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

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Indian JOURNAL of CLINICAL PRACTICE

A Multispecialty Journal

Volume 33, Number 5 October 2022, Pages 1–60 **Single Copy Rs. 300/-**

Peer Reviewed Journal

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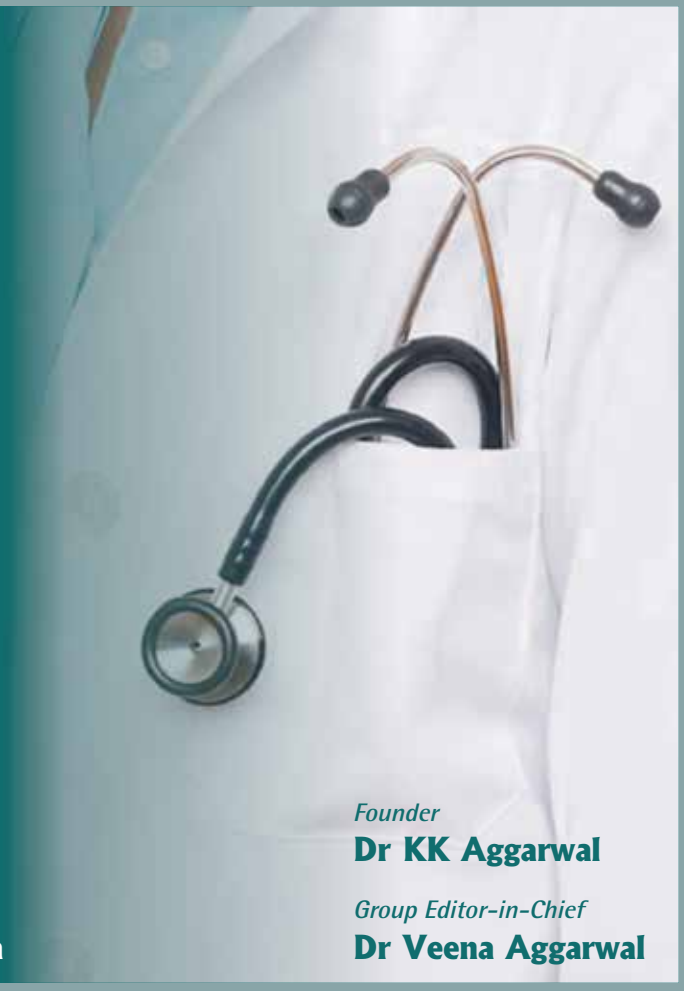

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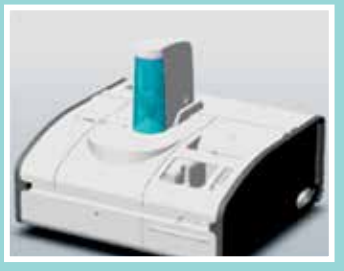

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Indian JOURNAL of CLINICAL PRACTICE
A Multispecialty Journal

Volume 33, Number 5, October 2022

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

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

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Updates in Medicine

RISK FACTORS FOR ACANTHAMOEBA KERATITIS AMONG CONTACT LENS USERS

The risk of acanthamoeba keratitis increases fourfolds among individuals who use reusable contact lenses compared to those who used disposable contact lenses daily. Taking a shower while wearing the contact lenses and sleeping with contact lenses were risk factors for the infection. Those who wore daily disposable lenses were at a higher risk if they reused them… (*Source: Ophthalmology, Aug. 8, 2022*)

USPSTF DRAFT STATEMENT RECOMMENDS SCREENING ADULTS ≤64 YEARS FOR ANXIETY

Marking a first, the US Preventive Services Task Force (USPSTF) has recommended screening for anxiety among adults aged ≤64 years in a draft statement posted on its website. Pregnant and postpartum women should also be screened for anxiety. However, the statement does not recommend screening older adults citing lack of sufficient evidence. The draft recommendations are available in public domain for comments till 17th October.… (*Source: USPSTF, Sept. 20, 2022*)

WEARING A PEDOMETER MAY HELP INCREASE DAILY STEPS

Wearing a pedometer has a moderate effect in increasing the number of daily steps, finds a study published in the September 2022 issue of *American Journal of Health Behavior*. The participants walked 388 steps more when they wore a pedometer while walking than those who did not wear one… (*Source: American Journal of Health Behavior, Sept. 2022*).

SURGERIES WITH HIGHEST RISK FOR BLOOD TRANSFUSION

A study published in the *British Journal of Surgery* has identified 20 surgeries that are associated with the highest risk of blood transfusion. These include: Cardiac valve replacement, coronary artery bypass grafting (CABG), aortic aneurysm repair, radical cystectomy with urinary diversion, open femoral fracture repair, open radical nephrectomy, abdominal/retroperitoneal tumor excision >10 cm, vascular bypass, splenectomy, leg amputation, pancreatectomy, liver resection, bowel resection, spinal arthrodesis, arterial embolectomy, gastrectomy, myomectomy, open radical prostatectomy, total abdominal hysterectomy and endovascular repair of thoracic or abdominal aortic aneurysm… (*Source: British Journal of Surgery, Dec. 2020*)

IMPACT OF COVID-19 VACCINATION ON MENSTRUAL CYCLE LENGTH

The length of the menstrual cycle may increase by less than 1 day following coronavirus disease 2019 (COVID-19) vaccination in some women, according to a new National Institutes of Health (NIH) study published in the *BMJ Medicine*. However, these changes are temporary. The international retrospective study analyzed 19,622 women aged 18 to 45 years mostly from the UK, US, Canada and Europe to study the change in the menstrual cycle including its length following COVID-19 vaccination. Majority were below 35 years of age. Out of these, the vaccinated group included 14,936 women with data available for at least 3 consecutive cycles before vaccination and the unvaccinated group

included 4,686 women with data available for a minimum of 4 consecutive cycles. Data was sourced from the menstrual cycle tracking application, Natural Cycles. Among the vaccinated participants, the length of the cycle in which they were vaccinated increased by less than 1 day compared with those who were not vaccinated. On average, the cycle length increased by 0.71 day after the first dose and 0.56 day after the second dose. Among those who received the two doses in one cycle, the length increased by 3.91 days. No differences in the cycle length were noted according to the type of the vaccine taken. These changes were observed more among younger women and those who had a longer cycle length prior to taking the vaccination. The increase in cycle length was temporary except among those who received both doses in the same cycle, in whom the increased length was decreased in the next cycle, but was still more than those in the unvaccinated group. Hence, women taking the COVID-19 vaccine can be counseled about the changes that may occur in the menstrual cycle length post-vaccination. They should be reassured that these changes are small and transient in nature.

(*Ref: Edelman A, et al. Association between menstrual cycle length and COVID-19 vaccination: a global cohort. BMJ Medicine. 2022;1:e000297.*)

PREGNANCY ANXIETY WITH PRETERM BIRTHS

Anxiety during pregnancy, including pregnancy anxiety is associated with preterm birth, suggests a recent study published in the journal *Health Psychology*.[1] A total of 196 women who had participated in the Healthy Babies Before Birth study were subjected to four different anxiety scales in the first and third trimester of pregnancy to study the association between anxiety and length of gestation. These questionnaires were related to general anxiety, pregnancy anxiety and pregnancy stressors. After adjusting for confounding variables such as age, educational status, parity and obstetric risk, a robust association was seen between pregnancy-related anxiety during the third trimester and shorter gestation. Assessment of general anxiety during the first trimester also correlated with a shorter gestation. Anxiety measured by the Overall Anxiety Severity and Impairment Scale (OASIS) was predictive of early birth. Participants who had general anxiety symptoms during the first trimester and developed pregnancy anxiety in the third trimester were most likely to have a preterm delivery. Pregnant women are routinely screened for depression. Similar to depression, anxiety too is associated with adverse maternal and neonatal outcomes. Based on their findings, the authors suggest pregnancy-related anxiety as a risk factor for premature birth and recommend screening pregnant women also for symptoms of anxiety in early pregnancy and anxiety specifically due to pregnancy in the third trimester. Women who exhibit significant general anxiety symptoms should be closely monitored all through the pregnancy for any increase in their symptoms. This would help identify mothers at risk of preterm births.

(*Ref: Dunkel Schetter C, et al. Anxiety in pregnancy and length of gestation: findings from the healthy babies before birth study. Health Psychol. 2022 Sept. 26.*)

■■■■

Study Reveals 80% Increase in Alzheimer's Diseases among Older Adults with COVID-19

A study of over 6 million individuals in the US found that older adults with COVID-19 have a 50% to 80% increased risk of Alzheimer's disease within a year.

The scientist evaluated the anonymous electronic health data of 6.2 million US senior citizens who were 65 and older and received medical care between February 2020 and May 2021 but were not diagnosed with Alzheimer's. The participants were divided into two groups: one with individuals who had COVID-19 during that time and the other with no COVID-19 infection. The COVID-19 study group had more than 4,00,000 participants, compared to 5.8 million in the non-infected group.

The study results were published in the *Journal of Alzheimer's disease*. It revealed that women at least 85 years old had the highest risk of developing the illness. The researchers stated that it is uncertain whether COVID-19 causes or hastens the onset of Alzheimer's disease. (*Source: The Print, Sept. 14, 2022*)

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Imeglimin: Finding a Place in Modern Diabetes Pharmacotherapeutics

ABSTRACT

Type 2 diabetes mellitus (T2DM) is a multifactorial disease. Newer facets of its causation, clinical course, complications and therapy are being unraveled regularly. This editorial describes imeglimin, a first-of-class oxidative phosphorylation inhibitor, that has been approved for T2DM in Japan and India.

Keywords: Gluconeogenesis, imeglimin, oxidative phosphorylation inhibitor, mitochondria, pharmacotherapeutics, type 2 diabetes mellitus

Newer facets of the pathophysiology of diabetes are being recognized by researchers. This has opened up novel possibilities and avenues for the treatment of this syndrome. Oxidative phosphorylation is a key biochemical reaction, which occurs in our cells, and ensures energy homeostasis. Modification of the pathways of oxidative phosphorylation is a promising therapeutic target for diabetes, and imeglimin, a novel drug, utilizes this mechanism. The clinical trial program of imeglimin has shown favorable results. This editorial analyzes this new molecule as a potential treatment of diabetes.

MECHANISM OF ACTION

Imeglimin has a dual mechanism of action. It acts simultaneously to increase insulin sensitivity as well as insulin secretion. Both these mechanisms are mediated through separate biochemical pathways (Table 1).[1]

Insulin Secretagogue

Imeglimin enhances insulin secretion of nicotinamide phosphoribosyltransferase (NAMPT). NAMPT is the rate-limiting enzyme for nicotinamide adenine dinucleotide (NAD) synthesis. If expressed properly, it increases intracellular NAD^+ concentration, which in turn optimizes the efficiency of the mitochondrial electron transport chain, and increases mitochondrial adenosine triphosphate (ATP) content in the beta cells. This inhibits ATP-sensitive potassium (K_{ATP}) channel activity, encourages calcium influx into the beta cells, and promotes insulin secretion. A NAD^+ metabolic known as cyclic ADP-ribose (cADPR) also increases glucose-stimulated release from the beta cells.[1]

Insulin Sensitization

Imeglimin also optimizes mitochondrial function in hepatocytes. It inhibits complex I activity, restores

Table 1. Mechanism of Action of Imeglimin

Biochemical
• Inhibition of oxidative phosphorylation
• Modulation of mitochondrial function and structure
Physiological
• Increase in insulin sensitivity (muscle uptake of glucose)
• Reduction of hepatic gluconeogenesis
• Increase in insulin secretion
Downstream
• Reduction in formation of reactive oxygen species (antioxidant effect)

complex III activity and suppresses formation of reactive oxygen species (ROS). In the muscle, it improves uptake of glucose by increasing the expression of a transcriptional coactivator termed as peroxisome proliferator-activated receptor-γ coactivator 1α (PgC1α).[1]

Imeglimin vs. Metformin

Imeglimin differs from metformin in that it is a competitive inhibitor of complex I activity and balances complex III: I function. Its insulinotropic effect also sets it apart from metformin. There is no risk of lactic acidosis with imeglimin. Metformin inhibits mitochondrial glycerophosphate dehydrogenase (mGPDH) and causes pyruvic acid to be converted to lactic acid, which may accumulate to toxic levels. However, imeglimin is not an mGPDH inhibitor and therefore this safety concern does not arise with its use.[2]

PLACE IN TAXONOMY

Imeglimin is the first of its class of oxidative phosphorylation inhibitors. It is thought to act by increasing the mitochondrial bioenergetic efficiency of cells in the pancreas, liver and skeletal muscle. Imeglimin does not find mention in contemporary classifications of glucose-lowering therapy,[3,4] though it is listed in a classification of obesity-lowering drugs.[5] However, it can be comfortably placed along with other insulin secretagogues as well as insulin sensitizers. Imeglimin does not lead to hepatic AMP kinase activation in murine models.[6]

CLINICAL TRIAL PROGRAM

A robust clinical trial program has been conducted using imeglimin as monotherapy as well as in combination with other glucose-lowering drugs in Caucasian and Japanese participants.

A recent meta-analysis of 8 studies involving 1,555 participants with type 2 diabetes mellitus (T2DM) reported a statistically significant reduction in glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG) as compared to the control group.[7] The Trials of Imeglimin for Efficacy and Safety (TIMES) 1 study compared imeglimin monotherapy with placebo in 213 Japanese participants over 24 weeks. It demonstrated a 0.87% reduction in HbA1c with a safety profile similar to that of placebo.[8] The open-label TIMES 2 study, assessed imeglimin in 714 participants, both as monotherapy and in combination with other glucose-lowering drugs (acarbose [n = 64], metformin [n = 64], dipeptidyl peptidase-4 inhibitors [n = 63], glinide [n = 64] glucagon-like peptide-1 receptor agonist [n = 70], sodium-glucose co-transporter 2 inhibitor [n = 63], sulfonylurea [n = 127] and glitazone [n = 65]). This Japanese study lasted 52 weeks, and showed an HbA1c reduction of 0.92%. Most adverse events were mild or moderate in nature.[9]

TIMES 3 was a 16-week long study with a 36-week open-label extension period conducted in 215 Japanese participants. It assessed the safety and efficacy of imeglimin in combination with insulin. An HbA1c reduction of 0.60% and 0.64% was noted at 16 and 52 weeks, respectively, with a satisfactory safety profile. Imeglimin use did not increase the risk of hypoglycemia.[10]

SAFETY

Imeglimin has shown a good safety and tolerability profile in both animal models and clinical studies. Angiomatous hyperplasia leading to development of hemangioma and possibly hemangiosarcoma has been observed in the small intestine of rats, but this appears less relevant to humans considering the relative dose used.[1] In clinical trials, no major safety or tolerability issue has been flagged. Imeglimin is well-absorbed orally, and is excreted through the kidney. The drug is safe for use even in severe renal insufficiency, albeit in reduced doses, though it has not been studied in severe hepatic impairment.

PLACE IN TREATMENT ALGORITHMS

The drug should be a welcome addition to our existing choice of glucose-lowering drugs. A rational approach incorporating both nonpharmacological and pharmacological modes of treatment is the way to successful diabetes management. Table 2 lists the

Table 2. Potential Indications for Imeglimin

Initiation

- If other drugs are contraindicated or considered to have averse risk-benefit ratio, e.g.;
  - Elderly
  - Renal insufficiency
- Isolated fasting hyperglycemia

Interchange

- If other drugs are not well-tolerated, e.g.;
  - Gastrointestinal effects
  - Risk of acidosis
  - Weight gain
  - Hypoglycemia

Intensification

- If other drugs are insufficient in achieving euglycemia

Table 3. Posology of Imeglimin

- Available as 500 mg tablets
- Dose 1000 mg twice a day post-meal
- Indication: type 2 diabetes
- Contraindications:
  - Pregnancy, lactation, preconception
  - Childhood
  - Intensive muscle exercise
  - Excessive alcohol intake
  - Estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 [for full dosage]
  - Significant hepatic dysfunction
  - Pituitary or adrenal dysfunction
- Dose 500 mg if eGFR 15-45 mL/min/1.73 m^2
- Dose 500 mg OD if eGFR <15 mL/min/1.73 m^2
- No clinically significant drug-drug or drug-food interactions

potential position for imeglimin in T2DM, and suggests some specific indications for its use. Table 3 highlights the important posological considerations, caveats and contraindications which must be kept in mind while prescribing the drug.

We take this opportunity to reiterate, however, that no drug, singly or in combination can address the wide spectrum of pathophysiological abnormalities that lead to and are associated with type 2 diabetes. We also iterate that a balanced lifestyle and mind style including focus on diet, exercise, stress and sleep management are integral to diabetes care.

SUMMARY

Imeglimin is now approved in India. The basic and clinical pharmacology of the molecule is encouraging and we hope that it will prove its mettle in the fight against diabetes.

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■■■■

Herd Immunity Reaches Almost 90% in Japan

Following the seventh Omicron wave, areas with high number of cases in Japan have attained a herd immunity of around 90%. The peak was reached in August. However, this immunity may soon decline. This has been aided by COVID-19 vaccination. Nearly 65% of the population in Japan has received at least one booster dose… (*Source: Reuters, Sept. 28, 2022*)

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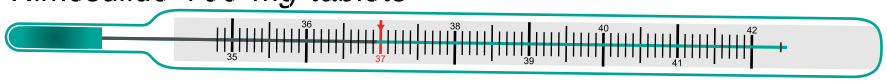

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REVIEW ARTICLE

Narrative Review of Nimesulide in Adults: Current Scenario

SHRIRAM V KULKARNI*, JAWED AHMED†, MAHI PAL‡, BINOD KUMAR DHAREWA#, VIKRAM VEER¥, ANUP UTTAM PETARE§, KRISHNA CHAITANYA VELIGANDLA§

ABSTRACT

Nimesulide, a nonsteroidal anti-inflammatory drug (NSAID), has been used as an effective treatment regimen for patients aged >12 years for fever, acute pain, acute tendinitis, osteoarthritis and dysmenorrhea. It is reported to be a superior antipyretic and anti-inflammatory drug than paracetamol and aspirin, respectively, and is equal to any of the NSAIDs alone in terms of analgesia. This paper reviews the current scenario of nimesulide in adult patients, concerning clinical evidence, use in special population and expert opinion. Overall, in comparison to other NSAIDs, including coxibs, nimesulide has a promising overall efficacy, safety and tolerability profile, as well as a satisfactory benefit/risk evaluation.

