing the overproduction of KFLC in CSF only) demonstrated high sensitivity and specificity towards MS diagnosis. Overall oligoclonal bands (OB) continues to be the gold standard for CSF analysis in MS.

The researchers suggested that the KFLC index is the most sensible and specific quantitative marker for diagnosing MS and suggested that CSF KFLC/IgG may be used to find whose RIS-CIS patients will convert to MS. (*A Faster, Cheaper Diagnostic Test for MS? [medscape.com]*)

Renal Outcomes in COVID-19 Pneumonia Patients with Acute Kidney Injury

Critically ill intubated COVID-19 patients with acute kidney injury (AKI) are at high risk of developing chronic kidney disease (CKD), suggests a new study presented at the recently concluded National Kidney Foundation Spring Clinical Meetings held in Boston, USA.

This retrospective case-control study included 125 intubated patients with pneumonia from January 1, 2020 to December 31, 2020. Of these 56 had confirmed COVID-19 pneumonia and 69 had bacterial pneumonia. Logistic regression analysis and Cox proportional hazard ratio were the statistical methods used to evaluate the probability and the risk of CKD at 90 days in intubated COVID-19 patients after incident AKI during hospitalization. Serum creatinine levels were measured at baseline, during the first incident AKI, at the time of discharge and at 90 days.

A total of 56 COVID pneumonia patients developed AKI during hospitalization, while 69 patients with bacterial pneumonia had AKI. However, renal recovery occurred in 68% COVID-19 pneumonia patients with AKI vs. 84% bacterial pneumonia patients with AKI.

Analysis of renal outcomes of AKI patients showed that the intubated COVID-19 patients with new onset AKI during hospitalization were 2.6 times more likely to progress to CKD within 90 days with a hazard ratio of 2.48 (148% higher risk). Thirty percent of COVID patients developed CKD vs. 16% in patients with bacterial pneumonia.

More COVID-19 patients needed emergent hemodialysis during hospital stay (20%) compared to bacterial pneumonia patients (7%) corresponding to higher incidence of post-discharge dialysis in COVID patients compared to bacterial pneumonia patients; 18% vs. 3%, respectively.

The average peak creatinine level in COVID-19 pneumonia patients was 2.16 mg/dL in comparison to a peak of 2.03 mg/dL in bacterial pneumonia patients. However, at 90 days, the average levels in both groups were 0.90 mg/dL.

These observations reiterate the high risk of AKI in critically ill intubated patients with pneumonia but the risk was higher and the prognosis was worse in patients with COVID-19 pneumonia than in bacterial pneumonia

patients regardless of comorbidities, duration of mechanical ventilation or highest AKI stage. These findings highlight the need to closely monitor renal function as inpatients and particularly after discharge, as outpatients, to check for disease progression and timely intervention.

Reference: *Edding S, et al. Renal function dynamics among mechanically ventilated patients with acute kidney injury (AKI) and COVID-19 pneumonia. NKF 2022; Poster #5. Available from: https://cme.kidney.org/spa/courses/resource/2022-spring-clinical-meetings/event/home/posters/abstracts?abstractId=8*

Healthy Plant-based Diet and the Risk of Type 2 Diabetes

Eating healthy plant-based foods reduces the risk of developing type 2 diabetes compared to those who consumed a diet rich in unhealthy plant-based foods. And, those who ate a healthy plant-based diet also had a different metabolic profile, suggests a recent study published in the journal *Diabetologia*.[1]

Researchers from the US evaluated the dietary patterns of 8,827 participants from the Nurses' Health Study, Nurses' Health Study II and Health Professionals Follow-up Study using semi-quantitative food frequency questionnaires. Three plant-based diets were examined and based on the answers, three indices were developed namely overall Plant-based Diet Index (PDI), a Healthy Plant-based Diet Index (hPDI) and an Unhealthy Plant-based Diet Index (uPDI), which were used to evaluate their adherence to plant-based diet. The mean age of the study subjects was 54 years and the mean BMI was 25.6 kg/m^2.

The *healthy plant-based* diet included whole grains, fruits, vegetables, nuts, legumes, vegetable oil, tea and coffee. The *unhealthy plant-based* diet included refined grains, fruit juices, potatoes, sugar-sweetened beverages and sweets and desserts, while the *animal-based* diet included animal fats, dairy, eggs, fish, meat and other animal-based products.