Keywords: COX-2 inhibitor, fever, inflammation, NSAID, pain

BACKGROUND, HISTORY AND INDICATION

Nimesulide was first approved in Italy in 1985 and is currently available in more than 50 countries.[1] It is a nonsteroidal anti-inflammatory drug (NSAID) and has been used globally as an effective treatment regimen for patients aged >12 years with fever, acute pain, acute tendinitis, osteoarthritis and dysmenorrhea.[2] Nimesulide was first approved in India by the Drugs Controller General of India (DCGI) in 1995 in various dosages including nimesulide 100 mg tablet, nimesulide 50 mg/5 mL as suspension, nimesulide transdermal 1% gel for topical use and nimesulide 50 mg/100 mg as a suppository (rectal administration). In 1999, 200 mg dose of nimesulide was also introduced in the market as suppository.[3]

Fixed-drug combinations (FDCs) have been widely accepted as treatment options for a variety of diseases because of their superior therapeutic efficacy and safety, improved patient compliance and adherence and reduced cost to patients when compared with single-drug therapies. However, concerns have been raised regarding their irrationality and utility. FDCs have been gaining popularity in the Indian pharmaceutical market.[4] Combinations of nimesulide with several other active drug compounds have been approved by DCGI.[5] It was banned in 2000 in countries such as Switzerland, Spain and the US. As per an order dated 10th March 2011, nimesulide is not indicated for use in children below 12 years of age in India.

Over 90,000 people have participated in more than 200 clinical trials examining the efficacy and safety profile of nimesulide in acute and chronic inflammatory and painful disorders, the results of which showed it to be significantly better than placebo and at least comparable or in a few cases superior to other active NSAIDs (ketoprofen, naproxen, ibuprofen) in the treatment of pain and inflammation. This paper aims to review the current scenario of nimesulide in adult patients and expert opinion.

MECHANISM OF ACTION

Nimesulide is a selective inhibitor of the cyclooxygenase (COX)-2 enzyme (Fig. 1). It has unique chemical and pharmacokinetic properties.[6] Nimesulide imparts its pharmacological properties through a multifactorial mechanism of action (Fig. 2). It also inhibits phosphodiesterase IV and neutrophil function and renders antioxidant effects in human chondrocytes at a

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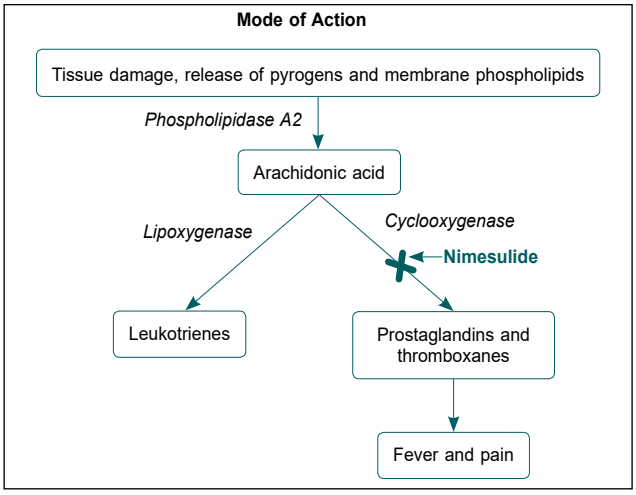

Figure 1. Mechanism of action of nimesulide.

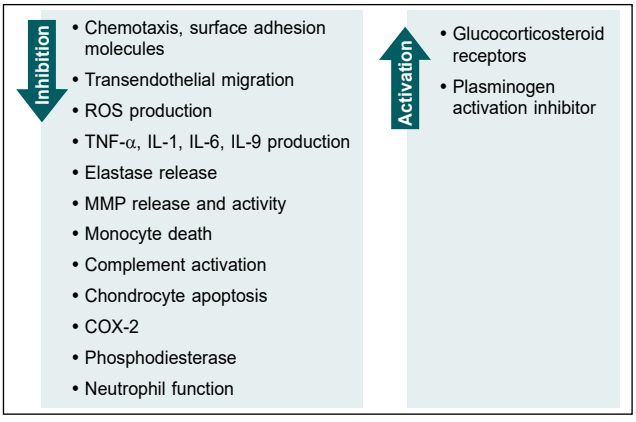

Figure 2. Multifactorial action of nimesulide.

ROS = Reactive oxygen species; TNF-α = Tumor necrosis factor α; IL = Interleukin; MMP = Matrix metalloproteinase; COX-2 = Cyclooxygenase-2.

pharmacologic level; inhibits overexpression of tumor necrosis factor α (TNF-α) thereby regulating the release of other hyperalgesic cytokines.[7] In an *in-vivo* study, nimesulide decreased interleukin (IL)-1β, IL-6 and TNF-α levels in a rat model of depression.[8] In patients with knee osteoarthritis, nimesulide significantly reduced the level of pro-inflammatory cytokine IL-6.[9]

CLINICAL EVIDENCE

Nimesulide in Fever

Multiple clinical trials have evaluated the antipyretic efficacy of nimesulide in comparison to paracetamol, diclofenac and acetylsalicylic acid. Nimesulide was found to be superior over the other antipyretic drugs in terms of safety, efficacy and tolerability, and was reported to normalize the body temperature in a short period of time.[2,10-12] Nimesulide starts its action within 15 minutes of its administration in comparison with other antipyretics like paracetamol.[2] In a recent Indian study of 302 adult patients with acute fever, the body temperature declined to (99.7 [1.8]°F) from the baseline body temperature of (103.2 [1.5]°F) following nimesulide treatment. Liver and renal profiles were reported to be normal from baseline to follow-up visit within 14 days; only 2% complained of nausea and dyspepsia.[2]

Reiner et al (1984), Reiner et al (1985) and Cunietti et al (1993) demonstrated that rectal administration of nimesulide (200 mg), diclofenac (100 mg), paracetamol (500 mg) reduced the body temperature from baseline and normalized heart rate and arterial pressure. Their efficacy was significantly comparable and well-tolerated. In comparison to the placebo, nimesulide was more efficient in fever management and shortened the duration of fever. Minor and temporary adverse effects were reported in drug-treated group with no side effects in placebo-treated group.[10-12]

Nimesulide in Pain

Nimesulide is an effective, safer and well tolerable therapeutic alternative for the treatment of a variety of painful inflammatory disorders. Compared to other NSAIDs such as etodolac, ibuprofen, naproxen and rofecoxib, nimesulide has a more effective, tolerable and rapid analgesic activity during the short-term usage.[6,13-20] There were no significant adverse events were reported among the various anti-inflammatory drugs and nimesulide.

Nimesulide delivered rapid analgesic effect and overall positive risk/benefit profile with no or minimal side effects in the management of osteoarthritis knee pain versus placebo and other oral NSAIDs such as celecoxib and rofecoxib in a comparative, double-blind, randomized clinical trial study.[6,13]

Zuckermann et al have reported the clinical effectiveness of nimesulide in the management of post-hemorrhoidectomy pain and inflammation.[21] Significant reduction in painful postoperative complications of various surgeries including ear, nose and throat surgery, dental surgery, oral surgery and arthroscopic knee surgery with nimesulide has also been reported.[22-25]

Comparison of efficacy of nimesulide with that of placebo and other analgesics such as ketoprofen (rectal administration), diclofenac (rectal administration), naproxen and niflumic acid has demonstrated the quick and effective analgesic activity of nimesulide over the other active drugs.[21]

A study by Pierleoni and co-workers compared the analgesic effects of nimesulide with ketoprofen in

46 patients who had undergone dental surgery. From day 2, night pain was absent in 69.5% of patients treated with nimesulide and 43.5% in patients treated with ketoprofen. Overall, 91.3% and 65.1% of patients treated with nimesulide and ketoprofen, respectively judged the efficacy as excellent or good. However, the quality of sleep improvement was consistent in both treatment groups following reduction in night pain.[23]

Binning evaluated the effect of nimesulide 100 mg compared to naproxen 500 mg and placebo on post-operative pain in 94 patients undergoing arthroscopic knee surgery.[25] The mean pain intensity was significantly reduced in nimesulide-treated patients (10.91) compared to placebo (6.29, $p < 0.001$) and naproxen-treated patients (7.07, $p = 0.003$). Estimated median time to 50% decrease in pain intensity was significantly shorter in patients treated with nimesulide (0.82 h) compared with those receiving naproxen (1.05 h; $p = 0.017$) or placebo (1.33 h; $p = 0.001$).[25]

Both nimesulide (300 mg) and rofecoxib (25 mg) were equally effective in improving pain and quality of life in patients with knee osteoarthritis. However, nimesulide was superior than rofecoxib in terms of pain relief (1.2 vs. 1.65; $p = 0.007$), scale of Western Ontario and McMaster Universities Osteoarthritis Index (9.3 vs. 12.96; $p = 0.009$) after 30 days of treatment.[14]

In a study comparing the efficacy of nimesulide versus ibuprofen in the treatment of acute low back pain, both NSAIDs significantly improved all measured parameters of the pain and back function. However, the patients' capacity for daily tasks was significantly improved in nimesulide-treated patients compared to ibuprofen-treated patients after 10 days (10.0 vs. 16.5; $p = 0.026$). In addition, nimesulide was more effective in improving lateral bending measurements ($p = 0.026$) with lower incidence of gastrointestinal (GI) side effects compared to ibuprofen.[17]

THERAPEUTIC ADJUNCT OF COVID-19

Various *in-silico* studies have shown nimesulide as a potential drug for the treatment of coronavirus disease 2019 (COVID-19).[26-28] As it can terminate the transport function of B0AT1, a target receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it can be considered a co-adjuvant in the treatment of COVID-19.[29] Selective inhibition of the COX-2 enzyme could be a potential therapeutic approach for the treatment of pain and inflammation.[30] Few NSAIDs were found to have anti-inflammatory activity in mice with influenza A infection by decreasing the pro-inflammatory cytokines (TNF-α and IL-6) and increasing the levels of granulocyte-colony stimulating factors (G-CSF) in bronchoalveolar lavage fluid.[31] This experimental evidence was the rationale behind recommending nimesulide as prophylactic treatment for early COVID-19 infection symptoms at home in cases with no sign of allergy or toxicity. The associated risk of hepatotoxicity is very minimal when it is taken at the prescribed time and dose. Nonetheless, treatment with nimesulide was found to be safer and well-tolerated in the recommended cohort, with just 1 patient complaining of GI pain.[32]

SAFETY PROFILE

COX-1 inhibition results in various adverse events such as GI discomfort, renal and urinary disorders and cardiac disorders. *In-vitro* studies have demonstrated nimesulide's high selectivity for COX-2 inhibition rather than COX-1 inhibition.[33] Even though GI symptoms such as dyspepsia and other nonserious complaints have been the most prevalent NSAID side effects, Bjarnason et al reported that nimesulide is superior and well-tolerated to other NSAIDs in terms of intestinal perforation, GI ulceration and bleeding.[34] Kress et al and Famaey have demonstrated nimesulide as one of the most preferred antipyretic agent with no substantial GI adverse events.[33,35]

Laporte et al have shown that the nimesulide associated risk of upper GI bleeding was significantly lower compared to that of ibuprofen and far lower than other established NSAIDs such as ketorolac, ketoprofen and piroxicam. Ketorolac and ketoprofen showed poor GI tolerability.[36]

Many NSAIDs have been linked to hepatic side effects that are usually idiosyncratic reactions associated with individual vulnerability. A systematic review by Sriuttha et al demonstrated clinically significant hepatotoxic events with NSAIDs including celecoxib, etoricoxib and diclofenac. The hepatotoxicity occurred most commonly in patients treated with diclofenac in the range of 0.015 to 4.3 ($\times 10^{-2}$), followed by celecoxib [0.13-0.38 ($\times 10^{-2}$)] and etoricoxib [0.005-0.930 ($\times 10^{-2}$).[37] There is an extremely low prevalence of hepatic reactions (1-5 among 1,00,000 exposed) and ranges from an asymptomatic and temporary elevation of hepatic enzymes to significant hepatic injury and liver dysfunction in nimesulide treated patients compared to other NSAIDs.[38,39]

In almost 64,000 nimesulide-treated patients, no occurrences of hepatitis or hepatic failure were documented in clinical investigations.[34]

Both COX-1 and COX-2 enzymes play a major role in renal function by regulating the renin-angiotensin system and renal tubular excretion/re-absorption systems, therefore it's very likely that nimesulide's major COX-2 inhibition action would only affect a proportion of renal function.[40,41] Nimesulide also has transitory effects on sodium and potassium excretion in healthy volunteers. In normal healthy subjects, nimesulide 200 mg BD was observed to attenuate the increase in plasma renin and aldosterone caused by furosemide, along with a reduction in urinary prostaglandin E_2 (PGE_2) excretion. With or without furosemide, nimesulide elevated urine flow and water excretion and decreased glomerular filtration rate and renal plasma flow.[42] Most NSAIDs exhibit similar physiological effects.[43] Cardiovascular events also influence its safety profile. Clinical trials have shown a minimal risk of cardiovascular events in patients receiving nimesulide.[34] Serious cardiovascular events such as myocardial infarction and congestive heart failure that have lately been observed with coxibs and other NSAIDs have been seldom seen with nimesulide.

EXPERT OPINION

Nimesulide versus Nimesulide + Paracetamol Combination

Paracetamol is an effective antipyretic and analgesic drug but shows poor anti-inflammatory effects. It is a non-selective COX-2 inhibitor, unlike nimesulide.

In terms of analgesia or commencement of an action, the combination of nimesulide and paracetamol had no pharmacological advantage over nimesulide or paracetamol alone.[44]

Both show antipyretic and analgesic effect by inhibiting the biosynthesis of prostaglandin (PG) that is responsible for inducing pain and inflammation.[45] Irrational drug combinations put the patients at risk of adverse effects. Although nimesulide has been reported as a superior analgesic drug over other NSAIDs in terms of safety and efficacy, its combination with paracetamol is associated with increased hepatotoxic effects, and therefore it is very crucial to make clinicians and consumers aware of this irrational combination and stop them from practicing such combination.[44]

Patient Profiles for Nimesulide

Arthritic conditions

In patients with a history of moderate to severe pain associated with osteoarthritis of the hip and knee, nimesulide (100 mg BD) and diclofenac (50 mg TID) had comparable overall tolerability and efficacy. However, nimesulide-treated patients had fewer GI side effects (36.3%) than the diclofenac-treated patients (47.2%). These results signify that the efficacy of nimesulide is equivalent to that of diclofenac as long-term therapy of osteoarthritis, and that nimesulide provides a superior gastric safety profile than diclofenac.[46]

Nimesulide was superior to other widely used NSAIDs such as celecoxib and rofecoxib in providing symptomatic relief in patients with knee osteoarthritis. It also showed a rapid analgesic effect in pain associated with walking in comparison to celecoxib, rofecoxib and etodolac. No significant adverse events were reported with any of the therapies, and the tolerability was comparable across treatment groups. These results show that nimesulide is superior or equivalent to the comparator drug in terms of rapid analgesic action, quality of life, tolerability and incidence of adverse events.[13,14,16]

In a study to determine the most promising/optimal dose of nimesulide for the treatment of osteoarthritis-associated pain in terms of efficacy/safety ratio, 392 patients were randomized to treatment with nimesulide (50 mg, 100 mg and 200 mg BD) and placebo for 1 month. Nimesulide-treated group showed a rapid onset of analgesia that lasted for 12 hours after the drug intake; however, a significant analgesic effect was observed in groups receiving 100 mg and 200 mg of nimesulide within 1.5 hours of drug intake.

Nimesulide 100 mg and 200 mg produced the best results. Doses of 50 mg and 100 mg were well-tolerated, while the dose of 200 mg showed a higher incidence of adverse events, although not significant. Thus, 100 mg twice a day was demonstrated to be the optimal dose of nimesulide for the treatment of osteoarthritis.[15]

These results provide evidence that nimesulide is a unique NSAID with analgesic properties producing the best results for the management of arthritic conditions.

Dysmenorrhea

Nimesulide was superior over other NSAIDs such as diclofenac, naproxen and mefenamic acid including placebo in reducing pain associated with primary dysmenorrhea.[47] Investigation of the therapeutic effect of nimesulide on overall intrauterine perfusion and PGs in menstrual blood showed that nimesulide reduced the concentration of $PGF_{2\alpha}$ (responsible for uterine contraction) and PGE_1 or PGE_2 (have relaxing/contractile effects) by 60% and 80%, respectively.[48,49] Nimesulide transforms smooth muscle from the pathological condition of dysmenorrheic contracture

to the physiological state of eumenorrheic contractions. It is also apparently linked with a decline in uterine artery vascular resistance.[50,51]

In a multicenter, randomized, double-blind clinical trial 308 women with primary dysmenorrhea were allocated to either nimesulide (3 tablets/day) or diclofenac (3 tablets/day) for the first 3 days of their menstrual cycle.[52] Both nimesulide and diclofenac treatments significantly reduced pain by 82% and 79%, respectively at the second hour. However, onset of analgesia was more rapid with nimesulide starting at 30 minutes, with a decline in abdominal discomfort by 35% versus 27% in both the first and second treatment cycles, respectively. Both drugs had comparable beneficial effects headache and backache. The two treatments were well-tolerated. The prevalence of gastric discomfort was found to be significantly lower in nimesulide-treated group.

No significant changes in uterine and ovarian blood flow were observed in eumenorrheic women receiving either placebo or nimesulide (100 mg) in a double-blind, placebo-controlled clinical trial.[53] In the same study, nimesulide improved symptoms and reduced uterine artery impedance (pulsatile index, PI) earlier than naproxen (500 mg, single oral dose) among women with moderate to severe dysmenorrhea. The clinical effect of both the active drugs on elevated uterine impedance was comparable. The fundus showed the most significant alterations. The ovarian branch remained unaffected. These results signify that nimesulide reduced elevated uterine vascular resistance in dysmenorrhea to normal eumenorrheic levels at a higher rate than naproxen.

Nimesulide also played a crucial role in the treatment of primary dysmenorrhea.

Post-surgical pain

Nimesulide was found to be comparatively similar to naproxen and more superior to placebo in reducing pain, inflammation and edema in patients suffering from post-hemorrhoidectomy associated pain and arthroscopic knee post-surgery associated pain. All the treatments were reported to be well-tolerated.[21,25]

Comparison of the analgesic effect of nimesulide with ketoprofen in patients undergoing dental surgery and third molar surgery showed that nimesulide was superior to ketoprofen in reducing pain and inflammation. The quality of sleep, mastication and swallowing function recovered more quickly among the nimesulide treated patients. Nimesulide was found to be effective in managing pain, edema and trismus after surgical removal of the third molar.[23,54]

Ramella and co-workers showed that treatment with nimesulide and diclofenac (rectal administration) significantly reduced pain, swelling, hyperemia, as well as the elimination of minor fever, without any adverse events among patients who underwent saphenectomy or inguinal hernioplasty.[55] Based on these observations, nimesulide can be recommended in the treatment of postoperative pain, with a rapid onset of analgesic action.

Cancer pain

Two studies were compared the analgesic efficacy and tolerability of nimesulide with naproxen in patients with advanced cancer pain.[19,20] Both studies revealed that 200 mg BD nimesulide and 500 mg BD naproxen have similar analgesic effects with lower incidence of adverse reactions.[19,20] This indicates that nimesulide can also be used in the treatment of cancer pain.

Ear, nose and throat disease

Several multicenter clinical trials have investigated the efficacy and tolerability of nimesulide and other anti-inflammatory drugs such as seaprose-S and ketoprofen, in the management of inflammatory disorders of ear, nose and throat (ENT).[22,56,57] Nimesulide efficiently reduced inflammatory signs and symptoms of ENT disorders. It had a more rapid onset of action than other NSAIDs. Both nimesulide and ketoprofen significantly reduced swelling and hyperemia in patients with postoperative inflammatory complications post-ENT surgery. However, all treatment regimens were well-tolerated with a low prevalence of mild adverse events.

Airway inflammation

Nimesulide has proven to be beneficial in regulating the inflammatory process in conditions such as rhinopharyngitis, rhinosinusitis, tubaritis, rhinitis and middle ear ailments. Nimesulide in combination with a mucolytic drug, ambroxol, has been shown to have similar anti-inflammatory effects.[58] Oral nimesulide has been proven to be effective and well-tolerated in the treatment of aspirin-sensitive asthmatic patients.[59]

In a study conducted on patients with chronic mucus hypersecretion, nimesulide administered for 3 weeks significantly reduced sputum viscosity. No severe adverse events were reported due to nimesulide medication.[60]

CONCLUSION

Nimesulide is a new generation NSAID with a unique chemical structure. It has a preferentially high inhibitory effect on the COX-2 enzyme with a low

preference for COX-1. This allows nimesulide its wide range of application as an anti-inflammatory agent through its multifactorial mode of action. The rapid onset of analgesic effects of nimesulide in the treatment of pain and inflammation is exerted both centrally and peripherally. Treatment with nimesulide has been proven safer, effective and well-tolerable in cases of acute pain associated with postoperative pain and inflammation, inflammation due to soft tissue injuries, odontostomatological inflammatory pain, extra-articular traumatism, osteoarthritis pain and cancer pain. The risk of liver reactions is comparable to that of other conventional NSAIDs and coxibs. In comparison to other NSAIDs, including coxibs, nimesulide has a promising overall efficacy, safety and tolerability profile, as well as a satisfactory benefit/risk evaluation. Nimesulide as antipyretic is effective and safer in fever management when used for shorter duration.

Disclosures

Source of funding: This initiative was funded by Dr Reddy's Laboratories Limited, Hyderabad, India.

Conflict of interest: Anup Uttam Petare and Krishna Chaitanya Veligandla are employees of Dr Reddy's Laboratories Limited, Hyderabad. All other authors have no conflict of interest to declare.

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REVIEW ARTICLE

Sodium-glucose Co-transporter 2 Inhibitors: A Novel Molecule for Health Care Practitioners in Diabetology, Cardiology and Nephrology

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ABSTRACT

Prevention and timely management of cardiovascular (CV) complications like myocardial infarction, heart failure (HF), stroke and renal complications, like chronic kidney disease (CKD) and end-stage renal disease, are important to improve the quality of life and survival in people with type 2 diabetes mellitus (T2DM). The multifaceted action of sodium-glucose co-transporter 2 inhibitors (SGLT2i) results in effective glycemic control with benefits on CV and renal risk factors, like body weight, blood pressure, uric acid and albuminuria. Robust CV and renal event reduction is reflected in the outcomes of large CV outcome trials, meta-analyses and real-world studies. Recent evidence has proven cardiac and renal benefits with SGLT2i in subjects with HF and CKD irrespective of their T2DM status. Until recently, SGLT2i was used as a glucose-lowering molecule with pleiotropic benefits, mainly by primary care practitioners and diabetologists. The potential for cardiac and renal protection in people with and without T2DM has shifted an interest in cardiologists and nephrologists to view it as a cardiac and renal molecule, respectively. Thus, the role of SGLT2i in the management of T2DM is undergoing a paradigm shift—straddling the interfaces of diabetology, cardiology, nephrology and primary care—moving away from being considered a pure antidiabetic molecule. We conducted a literature review of SGLT2i in management of T2DM along with their protective effects on CV and renal parameters in patients with or without baseline comorbidities.

Keywords: Cardiologist, diabetologist, nephrologist, primary care practitioners, SGLT2 inhibitors, type 2 diabetes mellitus

People with type 2 diabetes mellitus (T2DM) experience considerable micro- and macrovascular complications.[1] Cardiovascular disease (CVD), the main macrovascular complication (>30%) in subjects with T2DM, leads to subclinical or even overt heart failure (HF) (14.9%), with increased mortality (9.9%).[2] Additionally, silent coronary ischemia 10% to 20% in diabetics vs. 1% to 4% in nondiabetics[3] makes the T2DM population vulnerable to an increased morbidity and mortality. The American Diabetes Association (ADA) recommends calculating the 10-year atherosclerotic cardiovascular disease (ASCVD) risk, besides including strong measures, like diet modification and tight control of blood pressure (BP) and lipid levels to reduce CVD.[4] Several large studies have documented that conventional therapies are unable to reduce the macrovascular complications.[5,6]

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) have demonstrated an improvement in cardiovascular (CV) outcomes. SGLT2i have reduced the rate of hospitalization for heart failure (HHF) and CV death in patients with or without pre-existing HF or ASCVD.[7-9] Along with CVD protection, trials with SGLT2i have demonstrated renal protection. Diabetic kidney disease (DKD)—a leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD)—occurs in ~40% of people with T2DM and is additionally associated with increased CVD.[10] SGLT2i have shown renal protection in multiple large cardiovascular outcome trials (CVOTs), which depict CV safety of this class of drugs with encouraging results on albuminuria and

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ESRD outcomes.[7,11-14] These renal benefits and recommendations are causing nephrologists to change their perception of SGLT2i in being just glucose-lowering drugs (GLDs). This review aims to provide an overview of SGLT2i dynamics in clinical practice from the perspective of diabetologists, cardiologists, nephrologists and primary care practitioners (PCPs).

METHODOLOGY

We searched for published literature on PubMed and Embase databases using the keywords – "type 2 diabetes mellitus", "sodium-glucose co-transporter 2 inhibitor", "SGLT2 inhibitor", "dapagliflozin", "canagliflozin", "empagliflozin", "efficacy" and "safety", etc. Instead of following systematic literature review methodology (using checklists and systematic screening), we focused on our specific area of priority. The data published up to November 2020 with language restriction in English were considered. Conference abstracts and available results from clinicaltrials.gov database were hand searched. The references cited in all the above retrieved publications were also reviewed for relevance and were obtained when applicable.

MECHANISM OF ACTION

What Makes it an Molecule for Diabetologists?

The unique insulin-independent action of SGLT2i contributes to minimal hypoglycemia and a low potential for beta-cell exhaustion.[15] The enhanced insulin sensitivity and innate insulin release from beta cells can reduce the need for external insulin injections and expenses associated with insulin therapy.[16] Randomized controlled trials have shown that SGLT2i therapy reduces insulin resistance[17] ($p < 0.001$) and improves insulin sensitivity[18] ($p = 0.0059$). SGLT2i may play a role even in advanced T2DM stages, characterized by irreparable decline in beta-cell function, because of their insulin independent mechanism.[19]

The ADA 2021 guidelines[4] recommend SGLT2i as the first-line treatment after metformin if there is a compelling indication to minimize hypoglycemia or weight gain, or to encourage weight loss. The European Society of Cardiology/European Association for the Study of Diabetes (ESC/EASD) guidelines place SGLT2i before metformin with a IA recommendation for empagliflozin, canagliflozin or dapagliflozin in subjects with T2DM and CVD or at very high or high CV risk to reduce CV events – with an recommendation for empagliflozin use in T2DM with CVD to reduce the risk of death.[20]

What Makes it an Molecule for Cardiologists?

What attracts physicians and cardiologists is the positive impact of SGLT2i on CV comorbidities; efficacy in subjects with risk factors for CVD, alongside benefits in subjects with HF (with and without T2DM). Although the precise mechanism of CV benefits of SGLT2is is still under scrutiny, they are likely to be due to the hemodynamic and metabolic effects unrelated to their glucose-lowering efficacy.[21] Both ADA[4] and ACC/American Heart Association (AHA) guidelines[22] recommend the first-line addition of SGLT2i when ASCVD predominates, for reducing CV risk (secondary prevention), while the Food and Drug Administration (FDA) approval for dapagliflozin use in T2DM with multiple CV risk factors (along with those with established CVD [eCVD]) to reduce the risk of HHF suggests a primary preventive role in subjects with T2DM.[23]

Hemodynamic effects

High BP is a known CV risk factor; hence, lowering BP in T2DM population reduces CV events. The mechanism of BP reduction with SGLT2i occurs by osmotic diuresis and a lower sympathetic tone. The latter mechanism lowers BP, without causing a compensatory increase in heart rate.[24] Several studies have explored the adaptive ketogenesis theory, reduction in body weight and arterial stiffness to explain the BP-lowering benefit.[25,26] SGLT2i also inhibit the heart Na^+-H^+ exchanger, thereby improving mitochondrial function, reducing cardiac remodeling and enhancing heart function.[27]

Metabolic effects

Metabolic benefits with SGLT2i in cardiac protection include a lower risk for hypoglycemia; adaptive ketogenesis; calorie restriction mimicry and improvement in body weight and lipid and uric acid levels. The lower incidence of hypoglycemia with SGLT2i is because of their insulin-independent mode of action, which also aids in reducing the CV risk.[28] Adaptive ketogenesis with increased ketones occurs with SGLT2i use because of the elevated glucagon levels. Ketones are an efficient fuel source for the ischemic heart, with added benefits of reducing free-radical injury, resulting in a better cardiac function.[29] Reduction in body weight and waist circumference has a positive impact on CV outcomes and insulin resistance.[30] A dose-dependant reduction in body weight of 1.6-2.5 kg was shown in a meta-analysis, while another study demonstrated that this weight reduction could be sustained at the 4-year follow-up.[31,32] The preferential loss of visceral and subcutaneous fats compared with lean tissue is a benefit.[33]

Elevated uric acid levels are a CV risk factor and mediate renal damage. The loss of uric acid in urine due to the inhibition of absorption in the renal proximal convoluted tubule by SGLT2i enables the reduction of CV risk and slows CKD progression.[11,34] Hematocrit improvement (2-4%) has been consistently seen with SGLT2i use, even in patients with CKD (except stage 4 CKD). This improvement is attributed to an enhanced erythropoietin levels. Elevated hematocrit levels may correct sympathetic hyperactivity in T2DM leading to a reduction in CV mortality and risk for HHF.[35] SGLT2is also favorably affect albuminuria, a CV risk factor, by restoring the tubuloglomerular feedback and reducing intraglomerular pressure.[36] An improvement in albuminuria translates into cardiac and renal protection.

Benefits in subjects with heart failure

People with T2DM are at a high risk for developing HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF) and renal hypoxia leading to new-onset HF or HF progression.[20,37] SGLT2i action reduces sympathetic outflow to the heart, lowering cardiac wall stress, fibrosis and volume overload.[37] The HHF endpoint being the most sensitive to SGLT2i use in the completed CVOTs led to the theory that SGLT2i reduce CV events mainly by HF prevention rather than atherothrombosis inhibition.[38] SGLT2i can reduce morbidity and mortality in pure HF patients with or without comorbid diabetes. Ongoing SGLT2i trials in HF may confirm if it is a class effect. The CANOSSA trial in subjects with T2DM and HFpEF reported improved endothelial and diastolic functions with canagliflozin. HF markers like atrial natriuretic peptide ($p = 0.0001$), brain natriuretic peptide ($p < 0.0001$) and ejection fraction (EF) ($p = 0.005$) improved at 12 months compared with baseline.[39]

The EMPA-HEART trial[40] showed benefits on left ventricular remodeling in T2DM patients with eCVD. The improvement in left ventricular mass index (–2.6 vs. 0.01 g/m^2, $p = 0.01$) at 6 months mechanistically explained the HF benefits demonstrated in the EMPA-REG OUTCOME trial. The DAPA-HF[8] trial with dapagliflozin demonstrated a reduction in the composite of HHF or CV death or urgent HF visit (hazard ratio [HR]: 0.74; 95% confidence interval [CI]: 0.65-0.85; $p < 0.001$), HHF (HR: 0.70; 95% CI: 0.59-0.83), CV death (HR: 0.82; 95% CI: 0.69-0.98), and all-cause death (HR: 0.83; 95% CI: 0.71-0.97) in HFrEF patients with (42%) and without T2DM. DEFINE-HF results demonstrated a clinically meaningful improvement in the dual primary outcome of HF-related quality of life or natriuretic peptides (61.5%, dapagliflozin vs. 50.4%, placebo, adjusted odds ratio: 1.8, 95% CI: 1.03-3.06, $p = 0.039$), with similar results in subjects with or without T2DM.[41] The EMPEROR-Reduced trial reported a significant reduction in the composite of CV death and HHF (HR: 0.75; 95% CI: 0.65-0.86; $p < 0.001$) with consistent benefits in subjects with (49.8%) and without T2DM. These benefits with empagliflozin may broaden the target HF patient group to advanced New York Heart Association stages, as most participants (73%) had an EF <30%.[9]

The ADA 2021 guidelines already recommend SGLT2i as the first-line therapy in subjects with T2DM and comorbid HF.[4] The FDA approved dapagliflozin to reduce risk of HF in adults with T2DM and multiple CV risk factors or with eCVD.[42]

What Makes it an Molecule for Nephrologists?

The renal benefits, evidenced by the reduction in albuminuria, slowdown in progression to ESRD and reduced need for renal replacement therapy (RRT), are mediated by several mechanisms.[7,11-13] Increased sodium access to the macula densa due to SGLT2 inhibition lowers the intraglomerular pressure, decreases albuminuria and possibly slows the decline of kidney function in people with diabetes.[42] Hypoxia in the milieu of proximal convoluted tubule is alleviated as SGLT2is reduce oxygen consumption by the Na^+/K^+ pump in the epithelial cells.[35] Reduction in sympathetic outflow to the kidney by SGLT2i action reduces the renin-angiotensin-aldosterone system (RAAS) activity and corrects fluid overload. Adaptive ketogenesis by SGLT2i action improves renal function by ensuring a more efficient metabolic substrate like ketones.[43] EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI 58 trials demonstrated improved renal outcomes, albeit as secondary endpoints with empagliflozin, canagliflozin and dapagliflozin.[7,11,12]

In the CREDENCE study involving T2DM subjects with albuminuric CKD, canagliflozin significantly reduced the composite of ESRD, a doubling of serum creatinine level or death from renal or CV causes by 30%.[13] DAPA-CKD results reported a significant impact (HR: 0.61; 95% CI: 0.51-0.72; $p < 0.001$) of dapagliflozin on the composite primary outcome of sustained decline in the estimated glomerular filtration rate (eGFR) of at least 50%, ESRD or death from renal or CV causes in subjects with CKD ($n = 4,304$) – with or without T2DM. This extension of benefit to pure CKD patients without T2DM (32.5%), and to patients with lower eGFR threshold (14.5% had eGFR <30 mL/min/1.73 m^2) confirmed renal protection

in a broader group of patients. Moreover, a reduction was seen in the composite of sustained decline in eGFR of at least 50%, ESRD or death from renal causes (HR: 0.56; 95% CI: 0.450.68; p < 0.001), the composite of CV death or HHF (HR: 0.71; 95% CI: 0.55-0.92; p = 0.009), and mortality (HR: 0.69; 95% CI: 0.53-0.88; p = 0.004).[14]

Significant improvement in the urine albumin-creatinine ratio was seen with dapagliflozin vs. placebo in the DELIGHT trial[44] (−21.0%; 95% CI: −34.1, −5.2; p = 0.011) on follow-up at the end of 24 weeks while in the DERIVE trial,[45] a significant reduction at week-12 (−41.7%; 95% CI: −57.1, −21.0; p < 0.001) was maintained, but did not reach significance at week-24 (−14.0%; 95% CI: −42.3, 28.0; p = 0.454). Ertugliflozin revealed glycemic efficacy and an acceptable safety profile in 468 subjects with T2DM and stage 3 CKD over a 52-week period in the VERTIS-RENAL trial.[46]

However, the VERTIS-CV trial with ertugliflozin did not show a significant benefit for the renal composite endpoint (secondary endpoint) of death from renal causes, RRT or doubling of serum-creatinine level.[47] The ACC 2018 consensus pathway on novel therapies recommends the first-line addition of SGLT2i to metformin in T2DM and CKD subjects, with or without ASCVD, provided there is no ESRD.[21] The ADA 2021 guidelines[4] also recommend SGLT2i as a preferable option when CKD predominates. Canagliflozin received FDA approval for use in subjects with DKD (with albuminuria) to reduce the risk of ESRD, worsening of renal function, CV death and HHF.[48] Thus, the question remains – should SGLT2i form a targeted treatment option for DKD? SGLT2is with their multifaceted action at the level of the pancreas, heart and kidney, allow PCPs, diabetologists, cardiologists and nephrologists to provide multiorgan-targeted benefits for subjects with T2DM (Fig. 1).