The plant metabolites were measured to develop metabolite profile scores for the participants and their association with the risk of incident type 2 diabetes was examined. Fifty-five metabolites were found to correlate with an overall plant-based diet, 93 metabolites with a healthy plant-based diet and 75 metabolites with an unhealthy plant-based diet.

Analysis of different metabolites revealed a difference between the healthy and unhealthy plant-based diets and the risk of type 2 diabetes. Participants with high PDI and hPDI scores were at a lower risk of type 2 diabetes with an adjusted hazard ratio of 0.83 and 0.8, respectively.

Gamma-aminobutyric acid, C5-carnitine and three triacylglycerol metabolites were associated with lower PDI score and consequently a higher risk for type 2 diabetes. On the other hand, an inverse association was noted between isoleucine, C22:0 ceramide and six triacylglycerol metabolites and a hPDI and therefore an increased risk of type 2 diabetes.

Metabolites such as trigonelline, betaine and glycine showed an association with higher PDI score and lower risk for type 2 diabetes. Likewise, trigonelline, hippurate and C22:6 ceramide were associated with a higher hPDI score and a lower risk for type 2 diabetes.

This study recapitulates the beneficial role of plant-based diets, especially a healthy plant-based diet on the risk of type 2 diabetes as well as in the management of type 2 diabetes in achieving glycemic control. A healthy plant-based diet is also heart-friendly. This study has also shown a correlation between the plant metabolites and risk of type 2 diabetes, which warrants further investigation to validate their role in the risk of developing type 2 diabetes. "The metabolite profiles we identified could be used to assess the adherence and metabolic response to plant-based diets during dietary interventions", suggest the authors.[2]

References: *[1]Wang F, et al. Plasma metabolite profiles related to plant-based diets and the risk of type 2 diabetes. Diabetologia. 2022 Apr 8. [Epub ahead of print]. [2]Available from: https://www.healio.com/news/endocrinology/20220411/healthy-plantbased-diet-linked-to-lower-risk-for-type-2-diabetes*

■■■■

Who am I? Know Your Soul Profile

"*I am not my physical body, as I know, once my body dies, nobody wants to touch it.*" (Adi Shankaracharya in the Bhaja Govindam)

"*I am not my mind as I know whenever I am in trouble; the mind asks the heart for help.*" (Deepak Chopra in the Seven Spiritual Laws of Success)

"*I am my consciousness which is residing in the core of my heart.*" (Svetasvatara Upanishad 5.8)

"*This consciousness is nothing but a web of energized information situated in the void.*" (Chandogya Upanishad Chapter XII — the Birth of the Gross from the Subtle)

"*The consciousness is timeless, has no beginning, no end, weapons cannot cut it, air cannot dry it, water cannot wet it and fire cannot burn it.*" (Bhagwad Gita 2.23, 24)

Each one of us has a physical profile (as defined by our height, complexion, collar number, waist size, etc.) and a mental or ego profile. A few examples of ego profile are: my bank balance, my car, my job designation, my locality of residence, my size of house, my contacts, my power, my clothes', etc.

Similarly, each one of us also has a soul profile. We should give sometime to ourselves to know our soul profile and revisit it at least once in a week.

According to Dr Deepak Chopra, to know the soul profile, one should ask the following 7 questions to one's consciousness while sitting in a meditative poise or in state of relaxation. The answer to each question should be either in 3 words or 3 phrases.

1. What is my purpose of life?
2. What is my contribution going to be for my friends and family?
3. Three instances in my life when I had my peak experiences.
4. Names of three people who inspire me the most.
5. Three qualities which I admire the most in others.
6. Three of my unique talents.
7. Three qualities I best express in my relationship.

These 21 answers will characterize your soul profile or will be your passport for every action you perform in your life.