EVIDENCE WITH SGLT2I FOR DIABETOLOGISTS, CARDIOLOGISTS AND NEPHROLOGISTS

Evidence from Randomized Controlled Trials

Table 1 summarizes the main CV and renal endpoints in the landmark CVOTs with SGLT2i. In EMPA-REG OUTCOME, the empagliflozin group demonstrated lower rates of 3-point major adverse cardiac events (MACE), death from CV causes, HHF and death from any cause.[49] EMPA-REG renal analysis demonstrated

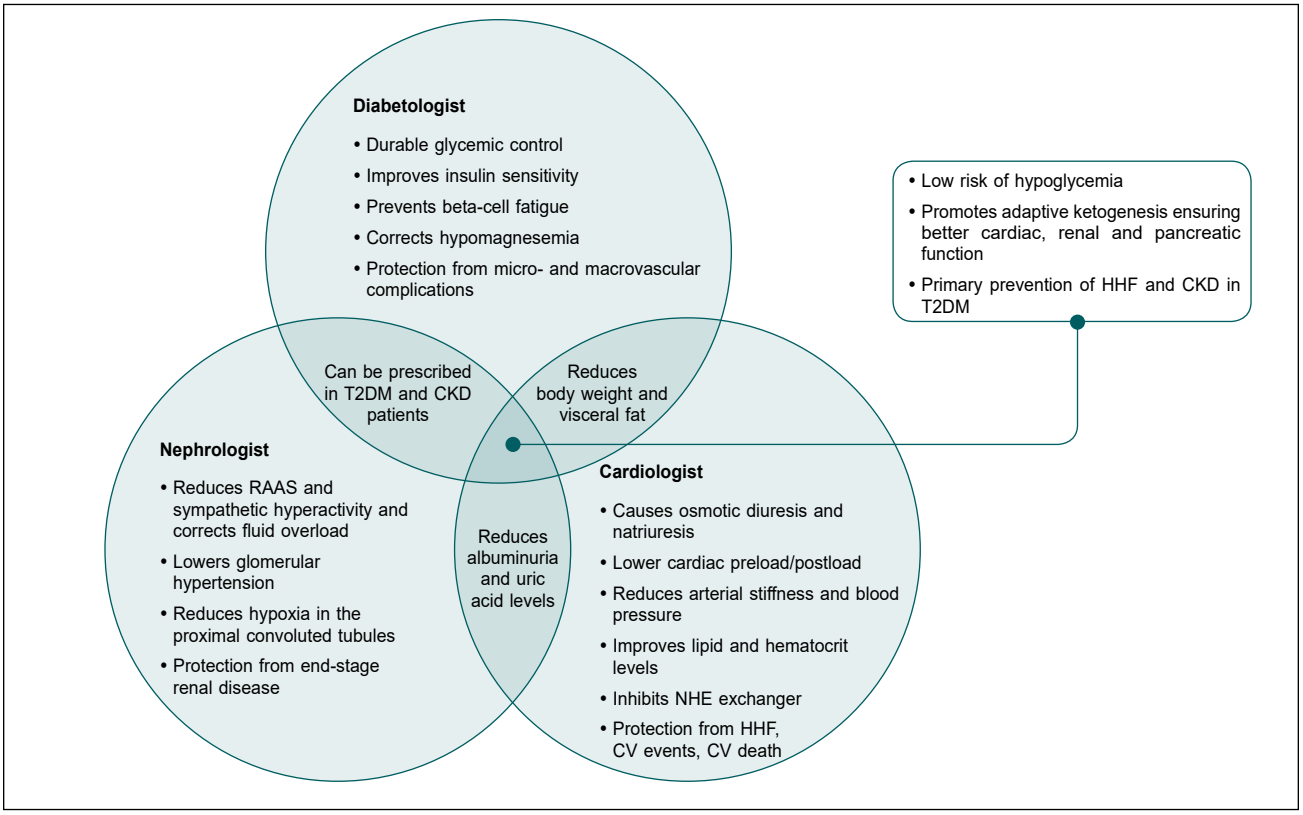

Figure 1. SGLT2i benefits for a diabetologist, cardiologist and nephrologist.

CKD = Chronic kidney disease; CV = Cardiovascular; HHF = Hospitalization for heart failure; NHE = Sodium-hydrogen exchanger; RAAS = Renin-angiotensin-aldosterone system; T2DM = Type 2 diabetes mellitus.

Table 1. Summary of Cardiovascular and Renal Benefits with SGLT2i

	EMPA-REG OUTCOME (n = 7,020, T2DM)	CANVAS (n = 10,142, T2DM)	DECLARE-TIMI 58 (n = 17,160, T2DM)	CREDENCE (n = 4,401, T2DM with albuminuric CKD)
Patients with established CVD (n, %)	7,020 (100%)	6,656 (66%)	6,974 (40.6%)	2,220 (50.4%)
Follow-up (years)	3.1	2.4	4.2	2.62
SGLT2i	Empagliflozin 10 or 25 mg vs. placebo daily	Canagliflozin 100 or 300 mg vs. placebo daily	Dapagliflozin 10 mg vs. placebo daily	Canagliflozin 100 mg vs. placebo daily
Primary endpoint: Composite of CV death, MI or stroke	HR: 0.86 (0.74-0.99), p < 0.001 for NI, p = 0.04 for superiority	HR: 0.86 (0.75-0.97) NI, p < 0.001 Superiority, p = 0.02	HR: 0.93 (0.84-1.03) NI, p < 0.001 Superiority, p = 0.17	HR: 0.80 (0.67-0.95), p = 0.01
CV death	HR: 0.62 (0.49-0.77), p < 0.001	HR: 0.87 (0.72-1.06), p = NS	HR: 0.98 (0.82-1.17), p = NS	HR: 0.78 (0.61-1.00), p = 0.05
HHF	HR: 0.65 (0.50-0.85), p = 0.002	HR: 0.67 (0.52-0.87), p = NS	HR:0.73 (0.61-0.88), p = 0.005	HHF: 0.61 (0.47-0.80), p < 0.001
All-cause mortality	HR: 0.68 (0.57-0.82), p < 0.001	HR: 0.87 (0.74-1.01), p = NS	HR: 0.93 (0.82-1.04), p= NS	HR: 0.83 (0.68-1.02), p = NS
Worsening nephropathy*	HR: 0.61 (0.53-0.70) p < 0.001	HR: 0.60 (0.47-0.77)	HR: 0.76 (0.67-0.87)	HR: 0.66 (0.53-0.81), p < 0.001

*Worsening nephropathy was defined as doubling of serum creatinine level and an eGFR of $\leq$45 mL/min/1.73 m^2, the need for continuous renal-replacement therapy or death due to renal events in EMPA-REG OUTCOME; 40% reduction in eGFR, renal-replacement therapy or death from renal causes in CANVAS; sustained decrease of $\geq$40% in eGFR to $<$60 mL/min/1.73 m^2, new end-stage renal disease or death from renal or CV causes in DECLARE-TIMI 58; end-stage kidney disease, doubling of serum creatinine or renal death in CREDENCE.

CKD = Chronic kidney disease; CV = Cardiovascular; CVD = Cardiovascular disease; eGFR = Estimated glomerular filtration rate; HHF = Hospitalization for heart failure; HR = hazard ratio; MI = Myocardial infarction; NI = Noninferiority; NS = Nonsignificant; SGLT2i = Sodium-glucose co-transporter 2 inhibitor; T2DM = Type 2 diabetes mellitus.

a reduction in the composite of incident or worsening nephropathy (HR: 0.61, 95% CI: 0.53-0.70), progression to macroalbuminuria (HR: 0.62, 95% CI: 0.54-0.72), serum-creatinine doubling (HR: 0.56, 95% CI: 0.39-0.79), and RRT initiation (HR: 0.45, 95% CI: 0.21-0.97).[11]

A recent post hoc analysis of EMPA-REG study observed consistent CV and renal benefits among all Kidney Disease Improving Global Outcomes (KDIGO) categories confirming benefits across the CKD spectrum.[50] In the CANVAS program, the canagliflozin group demonstrated lower rates of 3-point MACE, CV death, all-cause mortality and HHF with no heterogeneity of treatment effect across primary and secondary prevention groups and a significant reduction in albuminuria progression (HR: 0.73, 95% CI: 0.67-0.79).[49]

In the DECLARE-TIMI 58 trial of 17,160 patients, 10,186 patients did not have eCVD, but they had multiple risk factors for ASCVD. Dapagliflozin achieved the MACE criterion for noninferiority, with therapy results demonstrating lower risks for HHF (HR: 0.73, 95% CI: 0.61-0.88) and renal events (HR: 0.76, 95% CI: 0.67-0.87).[7] The CREDENCE trial with canagliflozin in subjects with T2DM and albuminuric CKD demonstrated a significant reduction in the primary outcome of composite of ESRD, serum creatinine doubling or death from renal or CV causes (HR: 0.70, 95% CI: 0.59-0.82, p < 0.00001), in addition to a reduction in the risk of CV death, myocardial infarction or stroke, and HHF.[13] It showed that the CV and renal benefits were observed even at lower eGFR levels (30-45 mL/min/1.73 m^2), suggesting that SGLT2i can be used in more severe stages of CKD.

Evidence from Systematic Review and Meta-analyses and Post Hoc Analyses

A systemic review and meta-analyses (SRMA) of EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI 58 trials showed a significant reduction in MACE (HR: 0.86, 95% CI: 0.80-0.93, p = 0.0014) with SGLT2i in those with eCVD. Further, a 45% reduction in renal disease progression was also seen to be similar in subjects with and without ASCVD.[51]

Another SRMA confirmed SGLT2i benefits by demonstrating a significant reduction in CV outcomes (relative risk [RR]: 0.81, 95% CI: 0.70-0.94) and renal outcomes (composite renal outcome, HR: 0.71, 95%

Table 2. Phase 2/3/4 Trials Evaluating SGLT2i in HF

Trial (NCT Number)	Study population	Expected outcomes	Study status
Phase 2 trial evaluating SGLT2i in HF			
EMPIRE-HF (NCT03198585)	190 participants Stable, symptomatic HFrEF (LVEF ≤40%)	Evaluate empagliflozin 10 mg on cardiac biomarkers, cardiac function at rest, at stress and during exercise, renal function, metabolism, daily activity and health-related QoL	Completed: January 2020*
Phase 3 trials evaluating SGLT2i in HFrEF			
EMPERIAL-Reduced (NCT03448419)	312 participants Chronic HFrEF LVEF ≤40%	Evaluate empagliflozin 10 mg vs. placebo on exercise capacity using 6MWT	Completed: October 2019
DETERMINE-Reduced (NCT03877237)	313 participants HF (NYHA class II-IV) with reduced ejection fraction defined as LVEF ≤40%	Evaluate dapagliflozin 10 mg on exercise capacity in patients with HFrEF (LVEF ≤40%)	Completed: March 2020*
Phase 3 trials evaluating SGLT2i in HFpEF			
EMPERIAL-Preserved (NCT03448406)	315 participants Chronic HFpEF (NYHA class II-IV) LVEF >40%	Evaluate empagliflozin 10 mg vs. placebo on exercise ability using 6MWT	Completed: October 2019*
DETERMINE-Preserved (NCT03877224)	504 participants Chronic HFpEF (NYHA class II-IV) LVEF >40%	Evaluate dapagliflozin 10 mg on exercise capacity using 6MWT	Completed: July 2020*
EMPEROR-Preserved (NCT03057951)	5,988 participants Chronic HFpEF (NYHA class II-IV) LVEF >40%	Evaluate efficacy and safety of empagliflozin 10 mg vs. placebo on top of guideline-directed medical therapy	April 2021
DELIVER (NCT03619213)	6,100 participants HFpEF (NYHA class II-IV) with LVEF >40%	Evaluate dapagliflozin 10 mg on reducing CV death or worsening HF	November 2021
Phase 4 trials evaluating SGLT2i in HF			
EMBRACE-HF (NCT03030222)	60 participants NYHA class II-IV HFpEF (LVEF >40%) or HFrEF (LVEF ≤40%) ischemic or nonischemic etiology who already have a CardioMEMs device	Evaluate empagliflozin 10 mg on hemodynamic parameters (pulmonary artery diastolic pressures)	October 2020 (not recruiting)
PRESERVED-HF (NCT03030235)	320 participants Dyspnea (NYHA class II-IV) without evidence of a noncardiac or ischemic explanation for dyspnea LVEF ≥45%	Evaluate dapagliflozin 10 mg on HF-specific biomarkers (NTproBNP and BNP), symptoms, health status and QoL	February 2021

*Results not published

BNP = Brain natriuretic peptide; CV = Cardiovascular; HF = Heart failure; HFpEF = Heart failure with preserved ejection fraction; HFrEF = Heart failure with reduced ejection fraction; LVEF = Left ventricular ejection fraction; NTproBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; QoL = Quality of life; SGLT2i = Sodium-glucose co-transporter 2 inhibitor; T2DM = Type 2 diabetes mellitus; 6MWT = 6-minute walk test.

CI: 0.53-0.95) in subjects with T2DM and CKD, with a mitigation in the annual decline in eGFR slope (difference of 1.35 mL/min/1.73 m^2/year; 95% CI: 0.78-1.93).[52] Another SRMA reported consistency of SGLT2i effect across trials and different levels of eGFR (baseline eGFR 30-45 mL/min/1.73 m^2) and albuminuria with a reduction in the risk of dialysis, transplantation or death due to renal causes (RR: 0.67, 95% CI: 0.52-0.86, p = 0.0019),

Table 3. Emerging Evidence with SGLT2i in HF with T2DM and CKD With and Without T2DM

Trial (NCT number)	Sample size	Study objective and population	Study status
In subjects with T2DM and HF			
Treatment of DM in HFrEF (NCT02920918)	36	Evaluate canagliflozin 100 mg vs. sitagliptin 100 mg on exercise capacity, cardiac function and cardiac biomarkers in HFrEF (EF ≤40%)	Completed*: September 2018
RECEDE-CHF (NCT03226457)	23	Compare empagliflozin 25 mg, to placebo in patients with T2DM and chronic HF (NYHA II/III) with left ventricular systolic dysfunction and who are already on a loop diuretic	Completed: January 2019
ELSI (NCT03128528)	84	Evaluate empagliflozin 10 mg vs. placebo on reduction of tissue sodium content in patients with chronic HFrEF (<40%) and HFmEF (40-49%) with T2DM	Completed: April 2020
IDDIA (NCT02751398)	60	Evaluate dapagliflozin on diastolic dysfunction in T2DM patients with ≥ grade 1 diastolic function at resting echocardiography	Completed: June 2020
SOLOIST-WHF (NCT03521934)	1,222	Evaluate sotagliflozin on clinical outcomes in hemodynamically stable patients with T2DM post-WHF (EF <40%).	Terminated prematurely: June 2020
ERADICATE-HF** (NCT03416270)	36	Evaluate mechanism by which ertugliflozin 15 mg modifies cardiorenal interactions that regulate fluid volume and neurohormonal activation in T2DM and HF (EF ≥20%).	Completion: March 2021
EXCEED (UMIN000027095)	100 (target)	Evaluate ipragliflozin on cardiac function in patients with chronic HF (NYHA I-III) and T2DM vs. non-SGLT2i antidiabetic drugs	Completion: Date not available
In subjects with CKD (with and without T2DM)			
SCORED (NCT03315143)	10,584	Evaluate sotagliflozin, on time to: a) first MACE or b) CV death or HHF. Patients eligible if T2DM and eGFR ≥25 and ≤60 mL/min/1.73 m^2	Terminated prematurely: July 2020
RACELINES (NCT03433248)	66	Evaluate empagliflozin 10 mg and linagliptin 5 mg monotherapy or combination vs. gliclazide 30 mg on changes in GFR Patients eligible if T2DM and eGFR ≥45 and on treatment with RAAS blockers	Completion: December 2021
EMPA-KIDNEY (NCT03594110)	6,000	Evaluate empagliflozin, on composite of time to first occurrence of kidney disease or CV death Patients eligible if CKD and eGFR ≥20 to <45 or ≥45 to <90 with UACR ≥200 mg/g	Completion: October 2022

*Results not published; **Not yet recruiting

CKD = Chronic kidney disease; CV = Cardiovascular; DM = Diabetes mellitus; EF = Ejection fraction; eGFR = Estimated glomerular filtration rate; ESRD = End-stage renal disease; HF = Heart failure; HHF = Hospitalization for heart failure; HFmEF = Heart failure with mid-range ejection fraction; HFrEF = Heart failure with reduced ejection fraction; MACE = Major adverse cardiovascular events; NYHA = New York Heart Association; RAAS = Renin-angiotensin-aldosterone system; SGLT2i = Sodium-glucose co-transporter 2 inhibitor; T2DM = Type 2 diabetes mellitus; UACR = Urine albumin-to-creatinine ratio; WHF = Worsening heart failure.

ESRD (HR: 0.65, 95% CI: 0.53-0.81, p < 0.0001) and acute kidney injury (HR: 0.75, 95% CI: 0.66-0.85, p < 0.0001).[53] A prespecified meta-analysis of the EMPEROR-Reduced and DAPA-HF trials reported significant reductions in the all-cause death (HR: 0.87; 95% CI: 0.77-0.98; p = 0.018), CV death (HR: 0.86; 95% CI: 0.76-0.98; p = 0.027), and composite renal outcome (HR: 0.62; in patients with HFrEF, with benefits consistent across subgroups, such as age, sex, diabetes and baseline eGFR.[54]

Real-world Evidence

In CVD-REAL[55] (n = 3,09,056), the use of SGLT2i (n = 1,54,528) versus other GLDs demonstrated a lower risk for HHF (HR: 0.61, 95% CI: 0.51-0.73, p < 0.001), death (HR: 0.49, 95% CI: 0.41-0.57, p < 0.001); and HHF or death (HR: 0.54, 95% CI: 0.48-0.60, p < 0.001) without a country-wise difference. An analysis of the CVD-REAL study (n = 1,53,078) reported that SGLT2i

use was associated with a lower risk of mortality in patients with (HR: 0.56, 95% CI: 0.44-0.70) and without (HR: 0.56, 95% CI: 0.50-0.63) CVD. Furthermore, HF (HR: 0.72, 95% CI: 0.63-0.82 and HR: 0.61, 95% CI: 0.48-0.78, with and without CVD, respectively) and the composite of HF or death (HR: 0.63, 95% CI: 0.57-0.70 and HR: 0.56, 95% CI: 0.50-0.62, with and without CVD, respectively) were lowered significantly.[56]

Preliminary results of the EMPRISE study demonstrated a 50% risk reduction with empagliflozin in HF discharge diagnosis in the primary position (HHF-specific) (HR: 0.50, 95% CI: 0.28-0.91) and 49% in HF discharge diagnosis in any position (HHF-broad) (HR: 0.51, 95% CI: 0.390.68) compared with sitagliptin. The results were consistent for both doses of empagliflozin (10 and 25 mg) and irrespective of the baseline CVD status.[57]

The CVD-REAL 3 study showed a lower risk of eGFR decline (difference in slope 1.53 mL/min/1.73 m^2, 95% CI: 1.34-1.72, $p < 0.0001$) and renal outcomes (HR: 0.49, 95% CI: 0.35-0.67, $p < 0.0001$) in the group receiving SGLT2i.[58]

Emerging Evidence in Chronic Heart Failure with HFrEF and HFpEF

Table 2 shows emerging evidence with multiple phase 2/3 and 4 trials evaluating SGLT2i in subjects with pure HF (HFrEF and HFpEF), without comorbid T2DM, on parameters like cardiac biomarkers, exercise capacity, quality of life, echocardiographic features, HF symptoms, worsening HF and CV death. These study results may elevate the importance of SGLT2i in the clinical practice of a cardiologist.

Emerging Evidence with SGLT2i for Coexistent T2DM and HF

Several trials currently investigating the benefits of SGLT2i in subjects with the dual burden of T2DM and HF are described in Table 3. These trials will assess the mechanisms and effects of SGLT2i on exercise capacity, systolic and diastolic cardiac function, and HF biomarkers when T2DM and HF coexist, and their results may augment the importance of SGLT2i in the practice of diabetologists and cardiologists.

Emerging Evidence with SGLT2i in CKD (With and Without T2DM)

Trials currently investigating SGLT2i in subjects with CKD (with and without T2DM) are described in Table 3. These trials will assess the renal physiology, biomarkers and renal and CV endpoints at different CKD stages. The EMPA-KIDNEY trial[59] like the DAPA-CKD trial[14] specifically plans to evaluate renal outcomes in CKD subjects without T2DM. Results from these trials may cause a paradigm shift in the practice of nephrologists.

ROLE OF PCPS FOR SGLT2I USE

PCPs form the first touch point of care for T2DM in many countries; 90% of people with T2DM were treated by PCPs in the United States.[60] In the United Kingdom, only 20% of people with T2DM see a specialist, implying 80% are seen by PCPs.[61] T2DM management in primary care is complex with multiple challenges including clinician and patient inertia in ensuring treatment compliance and implementing therapeutic advances.[62]

A Canadian survey highlighted the importance of PCPs in individualizing treatment decisions when initiating SGLT2i therapy.[63] While the PCP role is important in the everyday management, expert evaluation for diabetes-related complications, CV risk and renal status by diabetologists/endocrinologists, cardiologists and nephrologists, is essential to optimize treatment decisions and improve clinical outcomes.[64]

CONCLUSION

PCPs, diabetologists and endocrinologists play a prime role as the first contact for most subjects with T2DM and rely on novel therapies like SGLT2i for effective glycemic control and microvascular and macrovascular risk reduction. Cardiologists and nephrologists can play an equally prime role by routinely screening their patients for T2DM, and optimally managing CV and renal risk factors by assimilating SGLT2i use in their clinical practice. SGLT2i offer a meeting point for PCPs, diabetologists, cardiologists and nephrologists by delivering benefits as antidiabetic, cardiac and renal molecules.

Acknowledgment

The authors would like to thank AstraZeneca Pharma India Ltd. for the development of this manuscript in collaboration with Dr Anita Bhat, Covance Scientific Services & Solutions Pvt. Ltd. in accordance with GPP3 guidelines (http://www.ismpp.org/gpp3).

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article and take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

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This article is being published simultaneously in the Indian Journal of Clinical Practice and in the Asian Journal of Diabetology.

CASE REPORT

Pyrexia of Unknown Origin: A High Suspicion of COVID-19

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ABSTRACT

We report a case of pyrexia of unknown origin (PUO) in a 19-year-old male, who was admitted with a history of pyrexia for 2 weeks. The diagnosis remained uncertain despite multiple investigations and the patient subsequently had various clinical manifestations similar to those seen in coronavirus disease 2019 (COVID-19). Since it was initially presumed to be pyrexia due to viral origin or enteric fever, patient was started on empirical treatment. The diagnosis of COVID-19 was confirmed by corroborating various biochemical markers that had a greater association with COVID-19. Patient was discharged after 21 days with empirical antibiotics, anticoagulants and other supportive medications. He required no further hospital admissions and has been on regular follow-up.

Keywords: Pyrexia of unknown origin, COVID-19, pyrexia, enteric fever, D-dimer, empiric

Pyrexia of unknown origin (PUO) is defined as fever ≥38.3°C (≥101°F) on at least two occasions, illness duration of ≥3 weeks and no known immunocompromised state.

The diagnosis remains uncertain after thorough history-taking, physical examination and the following obligatory investigations: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelet count, total and differential leukocyte counts, hemoglobin, electrolytes, creatinine, total protein, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine kinase, ferritin, antinuclear antibodies and rheumatoid factor, protein electrophoresis, urinalysis, blood culture, urine culture, chest X-ray, abdominal ultrasonography (USG) and tuberculin skin test (TST) or interferon-γ release assay (IGRA).[1]

Coronavirus disease 2019 (COVID-19) is the latest crisis that has affected the world and it has challenged the leadership and health infrastructure worldwide. COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), began as an outbreak of pneumonia of unknown cause at a local seafood market in Wuhan, China. It soon spread globally and has since claimed over 6 million lives. It predominantly affected the middle-aged adults and elderly and males, though no gender or age group has been spared.[2]

The virus has a wide spectrum of symptoms due to the ability of the spike(S) protein to bind to the angiotensin-converting enzyme 2 (ACE2) receptors on various tissues. It spreads predominantly as a respiratory droplet infection from person to person.[3] Airborne transmission also occurs through aerosols. COVID-19 encompasses a spectrum of illness ranging from asymptomatic or presymptomatic, mild, moderate and severe to life-threatening critical disease. Most common symptoms are cough (53%), fever (43%), myalgia (36%), headache (34%), dyspnea (34%) and sore throat (20%).[4]

Gastrointestinal (GI) symptoms and dermatological manifestations are less common. Lab findings reveal lymphopenia, elevated CRP, transaminases, LDH, D-dimer, serum ferritin and troponin T.

The most common imaging findings are bilateral peripheral lower lung ground-glass opacities on high-resolution computed tomography (HRCT) chest. Reverse transcriptase-polymerase chain reaction (RT-PCR) of nasopharyngeal or oropharyngeal swab confirms the diagnosis.

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CASE REPORT

A young 19-year-old male from Hyderabad, India presented to St. Theresa's Multispeciality Hospital with a history of on and off high-grade fever for 10 days associated with chills and rigors. He also had altered bowel movements for 4 days. Bacterial infection, viral pyrexia, COVID-19, enteric fever were considered in the differential diagnosis and he was managed conservatively with antibiotics, antipyretics and other supportive medications. There was no history of loss of appetite, weight loss, night sweats, pain abdomen, rash, joint pain, chest pain, syncope, shortness of breath or burning micturition. He denied long-standing cough, headache, altered sensorium or blurred vision. There were no known comorbidities. His past medical history was unremarkable. He was an inter 2nd year student, and had been smoking for 1 year. He denied any family history, past history or contact history of tuberculosis (TB).

On examination, he had temperature of 101°F at the time of admission. His blood pressure (BP) was 100/80 mmHg, pulse 108 beats/min and respiration rate 18 breaths/min. There was no rash and lymphadenopathy. Cardiovascular and respiratory system examinations were unremarkable; abdominal examination revealed a soft and nontender abdomen. The neurological examination, including higher functions, was unremarkable. There were no features of meningism.

On admission, patient was started on normal saline, ringer lactate 100 mL/hour, IV antibiotic empirically after blood and urine samples sent for cultures. He was treated with proton pump inhibitors (PPI) and ondansetron and doxycycline was subsequently added to the treatment regimen. He continued to have high fever spikes, and his condition deteriorated. Complete blood count reveal hemoglobin - 14.4 gm, white blood count - 5,500 cu mm and platelets - 2,30,000. The D-dimer was 5,600 μg, serum creatinine - 1.27 mg, CRP level - 43.91 mg and ESR - 18 mm in first hour. His chest radiograph was unremarkable. His renal functions were normal. Liver function test (LFT) showed mild transaminitis with ALT - 73 U/L, AST - 86 U/L and serum bilirubin - 1.38 mg/dL. Blood culture and urine cultures were sterile. Widal titers were TH - 1:160, TO - 1:160, smear for malarial parasite and leptospirosis and brucellosis antibodies were negative. The Paul Bunnell test for infectious mononucleosis was negative. CT abdomen and HRCT chest were unremarkable; RT-PCR for COVID-19 and Mantoux test were negative. Electrocardiogram (ECG) showed normal sinus rhythm. 2D echocardiogram showed ejection fraction of 64%; there was no evidence of vegetation and clots. Bone marrow aspiration and biopsy were negative for TB, malignancy and other infections. He had continuous high-grade fever, vomiting, worsening of liver enzymes, elevated D-dimer levels; hence, antibiotics were escalated to carbapenems. His fever spikes gradually subsided, liver enzymes normalized, D-dimer reduced; the patient was symptomatically better and discharged in stable condition.

DISCUSSION

Pyrexia of unknown origin (PUO) has always been a challenge for the physicians. The principal concept of PUO, despite variations in definition, is that there is a significant fever that has persisted for longer than an acute self-limiting illness and that the disease has not been identified despite reasonable investigations in whatever setting is appropriate, either inpatient or outpatient.[5] Over the decades, many infectious, noninfectious, neoplastic and miscellaneous causes of PUO have been reported.[6] Given the extensive variety of possibilities, it is important to narrow down the etiologies by taking a thorough history and possible investigations to direct subsequent management.[7] In this case, the patient's fever persisted for 3 weeks, with raised inflammatory markers; all other possible tests were unremarkable. One of the highest possibilities was TB as countries outside the western nations have risk of up to 50%.[8]

As the Mantoux test was negative, some neglected diseases could have been scrub typhus, visceral leishmaniasis, brucellosis, among others.[9-11] Nevertheless, there were no physical or clinical evidences for such diseases. The new emerging disease was COVID-19 and despite RT-PCR being negative twice in this patient, the raised markers of CRP, D-dimer and ESR raised suspicion. Quite a few number of COVID-19 patients have been reported with no lung infections and its clinical signs, rather only with flu manifestations.[12]

COVID-19 pathological, physiological and diagnostic approaches are at the discovery stage. RT-PCR is the most widely used diagnostic test. However, Pu et al have reported false negative rates ranging from 6% to 12% in a recent study suggesting that PCR is not the perfect gold standard for comparison of diagnostic accuracy with COVID-19.[13]

In this study, we found raised CRP levels and studies have proved that elevated CRP can be used to predict the risk of disease progression in asymptomatic and/or

mild to severely ill persons.[12] CRP is a serum protein produced by hepatic endothelial cells that can be increased by a number of mediating factors, such as interleukin-6. It is becoming a prognostic marker of acute infection and also linked to chronic inflammation and heart diseases. Additionally, early plasma CRP growth has been proved to improve the chance of developing plasma leakage. Therefore, CRP levels could be used to anticipate chronic bronchitis caused by COVID-19.[14] Though there would seem to be plasma indicators linked to high levels of intensity and death in this regard, CRP thresholds were markedly elevated in seriously SARS-CoV-2 susceptible individuals.[15] One retrospective study revealed most individuals with acute stages of COVID-19 had considerably greater CRP levels than patients with non-acute illnesses (100 vs. 9.65 mg/L).[16] Another research in Vietnam reported all COVID-19 patients, regardless of illness stage, had a greater extent of CRP.[17]

In addition, in a Chinese study, people who died of COVID-19 had a higher CRP level (85.3 mg/L) than those who were improved and discharged (53.5 mg/L).[18] Furthermore, a study in the United States of America and Turkey stated that CRP tests are quick, easy and cost-consuming technique for estimating the amount of tissue damage in COVID-19 individuals.[19,20] Based on the studies, physicians may find that investigating the CRP level may be critical for early identification and adequate therapy of COVID-19-related problems. However, more large-scale investigations, are required to corroborate these findings.

Furthermore, we also found elevated D-dimer and ESR levels in the patient. Many studies have suggested the raised levels of the immunological, biochemical and hematological biomarkers as predictors of COVID-19 mortality.[21] D-dimer is one such marker, which contains two D fragments of the fibrin and is formed by the activation of the plasmin enzyme. This shows the presence of a demolished fibrin in the bloodstream and represents the activation of coagulation and fibrinolysis systems.[22] D-dimers are raised in patients of venous thromboembolism (VTE), cancers, inflammation, pregnancy and are most importantly used in clinical practice to exclude deep vein thrombosis (DVT) and pulmonary embolism (PE) and confirm the diagnosis of disseminated intravascular coagulation (DIC).[23] Furthermore, several studies have shown that COVID-19 predisposes patients to thrombosis, both in arteries and veins resulting in patient at risk for DVT, VTE and possible PE up to 25%.[24] D-dimer in COVID-19 infection can rise due to several reasons at various time points in infection. In addition to this, some underlying diseases such as cancer, diabetes, stroke and pregnancy may also trigger an increase in D-dimer levels in COVID-19 patients. One study has reported an increase in fibrinogen concentrations and D-dimer levels in the initial stages of COVID-19 and a three- to fourfold rise of D-dimer levels has been linked to poor prognosis of the patient.[25] Therefore, estimating the D-dimer levels and coagulation parameters from the initial stages of the disease can be helpful in controlling and managing of COVID-19 disease.

On the other hand, Zhang et al identified ESR as the most powerful factor to predict disease progression of COVID-19.[26] ESR is affected by the shape, size and concentration of red blood cells and plasma characteristics.[27] One study suggested that COVID-19 can change the form of erythrocytes or plasma characteristics along with the immune system via an unknown mechanism to increase the ESR levels.[28]

Moreover, the sustained elevated levels of ESR could damage the joints leading to joint diseases such as osteoarthritis, which can give negative effect on COVID-19 patients' prognosis. Besides, it may be a precursor of hepatic and renal dysfunction.[29] Accordingly, this emerging disease may influence the long-term prognosis of patients; however, it is difficult to predict the long-term prognosis of COVID-19 patients based on ESR alone. More cases and evidence are needed to address this issue.

Besides, our patient presented with fever with transaminitis, which is likely to be of viral etiology. Several studies stated that the levels of serum AST, ALT and LDH, which are liver function tests, were higher in severe COVID-19 patients when compared to the mild COVID-19 patients.[30,31] According to Onur et al, AST, ALT and LDH levels were higher in deceased COVID-19 patients than the survivors.[32]

Another study found that the ALT and AST levels were higher in severe patients than in non-serious patients.[33] These results indicated that severe liver dysfunction may have developed in those who have severe COVID-19 infection or died from the disease.

CONCLUSIONS

The diagnosis of COVID-19 in our patient was based on clinical and laboratory findings. Empirical treatment was given and symptomatically improved during the course in the hospital. Extensive laboratory evaluation along with detailed history and clinical examination are important to make diagnosis of PUO. COVID-19 can

present as fever of long duration even with RT-PCR testing negative; however, other biochemical markers always give a clue regarding the diagnosis.

Conflict of Interest Statement

The authors declare no competing interests.

Funding Source

Not applicable.

Ethics Approval

Ethical approval was not obtained for the publication of this case report because the report does not involve sharing of the personal details and personal photographs of the patient.

Authors' Contributions

AC, AB and SL examined and assessed the patient. AC and AB were involved in the management of the patient. SL and AB collected and analyzed data. SSP helped in guidance over compiling data, AC supervised the study. All the authors read and approved the final manuscript.

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■■■■

Lung Volume Reduction Surgery vis-a-vis Bronchoscopic Lung Volume Reduction for Emphysema

Results of the CELEB (Comparative Effectiveness of Lung volume reduction surgery for Emphysema and Bronchoscopic lung volume reduction with valve placement) trial presented at the concluding day of European Respiratory Society Congress 2022 in Barcelona show no differences in outcomes following lung volume reduction surgery (LVRS) and bronchoscopic lung volume reduction (BLVR) among patients with emphysema.[1]

Buttery et al compared the outcomes of LVRS and BLVR in this randomized-controlled single-blind superiority trial, which enrolled 88 patients with male preponderance (52%) and mean age of 64 years. There were 41 patients in the LVRS group and 47 in the BLVR group. The iBODE index composite score was used to evaluate the outcomes. The components of the iBODE index are body composition, airway obstruction, dyspnea and exercise capacity (incremental shuttle walk test).

At the end of the follow-up period of 1 year, the improvement in both intervention groups was equivalent as reflected by the i-BODE composite scores of –1.10 with LVRS and –0.82 with BLVR. The percentage predicted residual volume (RV% predicted) suggestive of air trapping in emphysema was –36.1 among patients who underwent LVRS versus –30.5 among those who underwent BLVR. Patient survival was also comparable with one death reported in each group.

This study designed as a superiority trial has for the first time compared the two interventions and concluded that the two procedures were comparable in outcomes (dyspnea, lung function and exercise capacity) and neither intervention was superior to the other with regard to safety and efficacy. Hence, not just clinicians, but patients with emphysema who are candidates for surgery, too can opt for BLVR in place of the more invasive lung volume reduction surgery as part of informed decision making. Noting these findings as "encouraging", the authors, however, advocate the need for larger trials to further examine the safety and effectiveness of the two procedures.

(Ref: [1]European Respiratory Society International Congress 2022. Abstract RCT44448. Buttery S. Comparative effect of lung volume reduction surgery for emphysema and bronchoscopic lung volume reduction with valve placement: the CELEB trial. Presented September 6, 2022. Available from: https://img.medscapestatic.com/article/980/491/Abstract_LVRS_BLVRS.pdf.)

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VIEWPOINT

Choosing Glucose-lowering Therapy: A Collaborative Choice Model

SANJAY KALRA*, SAURABH ARORA†, NAVNEET AGRAWAL‡, RAJAT GUPTA#, SUNEET VERMA¥, NITIN KAPOOR£

ABSTRACT

Diabetes care is challenging, and the increasing number of available therapeutic options has made it even more complex. Moreover, with an increasing prevalence across the world, it needs to be managed right from the primary care level to a quaternary care hospital. This calls for an easy-to-use algorithm that can be used by a general practitioner, who is often the first contact of a patient to manage diabetes in many countries. There are multiple models to assist in choice of pharmacotherapy, and these have evolved over time. We propose a user-friendly collaborative choice, as an aid to clinical decision-making. This alliterative framework supplements and strengthens existing guidance, by creating a comprehensive, yet simple, thought process for the diabetes care professional.