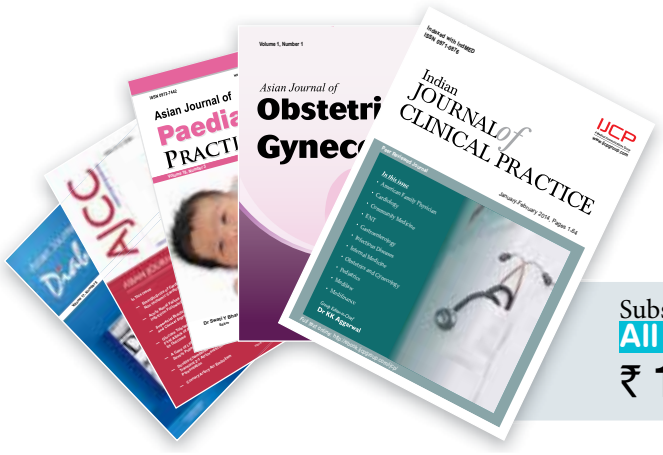
One should act from the soul profile in day-to-day life and not from the ego profile. Unlike the ego profile, the soul profile cannot be manipulated.

There are only 3 ways to improve one's soul profile and these are:

1. The choices one makes should be soul-profile oriented and not ego-profile oriented. Whenever there is an opportunity for an action, ask the head for choices, then ask the heart to choose one, and finally order the hand to take action. A soul-based action is one, which is based on the truth, is necessary and which makes the person and the people around him or her, all happy.
2. Total clarity of vision of "What do I want" and "What I do not want".
3. Learn to enter into discontinuity of thought processes using "beej mantra" or doing primordial sound meditation 20 minutes in the morning and 20 minutes in the evening.

These can also be equated to the eight limbs of Yoga Sutras of Patanjali, where the "choices I make" represent *Yama* and *Niyama*, "what do I want" represents *Dharna* and the "entering into discontinuity" represents *Dhyana* and *Samadhi*.

■■■■



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Lighter Side of Medicine

INSPIRATIONAL STORY

THE 12 GIFTS OF BIRTH

Once upon a time, a long time ago, when princes and princesses lived in faraway kingdoms, royal children were given 12 special gifts when they were born. Twelve wise women of the kingdom, or fairy godmothers as they were often called, traveled swiftly to the castle whenever a new prince or princess came into the world. Each fairy godmother pronounced a noble gift upon the royal baby.

As time went on, the wise women came to understand that the 12 royal gifts of birth belong to every child, born anywhere at any time. They yearned to proclaim the gifts to all children, but the customs of the land did not allow that. One day when the wise women gathered together they made this prophecy: Someday, all the children of the world will learn the truth about their noble inheritance…when that happens a miracle will unfold on the kingdom of Earth.

Here is the secret they want you to know.

At the wondrous moment you were born, as you took your first breath, a great celebration was held in the heavens and twelve magnificent gifts were granted to you.

1. Strength is the first gift. May you remember to call upon it whenever you need it.
2. Beauty is the second gift. May your deeds reflect its depth.
3. Courage is the third gift. May you speak and act with confidence and use courage to follow your own path.
4. Compassion is the fourth gift. May you be gentle with yourself and others. May you forgive those who hurt you and yourself when you make mistakes.
5. Hope is the fifth gift. Through each passage and season, may you trust the goodness of life.
6. Joy is the sixth gift. May it keep your heart open and filled with light.
7. Talent is the seventh gift. May you discover your own special abilities and contribute them toward a better world.
8. Imagination is the eighth gift. May it nourish your visions and dreams.
9. Reverence is the ninth gift. May you appreciate the wonder that you are and the miracle of all creation.
10. Wisdom is the tenth gift. Guiding your way, wisdom will lead you through knowledge to understanding. May you hear its soft voice.
11. Love is the eleventh gift. It will grow each time you give it away.
12. Faith is the twelfth gift. May you believe.

Now you know about your 12 gifts of birth. But there is more to the secret that the wise women knew. Use your gifts well and you will discover others, among them a gift that is uniquely you. See these noble gifts in other people.

HUMOR

FIRST DAY AT SCHOOL

A school teacher injured his back and had to wear a plaster cast around the upper part of his body.

It fit under his shirt and was not noticeable at all. On the first day of the term, still with the cast under his shirt, he found himself assigned to the toughest students in school.