Keywords: Pharmacotherapy, person-centered, type 2 diabetes

There are multiple algorithms and guides to choosing glucose-lowering therapy in persons with type 2 diabetes.[1,2] Continued evolution of internationally accepted recommendations underscores the dynamic and flexible nature of diabetes practice. It is challenging, however, to condense a complex syndrome into just one or two tables, figures or graphs. This is evident in conventional and current attempts at 'sanitizing' choice of therapy.

While earlier models were criticized for[3] being gluco-centric, modern rubrics have become cardiocentric and are equally tubular in their scope. It is heartening to note, however, that safety and economic considerations are now being highlighted in international guidelines.

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A COLLABORATIVE CHOICE MODEL

We have earlier proposed vasocentric and metabolic fulcrum-based frameworks[4,5] to help in clinical decision-making in diabetes. Classification of glucose-lowering therapies have also been crafted,[6,7] to make them easier to understand. We now share a chart, which simplifies the thought process behind choice of glucose-lowering therapy. The user-friendly format lists 4 domains, all alliteratively named, which must be kept in mind, while deciding treatment. The word 'collaborative' is used in the title to remind ourselves that the person living with diabetes is an active participant in his/her their treatment.

The hierarchy of the "C chart" (choice chart), as we term it, corresponds broadly to the conventional order of patient evaluation (history taking, examination, investigations), and assesses both biomedical and psychosocial issues. It retains person-centricity and pragmatism in its ethos, by considering habits, challenges/constraints and also analyzing the diabetes care ecosystem that he/she/they live in.

Table 1 presents the model that can act as a tool in clinical practice. This chart supplements existing guidance, and makes diabetes care easier, more efficient and perhaps more enjoyable, for practitioners and students alike.

SUMMARY

The C chart for collaborative choice is a simple model to remind a treating clinician about the different

Table 1. Glucose-lowering Therapy in Type 2 Diabetes: The C Chart for Collaborative Choice

Domains	Dos	Dont's
Complaints and concerns	Acknowledge complaints and concerns Endeavor to address them	Trivialize complaints and concerns Ignore them while choosing treatment
Complication and comorbidities	Institute appropriate therapy Refer if indicated	Ignore red flags Create iatrogenic complications with inappropriate therapy
Concomitant medication and culinary pattern	Take detailed history Optimize diet and lifestyle	Neglect to ask about complementary therapy Use regimes that are discordant with diet
Cost constraints and care ecosystem	Be mindful of bio-psychosocial health Be pragmatic in delivery of care	Take unilateral decisions Be dismissive of patient's reality

domains of patient characteristics that need to be kept in consideration before finalizing the prescription. This model can be applied across different types of diabetes, ethnicities and socioeconomic status of people living with diabetes.

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Efficacy of Povidone-Iodine Nasal and Oral Antiseptic Preparations against SARS-CoV-2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) primarily transmits amongst humans through aerosolization of respiratory droplets. Transmission through contact with contaminated surfaces and other fomites has also been documented. Consistent and diligent antisepsis of surfaces and the skin can prevent this communicable COVID-19.

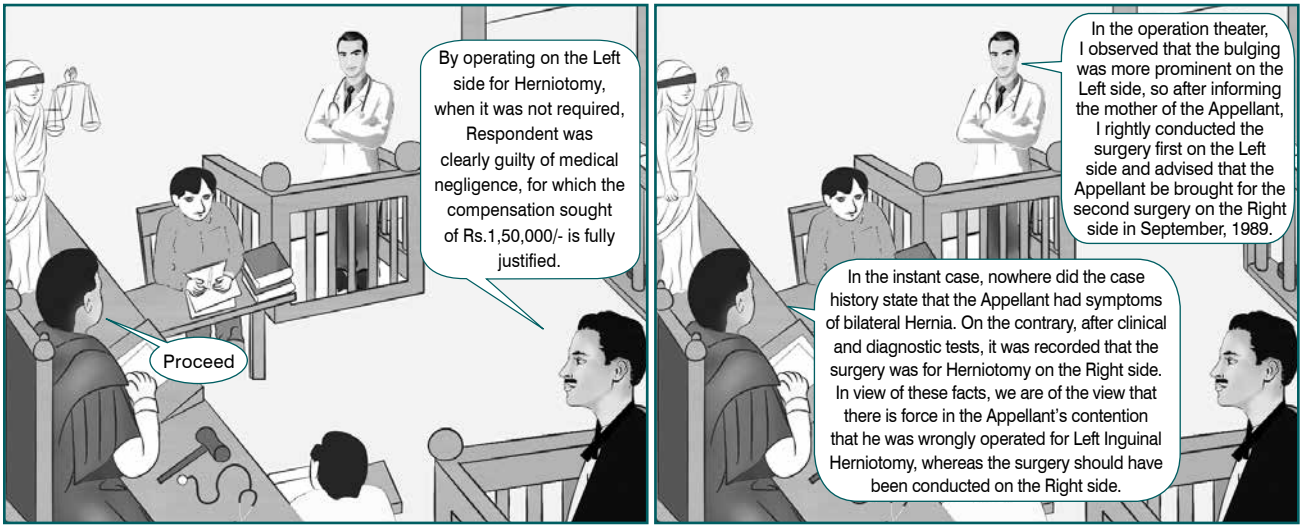
A recent study evaluated nasal and oral antiseptic formulations of povidone-iodine (PVP-I) (nasal antiseptic formulations and oral rinse antiseptic formulations from 1% to 5% concentrations) for the virucidal activity against SARS-CoV-2. Here, the virus was directly exposed to the test compound for 60 seconds, compounds were then neutralized and the surviving virus was quantified.

The results revealed that all concentrations of nasal antiseptics and oral rinse antiseptics used completely inactivated the SARS-CoV-2.

It was inferred that oral and nasal PVP-I antiseptic solutions are effective at inactivating the SARS-CoV-2 at a variety of concentrations after an only 60-second exposure. These formulations can aid in diminishing transmission of the SARS-CoV-2 with usage for oral decontamination, nasal decontamination or surface antisepsis.

(*Source: Pelletier JS, et al. Efficacy of povidone-iodine nasal and oral antiseptic preparations against severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). Ear Nose Throat J. 2021;100(2_suppl):192S-196S.*)

Wrong Site Surgery: An Act of Gross Medical Negligence



Lesson: In the Case No. 494 of 2007, the National Consumer Disputes Redressal Commission (NCDRC), the Commission ruled in the favor of the Appellant holding the Respondent guilty of medical negligence since he had wrongly operated for Left Inguinal Herniotomy, whereas the surgery should have been conducted on the Right side and directed him to pay the Appellant Rs.1,00,000/- as compensation for the unnecessary suffering and agony caused to him and to his family.

COURSE OF EVENTS

- Appellant, a 6-year-old boy was admitted to Respondent Hospital with complaint of temporary Inguinal Hernia (R) and after diagnostic tests, it was confirmed that he was suffering from Inguinal Hernia (R), and was thus advised surgery. He was taken up for surgery. However, instead of operating on the Right side, Appellant was operated for Left Inguinal Hernia and Herniotomy. This mistake was noted by the main doctor of the hospital.
- **26.08.1989:** The Appellant was discharged with advice to come back in September, 1989.
- **07.09.1989:** Appellant's father got him back to Respondent Hospital, when he was informed that an operation, Right Inguinal Herniotomy, is required.
- Appellant's father refused to get another surgery done and he was taken to Hospital B, where after a medical check-up he was informed by Dr A that Respondent had made a mistake in conducting the first surgery on the Left Inguinal Hernia.
- Being aggrieved by the medical negligence on the part of Respondent, Appellant filed a complaint before the State Commission and requested that Respondent be directed to pay him Rs. 1,50,000/- as compensation.
- Respondent on being served denied these allegations and stated that Hernia in children are often bilateral, as is in the instant case. Since, it is well-established that surgery cannot be done on both sides at the same time, Appellant's parents were informed that both sides would have to be operated through two separate surgeries, which they had agreed.
- At the operation theater, RW-2, the doctor conducting the surgery noted that the Left side scrotum was bulging more and, therefore, it was necessary to conduct an operation on the Left side first, about which the Appellant's mother, who was waiting outside the operation theater, was duly informed. The surgery was successfully conducted and after the wound was sutured on 26.08.1989. Appellant was discharged and was asked to

come back for the second surgery in September, 1989 during school vacations. In the meantime, Appellant was administered medicine and injection for the second surgery.

- However, when the Appellant was readmitted for repair of the Right side Herniotomy, his father for reasons best known to him got him discharged without waiting for the surgery. It was specifically denied that the Appellant's parents were informed that surgery was required only on the Right side. Thus, there was no medical negligence on the part of the Respondent.
- The State Commission after hearing the parties dismissed the complaint filed by the Appellant against the Respondent by stating as follows: *"The fact remained that the mother of the Complainant was aware of the operation of the Left side hernia as she had given consent for herniotomy which meant operation of both sides as explained by RW-2. Further, right through the treatment and surgery of the Complainant, only the mother of the Complainant was present and only on 08.09.1989, the father had as suggested in the cross-examination, had compulsorily asked for the discharge of the Complainant. This was with an intention to extort money from the opposite party. He had projected a false stand as if he was present throughout from the beginning till the complainant was discharged. RW-2 had also in her evidence clearly stated that in children, the swelling would appear and disappear and that was the reason why while operating a child for hernia, the consent was got only for herniotomy, which related to both sides of the scrotum. The opposite party had taken due care in the discharge of their duties and there was no negligence whatsoever in operating the complainant. As a competent surgeon, RW-2 had taken the necessary care and caution so that the child's life could be saved. The Complainant's father had also stated that he had consulted one Dr A. But, no evidence was produced to show that any other doctor had been consulted. There was also no proof produced by the Complainant with regard to the expenses incurred."*
- The State Commission also cited medical literature entitled "The Surgical Clinics of North America" [Vol. 65/Number 5, October 1985], confirming that Hernias in children are often bilateral but both may not always be diagnosed during a medical examination and further that Inguinal Herniotomy also has a silent side, which may not always be apparent on sight.
- Being aggrieved by the dismissal of his complaint, Appellant has filed the present first appeal.

ALLEGATION OF THE APPELLANT

- Learned Counsel for the Appellant stated that the State Commission erred in not taking cognizance of the medical records pertaining to the Appellant's case history in Respondent Hospital, which was in evidence before it.
- As per these records, a clear diagnosis of obstructed Inguinal Hernia on the Right side was made, which was also recorded. This diagnosis was again confirmed in the detailed case history recorded on 13.08.1989.
- On 25.08.1989 when the Appellant was admitted for surgery, it was again clearly noted that he was "Posted for (R) Herniotomy on 25.08.1989". However, it was only on 26.08.1989, i.e., just prior to the surgery that it was noted in the case sheet that Appellant had Left Inguinal Hernia, which required to be operated.
- Counsel for the Appellant stated that Respondent's contention that the Hernia was bilateral and that before the surgery, the Appellant's mother was informed that the surgery would be first done on the Left side, is not factually correct because nowhere does the diagnosis in the case history indicate that the Appellant was suffering from bilateral Inguinal Hernia.
- By operating on the Left side for Herniotomy, when it was not required, Respondent was clearly guilty of medical negligence, for which the compensation sought of Rs. 1,50,000/- is fully justified.

REJOINDER OF THE RESPONDENT

Learned Counsel for Respondent stated that the State Commission had rightly relied upon the medical literature as also the evidence on record to conclude that there was no medical negligence. It was clear from the record that the Appellant was suffering from bilateral Herniotomy, i.e., both on the Right and Left sides, which is a common phenomenon in children, and in the operation theater when a well-qualified pediatric doctor observed that the bulging was more prominent on the Left side, after informing the mother of the Appellant, she rightly conducted the surgery first on the Left side and advised that the Appellant be brought for the second surgery on the Right side in September, 1989.

This is evident from the consent letter signed by Appellant's parents as also the case history recorded on 07.09.1989.

OBSERVATIONS OF THE NCRDC

- It was noted from the recorded case history of the Appellant, that right from the time when he was brought to the hospital, i.e., on 12.08.1989, he was subjected to a number of diagnostic and clinical tests and on the basis of these tests, a clear cut diagnosis of obstructed Inguinal Herniotomy (R) was made. These findings were confirmed on 13.08.1989 following a physical examination when it was specifically noted that the Appellant was a known case of Inguinal Hernia (R) and there was no other complaint. This diagnosis was confirmed at the time of his admission for the required surgery on 24.08.1989 and again on 25.08.1989, when it was stated that the Appellant was posted for (R) Herniotomy.
- It was only on 26.08.1989 at the time of the operation that for the first time it was stated that this was a case of Left Inguinal Herniotomy. The consent letter signed by the Appellant's parents (since he was a minor) only states that the Appellant's mother had given permission for operation of Herniotomy. No mention is made about bilateral Herniotomy.
- Respondent has not been able to produce any evidence that Appellant's parents were informed that Appellant was suffering with bilateral Herniotomy or that just prior to the surgery they were informed that the surgery would be conducted on the Left side and not on the Right side.
- The letter dated 07.09.1989 only states that the Appellant is posted tentatively for Right Herniotomy, which does not help the Respondent and only proves the Appellant's contention that a surgery on the wrong side was carried out on 26.08.1989.
- In view of the overwhelming documentary evidence from Respondent's own hospital discussed in the foregoing paras, we are unable to agree with the finding of the State Commission that as per the evidence on record there was no medical negligence in the treatment of the Appellant. Clearly, Appellant was diagnosed for conducting a surgery for Right Inguinal Hernia, whereas without any evidence that it was the Left side which required the surgery, this surgery was conducted. Had the Respondent advised the Appellant's parents during their visit to the hospital that the Appellant had bilateral hernia, then perhaps there would be some case for the Respondent to explain how the surgery was conducted on the Left side. In the instant case, nowhere did the case history state that the Appellant had symptoms of bilateral hernia. On the contrary, as stated above, after clinical and diagnostic tests, it was recorded that the surgery was for Herniotomy on the Right side. In view of these facts, we are of the view that there is force in the Appellant's contention that he was wrongly operated for Left Inguinal Hernia, whereas the surgery should have been conducted on the Right side.
- What constitutes medical negligence is now well-settled through a number of judgments of this Commission as also of the Hon'ble Supreme Court of India. One of the principles to test medical negligence is whether a doctor exercised a reasonable degree of care and caution in treating a patient [Supreme Court Case Indian Medical Association v. V.P. Shantha (1995) 6 SCC 651 and this Commission case Tarun Thakore v. Dr Noshir M. Shroff (OP No. 215 of 2000)].

ORDER OF NCDRC

- In the instant case, the facts clearly indicate that the required reasonable degree of care and caution was not taken by Respondent in the treatment of the Appellant and, thus, Respondent was guilty of medical negligence, for which the Appellant should justifiably be compensated.
- In view of these facts and respectfully following the judgment of the Hon'ble Supreme Court cited above, we are unable to uphold the order of the State Commission and set aside the same. Respondent being guilty of medical negligence is directed to pay the Appellant Rs. 1,00,000/- as compensation for the unnecessary suffering and agony caused to him and to his family within 2 months from the date of this order.
- The present appeal stands disposed of on the above terms. No costs.

REFERENCE

1. NCDRC First Appeal No. 494 of 2007; Order dated 31.01.2013.

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HCFI Dr KK Aggarwal Research Fund

Minutes of an International Weekly Meeting held by HCFI Dr KK Aggarwal Research Fund

Topic: A Pandemic Snapshot

Speaker: Dr Monica Vasudev, *Allergist & Clinical Immunologist, Fellow of American Academy of Asthma, Allergy and Immunology, Advocate Aurora Health, Wisconsin, USA*

10th September, 2022 (Saturday, 9.30-10.30 am)

- There has been a significant drop in the life expectancy in the United States. The Centers for Disease Control and Prevention (CDC) has published data regarding this. Life expectancy at birth in the year 2021 is now 76.1 years. There has been an overall 2.7 years loss in total life in the last 2 years; for females, the life expectancy has declined by 2.3 years and for males by 3.1 years.
- The BA.5 Omicron sublineage accounts for 87.5% of total samples collected since the last 3 weeks. BA.4 has declined to just 2.2% of the total samples.
- There has been a reduction in vaccine efficacy in this period of BA.4/5. The variants are escaping the immune protection of the vaccine. This raises the need for a pan vaccine or novel vaccine.
- Many intranasal vaccines are under clinical trial including BBV154 from Bharat Biotech developed in collaboration with Washington University. Intranasal vaccines can be an alternative vaccine for those who are reluctant to take the injectable doses.
- The world's first inhaled coronavirus disease 2019 (COVID-19) vaccine developed by the Chinese company CanSino Biologics has been approved for use as a booster dose in China. It is an adenovirus-vectored COVID-19 vaccine similar to the injectable vaccine.
- The first nasal COVID-19 vaccine has been approved (emergency use authorization or [EUA]) in India. It has been developed by Bharat Biotech in collaboration with Washington University. This vaccine can be refrigerated. In this vaccine, the spike protein inserted adenovirus, which is unable to cause illness. The new vaccine also incorporates two mutations into the spike protein that stabilize it in a specific shape that is most conducive to forming antibodies against it.
- When the virus enters the body, the dendritic cells grab the pieces of virus. They recruit helper T cells, which match with the viral pieces. This is followed by the B cells that also match with the virus. The activated B cells form plasma cells that produce antibodies, which attach to the virus and fight off the infection. Some B cells become memory cells which remain in the body and are reactivated in case of reinfection with the same virus.
- The older antibodies are not a good match for the newer variants. The antibodies to the original virus may still be able to attach to some parts of a newer variant, which have not changed.
- The US Food and Drug Administration (FDA) has approved the updated Moderna and Pfizer-BioNTech bivalent COVID-19 vaccine for use as a booster dose.
- Bivalent vaccines have the same total antigen amount as the monovalent vaccines. Moderna's monovalent COVID-19 vaccine contains 50 μg of spike protein from the ancestral (original) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strain. The bivalent Moderna vaccine contains 25 μg of spike protein from the ancestral SARS-CoV-2 strain and 50 μg of spike protein from the Omicron (BA.4/BA.5) SARS-CoV-2 strain.
- Similarly, the Pfizer-BioNTech vaccine contains 30 μg of spike protein from the ancestral (original) SARS-CoV-2 strain. The updated booster vaccine contains 15 μg of spike protein from the ancestral SARS-CoV-2 strain and 15 μg of spike protein from the Omicron (BA.4/BA.5) SARS-CoV-2 strain.
- The US is planning to shift to annual COVID-19 booster doses similar to flu shots, though the elderly may require more frequent vaccination.
- For long COVID, the CDC requires an interval of more than 4 weeks after acute COVID-19. One in five COVID-19 survivors aged 18 to 64 years and one in four survivors 65 years and older experienced at least one incident condition that might be attributable to previous COVID-19.
- The incidence of post-acute sequelae of SARS-CoV-2 infection (PASC) is approximately 14% in adults and 21% in children and adolescents.

- A report from the US has documented the prevalence of SARS-CoV-2 infection and long COVID in US adults during the BA.5 surge in June-July 2022; 21.5% had symptoms more than 4 weeks. Nineteen percent were boosted, 25% were vaccinated but not boosted, while 22% were unvaccinated.
- The prevalence of long COVID in children varies from 1:4 to 1:100. About 25% continue to have symptoms months after hospitalization for COVID-19. The diagnosis is a challenge because of the heterogeneous symptoms. Symptoms persistent at 12 weeks are required to meet the definition of long COVID.
- An international consensus for a pediatric long COVID definition is anticipated in 2023; this will be an important step in the illness being recognized and managed consistently.
- At the population health level, there is a suggestion that the incidence of type 1 diabetes is increased in children with long COVID, although the cause of this is unclear and requires further investigation.
- New research has found the spike protein of the SARS-CoV-2 virus in the blood of long COVID patients up to a year after infection but not in people who have fully recovered from COVID. The virus has also been found in tissues including the brain, lungs and lining of the gut.
- The findings suggest that leftover reservoirs of the virus could be provoking the immune system in some people, causing complications such as blood clots and inflammation, which may fuel specific long COVID symptoms.
- Acute COVID-19 correlates with biomarkers of systemic inflammation, hypercoagulability and comorbidities that are less prominent in PASC.
- Macrovessel thrombosis, a hallmark of acute COVID-19, is less frequent in PASC.
- Female sex at birth is associated with reduced risk for acute COVID-19 progression but increased risk of PASC.
- Persistent microvascular endotheliopathy associated with cryptic SARS-CoV-2 tissue reservoirs has been implicated in PASC pathology.
- Autoantibodies, localized inflammation and reactivation of latent pathogens may also be involved, potentially leading to microvascular thrombosis, as documented in multiple PASC tissues.
- The US government has outlined a plan to get Americans the best available protection through free and easy access to new, updated COVID-19 vaccines and ensuring easy access to COVID testing and treatment to mitigate the spread of COVID-19. The plan also calls on all Americans to use every tool at their disposal to keep communities safe and schools and businesses open and to prepare for potential surges and new variants and building a resilient national COVID-19 response moving forward.

(Excerpts from presentation by Dr Monica Vasudev)

Participants – Member National Medical Associations: Dr Yeh Woei Chong, Singapore, Chair of Council-CMAAO; Dr Alvin Yee-Shing Chan, Hong Kong, Treasurer-CMAAO; 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; Dr Md Jamaluddin Chowdhury, Bangladesh; Dr Marie Uzawa Urabe, Japan; Dr Salma Kundi, Pakistan; Dr Mulazim Hussain Bukhari, Pakistan

Invitees: Dr Russell D'Souza, Australia UNESCO Chair in Bioethics; Dr Monica Vasudev, USA; Dr Nicholas Veliotes; Dr Pinki Chauhan; Dr Colin Goldberg; Dr EC Ng; Dr Roy Teow; Dr Rashid Mahmood; Dr Anita Jain; Dr S Sharma, Editor-IJCP Group

Moderator: Mr Saurabh Aggarwal

HCFI Round Table Environment Expert Zoom Meeting on "Battery Waste Management Rules 2022 – Part 2"

Speaker: Mr Sanjiv Kumar, *Re Sustainability Limited*

11th September, 2022 (Sunday, 12 noon - 1 pm)

- The 2001 battery rules were mainly focused on lead acid batteries. The new rules cover all types of batteries – electric vehicle batteries, portable batteries, automative batteries and industrial batteries.
- The draft rules were shared in 2020 and they came into effect from 27th August, 2022. They replace the 2001 Batteries (Management and Handling) Rules.
- These new rules have come after a gap of two decades.
- These rules function on the concept of extended producer responsibility (EPR). The responsibility of collection and recycling/refurbishment of waste batteries and use of recovered materials from wastes into new batteries lies with producers, importers and brand owners (PIBO).

- The objective is that every part of the battery is recovered, reused and recycled. Only the reject should go for disposal to secured landfill and not to Municipal Solid Waste (MSW) dumping grounds.
- The aim is to also ensure alignment with other rules that are coming up so that the system of Atmanirbhar Bharat is also in place by setting up new industries and entrepreneurship for collection, transportation and refurbishment of waste batteries by way of new technologies and investment.
- The rules also enable setting up a mechanism and centralized online portal for exchange of EPR certificates between producers and recyclers or refurbishers to fulfill the obligations of producers.
- The rules facilitate online registration and reporting, auditing and formation of a committee to monitor the implementation of the rules.
- The rules also work on the principle of Polluter pays Principle. Environmental compensation (EC) will be imposed for nonfulfillment of EPR targets, responsibilities and obligations set out in the rules.
- The funds collected under EC are to be utilized in collection and refurbishing or recycling of uncollected and non-recycled waste batteries. However, how it is to be used is not so clearly defined.
- The 2001 rules were more to create awareness, while the new rules are about creating a robust mechanism or steps as to how to execute the same.
- The 2022 rules apply to produce, dealer, consumer and entities involved in collection, segregation, transportation, refurbishment and recycling of waste battery. They cover all types of batteries regardless of shape, chemistry, volume, weight, composition and use. However, batteries used in equipment connected with the protection of the essential security interests and those specifically meant for military purposes or equipment designed to be sent into space are exempt from the new rules.
- The new rules have laid down responsibilities and functions of different stakeholders such as the producer, consumer, public waste management authorities, refurbisher, recycler, Central Pollution Control Board (CPCP) and State Pollution Control Board (SPCB). The 2001 Rules had defined the functions of the manufacturer, importer, assembler and reconditioner.
- It is the responsibility of the producer to ensure the attainment of the batteries they introduce in the market for their recycling or refurbishment obligations.
- The producer shall be completely accountable to meet their EPR. Year-wise targets have been defined for EPR for all types of batteries, if they are achievable.
- The producer has to register through an online centralized portal as the producer. He has to provide an EPR plan to the CPCB every year for the battery manufactured in the preceding financial year.
- Different schemes may be considered such as buy back or deposit for collection of the waste battery. It is left to the producer or dealer to decide which to use.
- To prevent somebody from absconding with the deposit money, a document can be issued at the time of purchase of a battery that can be encashed in any post office to get back the deposit.
- They also have to submit an annual return with regard to the waste battery collected or refurbished.
- Consumers have the responsibility to discard battery waste separately from other wastes such as mixed waste, domestic waste. They should handover the battery waste to entities engaged in their collection/refurbishment or recycling.
- It is the duty of the entities involved in collection, segregation and treatment to hand over the waste battery to the recycler or refurbisher registered with the SPCB.
- The recycler or refurbisher have the responsibility to ensure that the hazardous waste generated during the process of refurbishment (dismantling of batteries and recovery of metals) is strictly managed according to the Hazardous Waste Management Rules, 2016 and other wastes as per the Solid Waste Management (SWM) 2016 and Plastic Waste Management Rules (PWM) 2016 as the process can be harmful to the health of the workers.
- The 2022 rules talk of public waste management authority. However, they do not generally engage in private waste collections. The rules also say that the PIBOs can engage any entity. The rules are not very clear on how the PWMA and PIBOs will be engaged.
- There is also a need for waste audit; the rules are not very clear on this important issue.
- The manufacturers are expected to establish collection centers for collection of used batteries from dealers and consumers. They have to ensure the batteries collected are transported safely to the registered recyclers. They have to annually report sales and buybacks to the CPCB and SPCB.

- These rules pose many potential problems and challenges, which need to be debated such as the incentive to follow the rules is not explicitly mentioned. The rules fail to establish any regulatory standards for testing and classifying used batteries that have a secondary life and could still be used in other applications such as in households or energy backups.
- Energy conservation through storage batteries will have huge manufacturing potential and increase employment.
- There is not provision for a separate license for handling on lead acid batteries, separate from e-waste and there is no reduced minimum requirement for entry into the recycling of the lead acid batteries.
- Lot of research is required for lead acid batteries
- For effective implementation of the new battery waste management rules, there have to be demand measures, policy support, incentivizing and financing.
- An inventory of how much is being produced is needed as in the coming years, battery waste is going to increase because of the use of electric vehicles and electronic devices. We have not been able to determine the per capita e-waste and electric waste.
- Integration of the various waste management rules is required.
- Putting the rules in place without having any benefit for the manufacturer or recycler leads to noncompliance.
- Strengthening of SPCB is very important.
- All waste management rules need to be critically assessed if their objectives have been achieved and identify gaps, if any. The new rules should be reviewed to see that they do not suffer from these gaps.
- Creating awareness for consumers is very important. The Ministry needs to work on this.
- Health and environmental aspects of hazardous waste are intertwined. Being a technical subject, it requires lot of need-based research. However, environmental research has been neglected over the years.
- Whenever an amendment is made in the rules, its implementation must be covered, whether the responsibility allocation is completely un-challengeable.

Participants: Dr Anil Kumar, Mr Paritosh Tyagi, Dr Dipankar Saha, Mr Sanjiv Kumar, Dr SK Gupta, Mr Neeraj Tyagi, Mr Pankaj Kapil, Mr Rajeev Sharma, Mr RN Jindal, Prof Meenakshi Dhote, Mr Yash Sharma, Mr Achal Kumar, Mr Ankit Kumar, Mr Swabrinto Chatterjee, Dr S Sharma

Coronavirus Updates

World closer to the end of the pandemic, says WHO Director General

In a media briefing earlier this week, Dr Tedros Adhanom Ghebreyesus, the Director General of WHO (World Health Organization) said that "the end of the pandemic is now in sight", although its "not there yet". He urged all to not give up and continue to run to the finish line, just as the marathon runner runs harder nearer the finish line. To enable governments to finish this race, WHO has released six policy briefs (available on its website) outlining the actions regarding vaccination, testing and management of COVID-19, including the infodemic of COVID-19 that they can take to win this race… (*Source: UN, Sept. 14, 2022*)

Africa still facing the pandemic threat due to low vaccination

With just 22% of its population fully vaccinated against COVID-19, the continent of Africa is still facing the threat of the pandemic. Ahmed Ogwell Ouma, the acting director of the Africa CDC said that with the low vaccination uptake, "the levels of protection are still relatively low."… (*Source: Reuters, Sept. 15, 2022*)

Israel and Singapore approve the bivalent COVID-19 booster vaccine

Israel has approved Pfizer's COVID-19 bivalent booster for individuals aged 12 years and older. The vaccine would be available in the country by the end of this month. Those who have taken a vaccine dose at least 3 months back are eligible to take the updated booster. Health authorities have urged the high-risk persons to take the updated booster together with a flu vaccine.

Singapore has also authorized the use of Moderna's bivalent booster vaccine for adults aged 18 years and older, who have completed their primary vaccination series… (*Source: Medscape, Sept. 15, 2022*)

With inputs from Dr Monica Vasudev

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AIOC 2022: 80th Annual Conference of All India Ophthalmological Society

INTRAOPERATIVE IMAGING TECHNOLOGY IN CORNEAL SURGERY: AN UPDATE

Dr Jeewan S Titiyal, New Delhi

"I realized unless we have a quality robust Eye Bank, we cannot deliver good endothelial keratoplasty (EK) services."

- Cataract surgical rate in India is now seeing a new high; approximately 5,000/million/year. 6.5 million cataract surgeries were done in 2019-20.
- Every year therefore we are adding pseudophakic bullous keratopathy (PBK)/edema @ 0.2% which is equal to 13,000 new EK-patients in India.
- The number of patients with Fuchs' endothelial dystrophy is also significant.
- Manual DSEK (Descemet's stripping endothelial keratoplasty) is a good, reproducible, least costly and affordable procedure for the common people in India.
- Typical indications for DSEK include aphakia with large pupil, aniridia with glaucoma drainage device, post-VR Sx with bad pupil, congenital hereditary endothelial dystrophy (CHED)/buphthalmos, one-eyed poor A/C anatomy and extremely poor visibility.
- For India and any developing country, the choice of EK will be either manual DSEK or DMEK (Descemet membrane endothelial keratoplasty).
- We need more trained corneal surgeons with good incentives for them. At the same time, we need more good corneas. This is possible if we develop eye bank within our own community.
- There are needy patients; it is a matter of practice and attitude!

THICK CHOROID IN CSC: A GAME CHANGER

Dr Aniruddha Agarwal, Abu Dhabi

Situations, Management and Outcome

- Although choroidal thickening is a component of pachychoroid, within central serous chorio-retinopathy (CSC) this is a grey area as some patients do not have clearly thickened choroid.
- Patients with thick choroid are likely to respond better to eplerenone. The response is suboptimal in thin choroid and sick retinal pigment epithelium (RPE) syndrome.
- Very thick choroid could predispose to fibrinous CSC, which can take a long time to resolve; high chances of atrophy.

RD IN EYES WITH CHOROIDAL COLOBOMA

Dr Pramod S Bhende, Chennai

- Retinal breaks may occur within the intercalary membrane (ICM), at the locus minoris resistantiae or peripheral breaks outside the coloboma. Retinal detachment (RD) configuration changes with location of the break/s.
- RD may occur in 40% of these eyes. The occurrence of RD and location of the break/s do not follow classic rules. The classic principles of RD management cannot be applied.

DISORGANIZATION OF RETINAL INNER LAYERS IN DIABETIC MACULAR EDEMA: DOES IT CHANGE MY APPROACH?

Prof (Dr) Atul Kumar, New Delhi

- Disorganization of retinal inner layers (DRIL) is a novel optical coherence tomography (OCT) biomarker, which was first described by Sun et al due inability to distinguish inner retinal layers (ganglion cells layer – inner plexiform layer, complex, inner nuclear layer and outer plexiform layer).
- It is a marker of diabetic neuroretinal impairment. It is not specific to diabetic retinopathy (DR) but is a common response to retinal stress. Common in eyes with refractory diabetic macular edema (DME).
- Other OCT biomarkers in DME are integrity of external limiting membrane (ELM) and ellipsoid zone (EZ), hyperreflective foci, central foveal thickness, choroidal thickness/vascularity, ORTs.
- DRIL may predict visual acuity outcomes in patients with anti-VEGF (vascular endothelial growth factor) therapy.

- DRIL extent >500 um in a 1000 um foveal scan has visual acuity loss despite edema resolution.
- DRIL is looked for within the central 1-mm foveal zone. In eyes with no DRIL, one is able to segment the inner retinal layer boundaries, but in eyes with DRIL, one is unable to segment these layers. It is clearly visible on SS-OCT device.
- Even when adjusting for central retinal thickness and outer layer characteristics, DRIL is the most robust SD-ICT parameter associated with visual acuity change over time.
- Though DRIL can worsen and persist, it can also resolve and reverse.
- DRIL is a predictive tool for capillary nonperfusion. It correlates with macular capillary nonperfusion. The extent of DRIL correlates with size of foveal avascular zone in all grades of DR. Presence of DRIL correlates with severe DR. It is often associated with outer retinal alterations (EZ, ELM disruptions).
- The inner retinal layers consisting of axons, bipolar cells and nuclei of amacrine cells are disrupted in DRIL. The perfusion in the superficial, middle and deep capillary plexus is reduced.
- Eyes with persistent DRIL often do not do well. If central refractory DME persists, continue injecting anti-VEGF/steroids and then observe visual acuity, morphology and central subfield thickness. Check systemic parameters. If no response and macular atrophy sets in, then discontinue therapy.
- DRIL is a robust biomarker, although the correlation is not perfect. Some patients with DRIL do well visually, while others don't.

Take Home Message

"Don't just look at thickness", "also look at morphology". We still don't fully understand what the threshold is for the disorganization to correlate with prognosis.

CASES RELATED TO POLYPS

Dr Simar Rajan Singh, Chandigarh

- Documentation of polyps helps in confirming the diagnosis of polypoidal choroidal vasculopathy (PCV). Polyps can be documented in cases with peripheral exudative hemorrhagic chorioretinopathy (PEHCR) with wide field indocyanine green angiography (ICGA).
- Recurrent and massive bleeds are known presentations of PEHCR. Such cases are known to progress from the periphery to the center.
- This is important because PCV patients tend to have more asymmetry than age-related macular degeneration (AMD).
- PCV patients tend to present more often with precipitous visual loss with subretinal bleed and they also tend to have sudden and worse recurrences.
- It may be advisable to keep these patients on a treat and extend regimen with anti-VEGF to prevent recurrences and preserve vision.
- Plan for ultra-wide field fundus autofluorescence, fundus fluorescein angiography + indocyanine green to confirm the diagnosis of PEHCR.

ACUTE RETINAL NECROSIS

Dr Andrew W Eller, USA

- Panuveitis and retinal vasculitis lead to rapidly progressive necrotizing retinitis or acute retinal necrosis.
- Visual outcomes are often poor with 25% to 75% of eyes worse than 20/200. RD rates average around 51%. Most commonly caused by varicella-zoster virus followed by herpes simplex virus (HSV)-1 and HSV-2. Epstein-Barr virus (EBV) is rare.
- Patients are usually immunocompetent. The older age group may be immunocompromised and may have a history of shingles.
- HSV-1 and HSV-2 are common in younger age group; may have a history of neonatal herpes.
- Anterior chamber paracentesis for polymerase chain reaction. Repeat if negative with high suspicion.
- Initiate treatment immediately, if high suspicion with intravitreal foscarnet/ganciclovir/acyclovir and IV acyclovir, ganciclovir, foscarnet, cidofovir or oral valacyclovir 1000 mg twice daily.