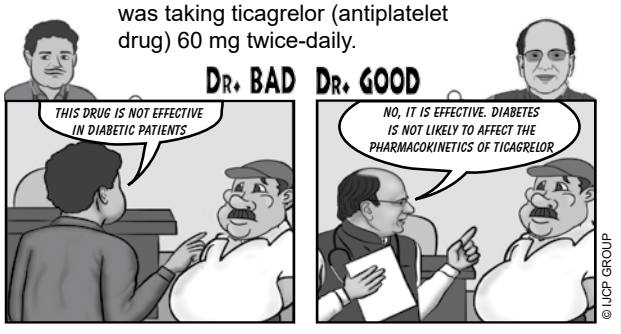
Walking confidently into the rowdy classroom, he opened the window as wide as possible and then busied himself with desk work.

When a strong breeze made his tie flap, he took the desk stapler and stapled the tie to his chest.

He had no trouble with discipline that term.

Dr. Good and Dr. Bad

SITUATION: A type 2 diabetic male with concomitant CVD was taking ticagrelor (antiplatelet drug) 60 mg twice-daily.



LESSON: It has been found that ticagrelor 60 mg twice-daily displays similar efficacy in reducing platelet reactivity, regardless of presence of diabetes.

Thromb Haemost. 2017;117(5):940-7.

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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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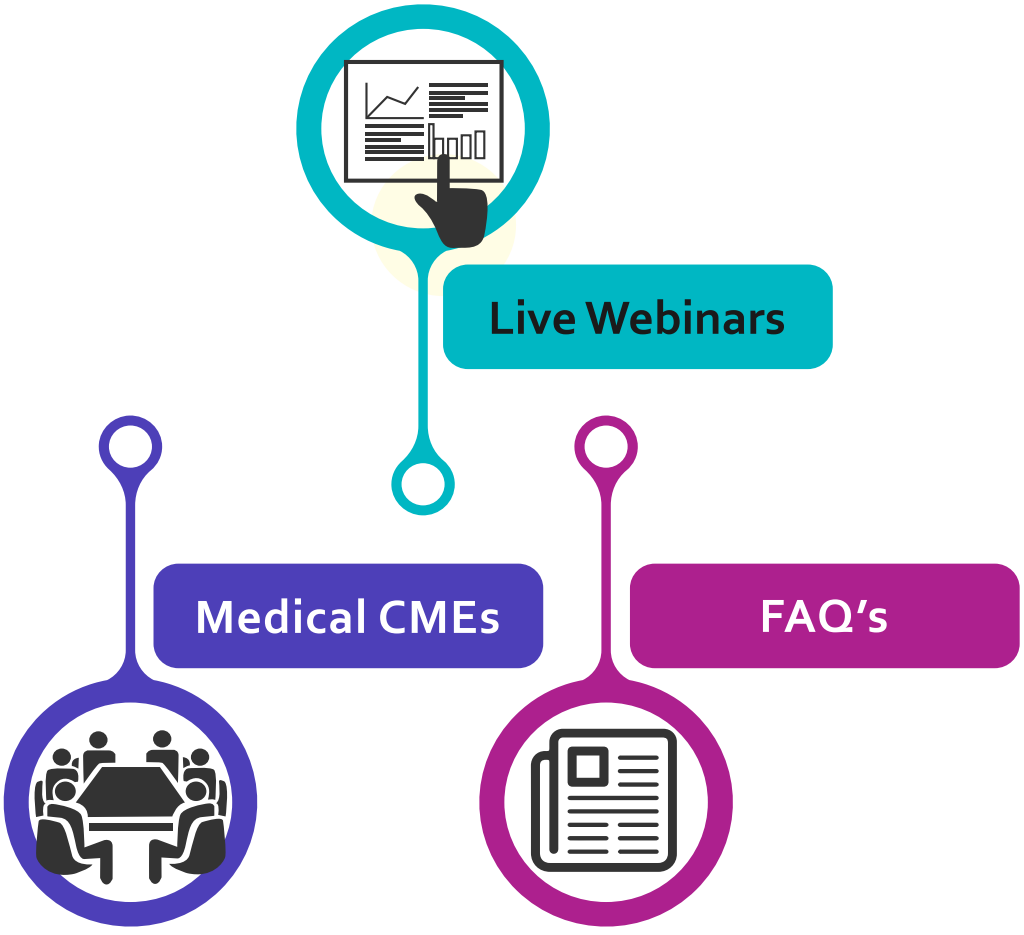

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