Clinical Pearl

Must perform fundus exam in all patients with uveitis.

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News and Views

CRP: A Potential Biomarker to Predict Risk of Delirium in Stroke Patients

Acute stroke patients with high C-reactive protein (CRP) levels >7.09 mg/L are at greater risk for developing delirium, suggests a study from Poland published in the journal *Acta Psychiatrica Scandinavica*.[1]

For this study, researchers retrospectively analyzed data from 459 patients who had been hospitalized for acute stroke or transient ischemic attack (TIA) within 24 hours with the aim to find out if including CRP with other clinical factors (Models A and B) could enhance prediction of delirium in these patients. The factors in Model A were age and stroke severity, while in Model B, severity of stroke, diabetes, atrial fibrillation, pre-stroke dependency and hemorrhagic stroke were the factors included. They were a part of the PRospective Observational POLIsh Study on delirium (PROPOLIS), which was an observational, prospective single-center study and had recruited patients with ischemic stroke, TIA or intracerebral hemorrhage from May 2014 to March 2016, within 48 hours of symptoms. Patients who had CRP measured at baseline were enrolled for this study. Their median age was 73 years and more than half (52.7%) the study population was comprised of women. Patients were evaluated for neurological deficits (National Institutes of Health Stroke Scale [NIHSS]), cognitive decline, pre-stroke dependency (modified Rankin Scale) and delirium (Brief Confusion Assessment Method for verbal patients and the Confusion Assessment Method for the Intensive Care Unit for nonverbal patients).

Nearly one-third (29.2%) of patients developed delirium with 46.2% experiencing mixed delirium, 39.2% hypoactive delirium and 14.2% hyperactive delirium. The delirious patients also had higher levels (median) of CRP than those who did not have delirium; 13.2 mg/L vs. 4.4 mg/L, respectively.

A cut-off level of 7.09 mg/L was identified as marking the distinction between the two groups. On univariate analysis, CRP and other clinical factors such as age, diabetes, atrial fibrillation, pre-stroke dependency, pre-stroke cognitive decline, NIHSS score on admission. Hemorrhagic stroke were associated with increased risk for delirium. But on multivariate analysis, this association remained significant only for CRP. The risk was threefolds higher in patients with CRP levels >7.09 mg/L with an adjusted odds ratio (aOR) of 2.98. The researchers also noted that addition of CRP to the two clinical models examined, the "area under receiver operator curve increased from 0.77 to 0.80 for Model A and from 0.81 to 0.84 for Model B."

Delirium in stroke patients is indicative of a poor clinical outcome. Identification of a factor that could predict development of delirium enables monitoring of at-risk patients and timely implementation of appropriate management strategies. CRP, a marker of systemic inflammation, is a commonly performed test in clinical practice. Based on their findings, the authors suggest CRP as a potential marker for risk of delirium in post-stroke patients. Acute stroke patients with high CRP levels, above the cut-off level defined in this study, should be closely monitored for delirium.

(*Ref: [1]Klimiec-Moskal E, et al. Serum C-reactive protein adds predictive information for post-stroke delirium: The PROPOLIS study. Acta Psychiatr Scand. 2022 Aug 23. [Epub ahead of print]*)

Strong Immune Response Induced by Monkeypox Vaccine

According to a study published recently in the journal *Viruses*, the vaccines based on the vaccinia virus (VACV) could create a potent immune response against the monkeypox virus that is causing the current outbreak.

The vaccine virus is a large, intricate, enveloped member of the poxvirus family. More than 52,000 cases have been confirmed in more than 90 countries and regions since the new virus was originally discovered in early May.

The study compared and contrasted the genetic makeup of VACV and MPXV-2022, focusing on the regions of the proteins that T cells or antibodies produced as a result of vaccination target. The study more broadly demonstrates that VACV and MPXV-2022 are highly genetically similar in the regions targeted by the immune system through vaccination. Researchers claim to have identified a small number of distinct mutations in MPXV-2022.

Based on the analysis, it is predicted that the immune responses produced by VACV-based vaccinations would continue to perform an excellent job of recognizing and responding to MPXV-2022.

Pre-exposure prophylaxis, commonly known as primary preventive immunization against the novel monkeypox virus, has been advised by the World Health Organization (WHO) for people who are at a high risk of exposure.

The researchers concluded that combining sequencing and immunological data provided evidence to expect a high immune response, but additional clinical studies were needed to precisely assess these vaccines' efficacy against MPXV-2022. (*Source: The Print, Sept. 9, 2022*)

Scientists Identify Two Antibodies which may be Effective against All Known COVID Strains

Israeli researchers have identified two antibodies from the immune systems of coronavirus disease 2019 (COVID-19) patients who have recovered that have a 95% chance of neutralizing all known strains of severe acute respiratory syndrome coromavirus 2 (SARS-CoV-2), including Omicron. The investigation, which was just published in the journal *Communications Biology*, is an extension of initial work done in October 2020 at the height of the COVID-19 crisis.

The researchers found nine antibodies after sequencing all of the B immune system cells from the blood of persons who had recovered from the initial COVID-19 strain in Israel at the time. According to the research, the new coronavirus variants, Delta and Omicron, can be neutralized by some of these antibodies.

The SARS-CoV-2 virus uses the spike protein to invade and enter cells. Researchers demonstrated that the Delta and Omicron variants could be effectively neutralized by two more antibodies, TAU-1109 and TAU-2310, which bind the viral spike protein in a different location than the sites where most antibodies have previously been focused.

According to experts, the first antibody, TAU-1109, is 92% successful at neutralizing the Omicron strain and 90% effective at neutralizing the Delta strain. The second antibody, TAU-2310, is 84% effective at neutralizing the Omicron variation and 97% effective at neutralizing the Delta variant. Thus, these findings may be a helpful alternative for vaccines, especially for high-risk groups and immunocompromised people. (*Source: Finance Express, Sept. 8, 2022*)

NIH Launches Trial of Tecovirimat for Monkeypox

The National Institutes of Health (NIH) has commenced a phase 3 randomized, placebo-controlled, double-blind clinical trial STOMP (Study of Tecovirimat for Human Monkeypox Virus; A5418) investigating the safety and efficacy of the antiviral drug tecovirimat in patients with monkeypox. The recruitment of patients, both adults and children, with monkeypox infection in the United States is now on. A total of 530 volunteers will be enrolled. Tecovirimat is currently available for US patients through an expanded access or "compassionate use" request put in by the clinicians. The multicenter trial is being led by the AIDS Clinical Trials Group (ACTG), which is the largest body engaged in global HIV research.

All patients with severe monkeypox and persons at risk of severe disease including children, pregnant and lactating women, immunocompromised patients or those with active inflammatory skin disease will be administered the drug in the open-label arm of the trial. Other patients would be randomized to receive tecovirimat or placebo orally for 14 days in a 2:1 ratio. Patients who develop severe disease or experience severe pain will have the option to move to the open label arm.

The impact of the drug on pain scores, progression to severe disease and clearance of monkeypox virus will be studied in addition to its safety. Pediatric dosing and safety will also be examined. Optimal dosing for pregnant women will also be a part of the study.

The follow-up period will be 8 weeks during which the participants will be required to maintain a symptom diary, carry out daily self-skin examination for the status of skin lesions and visit the clinic, both virtual and in-person. Blood samples and swabs from skin lesions will be collected.

(*Sources: National Institutes of Health (NIH) Press Release, September 9, 2022. AIDS Clinical Trial Group (ACTG) Press Release, September 9, 2022.*)

Short-term Benefits of Robotic Surgery for Rectal Cancer

The oncological quality of resection was better with robotic surgery in patients with middle and low rectal cancer with fewer positive resection margins compared to the standard laparoscopic surgery, reports a multicenter, randomized trial from China in the *Lancet Gastroenterology & Hepatology*.[1]

Researchers recruited 1,240 patients, aged 18 to 80 years, with low (≤5 cm from the anal verge) and middle (>5 to 10 cm from the anal verge) adenocarcinoma of the rectum, cT1-T3 N0-N1 or ycT1-T3 Nx stage with no sign of distant metastasis. They (620 patients in each group) were randomized 1:1 to undergo robotic or laparoscopic resection from July 2016 to December 2020.

Locoregional (pelvic/perineal) recurrence rate at 3 years was the primary outcome of the study, while a positive circumferential resection margin and complications within 1 month of the surgery were the secondary endpoints. The objective of this multicenter, randomized, controlled, superiority trial was to compare the two procedures in terms of surgical quality and outcomes in the long-term. This trial is ongoing and only the short-term outcomes have been reported at present. The primary endpoint results are expected by the end of next year.

Among the 1,171 patients in the modified intention-to-treat analysis, results showed fewer positive circumferential resection margins in 4% (22/547) patients who underwent robotic surgery versus 7.2% (39/543) among those in the laparoscopic surgery group. The postoperative complication rate within 30 days of surgery was 16.2% with robotic surgery versus 23.1% with laparoscopic surgery. Grossly, the resection was more complete in the robotic surgery group (95.4%; 559/586) compared to the laparoscopic surgery group (91.8%; 537/585). The benefits of robotic surgery were also evident intraoperatively with less estimated blood loss (40 mL vs. 50 mL) and fewer complications (5.5% vs. 8.7%). Ninety-nine (~17%) robotic surgery patients needed abdominoperineal resections for low rectal cancer, while this number was 133 (~23%) in the laparoscopic group.

Postoperatively, robotic surgery patients exhibited better gastrointestinal recovery (shorter time to first flatus and bowel movement); they also had shorter hospitalization (7 days vs. 8 days, respectively [median]). Just 10 patients in this group required conversion of the procedure to open surgery, whereas 23 patients in the laparoscopic group needed open surgery. Although the total costs incurred were higher with the robotic surgery, the costs in the postoperative period were less ($2,768 vs. $3,060).

The short-term results of the secondary endpoints of this study demonstrate better circumferential resection margins indicating "better oncological quality of resection" with robotic surgery compared to laparoscopic surgery with "better postoperative recovery" suggesting that robotic surgery was superior to laparoscopic surgery for patients with mid or low rectal cancer.

(*Ref: [1]Feng Q, et al. Robotic versus laparoscopic surgery for middle and low rectal cancer (REAL): short-term outcomes of a multicentre randomised controlled trial. Lancet Gastroenterol Hepatol. 2022;7(11):991-1004.*)

Bell's Palsy in Children Cured without Medication in 6 Months

A recent study from the Murdoch Children's Research Institute, which was published in *Neurology*, found that most children with Bell's palsy, which temporarily weakens or paralyses the muscles in the face, recovered without medication in less than 6 months. Prednisolone had no discernible impact on a child's Bell's palsy recovery, but it did minimize facial nerve swelling and temporal bone damage in adults.

The randomized controlled study included 187 Bell's palsy patients who visited emergency departments (EDs) between 6 months and 17 years. Within 72 hours of the onset of symptoms, they were enrolled and administered either prednisolone or a placebo for 10 days. The investigation was carried out in 11 EDs using sites provided by Australia and New Zealand's Paediatric Research in Emergency Departments International Collaborative (PREDICT) research network.

The observations found that 57% of those who did not take any medication had their facial function restored after 1 month, 85% had it back after 3 months and 93% had it back after 6 months. Recovery rates in individuals who received prednisolone were 49% after 1 month, 90% after 3 months and 95% after 6 months. During the testing, no adverse events were identified. Brief behavioral changes and an increase in hunger were the most frequent events observed.

Experts stated that the use of steroids in children with Bell's palsy had not been proven. However, knowing that early prednisolone therapy does not speed up recovery may help medical professionals, emergency room physicians and pediatricians to have better conversations with impacted families. (*Source: Hindustan Times, Sept. 10, 2022*)

Chances of Fertilization may be Enhanced by a New Protein MAIA

A large number of beads, each with a unique protein fragment, were used to create artificial eggs by an international team of researchers, enhancing the likelihood of fertilization. According to research results that were published in the journal *Science Advances*, just a small fraction of the beads had sperm attached to them when sperm was incubated with them.

Researchers eventually found that beads corresponded to one specific protein, MAIA, and sperm linked to all of these beads after going through numerous rounds of deleting beads that didn't have sperm bound to them. The novel protein MAIA, which bears the name of the

Greek motherhood goddess, is thought to be responsible for attracting sperm into the egg for fertilization. After inserting the MAIA gene into human culture cells, these cells became receptive towards the sperms precisely in a similar manner as they would in normal fertilization.

The discovery of the MAIA protein not only significantly advances the understanding of the human fertilization process but it also opens up new avenues for the treatment of infertility and will transform the development of future contraceptives. (*Source: The Tribune, Sept. 9, 2022*)

Similar CVD Risk Factors Found among Men and Women

Researchers found that the several risk factors for cardiovascular disease (CVD) are the same for both men and women. The study was published in the journal *The Lancet*. It included individuals from low- and middle-income nations, where the prevalence of CVD is higher, in addition to high-income ones.

The large-scale study evaluated risk variables in around 1,56,000 persons without a history of CVD between the ages of 35 and 70, including metabolic (such as high blood pressure, obesity and diabetes), behavioral (smoking and food) and psychosocial (economic status and depression). They were monitored for an average of 10 years while residing in 21 low-, middle- and high-income nations across five continents.

Similar CVD risk factors for men and women highlight the significance of a similar approach to preventing CVD in both sexes. In general, women had a lower risk of CVD than men, especially when younger. However, women's CVD risk was more strongly correlated with their dietary habits than men's.

Depression and high levels of bad (LDL) cholesterol were more significantly linked to CVD risk in males than in women. High-income, upper-middle-income, low-income and lower-middle-income countries generally showed similar patterns in these findings. (*Source: Hindustan Times, Sept. 09, 2022*)

First Oral Once-a-Day Treatment for Patients with Moderate to Severe Plaque Psoriasis

Deucravacitinib, the first-in-class tyrosinase kinase 2 (TYK2) inhibitor has been approved by the US Food and Drug Administration (FDA) for patients with moderate to severe plaque type psoriasis making it the only approved TYK2 inhibitor. It is indicated only for those patients who need systemic therapy or phototherapy.

This approval is based on the results of the phase III POETYK PSO-1 and PSO-2 clinical trials where deucravacitinib was superior to placebo and apremilast in improving skin clearance.

Dose: 6 mg orally once daily, with or without food.

Contraindication: Hypersensitivity to deucravacitinib or any of its components, severe hepatic impairment.

Side effects: Upper respiratory infection, increased creatine phosphokinase (CPK), herpes simplex, mouth ulcers, folliculitis, acne.

Warnings and precautions

- Avoid co-administration with other immuno-suppressant drugs or live vaccines. All age-appropriate immunizations should be complete prior to starting treatment.
- Avoid deucravacitinib in patients with active or serious/opportunistic infection.
- Monitor the patient for signs and symptoms of infection. Discontinue treatment in case serious infection develops.
- Examine the patient for tuberculosis before starting treatment with deucravacitinib.
- Regularly monitor serum triglycerides and liver enzymes.
- Stop the drug if CPK levels increase significantly.

(*Sources: US FDA Sotyktu prescribing information; Bristol Myers Squibb Press Release, Sept. 9, 2022*)

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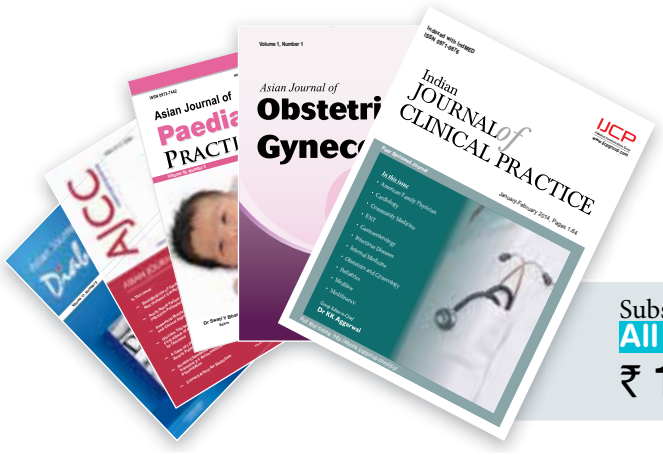

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Lighter Side of Medicine

INSPIRATIONAL STORY

THE TOUCHSTONE

When the great library of Alexandria burned, the story goes, one book was saved. But it was not a valuable book; and so a poor man, who could read a little, bought it for a few coppers.

The book wasn't very interesting, but between its pages there was something very interesting indeed. It was a thin strip of vellum on which was written the secret of the "Touchstone"!

The touchstone was a small pebble that could turn any common metal into pure gold. The writing explained that it was lying among thousands and thousands of other pebbles that looked exactly like it. But the secret was this: the real stone would feel warm, while ordinary pebbles are cold.

So the man sold his few belongings, bought some simple supplies, camped on the seashore, and began testing pebbles.

He knew that if he picked up ordinary pebbles and threw them down again because they were cold, he might pick up the same pebble hundreds of times. So, when he felt one that was cold, he threw it into the sea. He spent a whole day doing this but none of them was the touchstone. Yet he went on and on this way. Pick up a pebble. Cold - throw it into the sea. Pick up another. Throw it into the sea.

The days stretched into weeks and the weeks into months. One day, however, about mid-afternoon, he picked up a pebble and it was warm. He threw it into the sea before he realized what he had done. He had formed such a strong habit of throwing each pebble into the sea that when the one he wanted came along, he still threw it away. So, it is with opportunity. Unless we are vigilant, it's easy to fail to recognize an opportunity when it is in hand and it's just as easy to throw it away.

HUMOR

WHERE'S THE TOAST I ASKED FOR

An elderly husband and wife visit their doctor when they begin forgetting little things. Their doctor tells them that many people find it useful to write themselves little notes.

When they get home, the wife says, "Dear, will you please go to the kitchen and get me a dish of ice cream? And may be write that down so you won't forget?"

"Nonsense," says the husband, "I can remember a dish of ice cream."

"Well," says the wife, "I'd also like some strawberries and whipped cream on it."

"My memory's not all that bad," says the husband. "No problem – a dish of ice cream with strawberries and whipped cream. I don't need to write it down."

He goes into the kitchen; his wife hears pots and pans banging around. The husband finally emerges from the kitchen and presents his wife with a plate of bacon and eggs.

She looks at the plate and asks, "Hey, where's the toast I asked for?"

Dr. Good and Dr. Bad

SITUATION: A type 2 diabetic individual who presented with impaired cognitive performance was advised to do yogasanas and pranayama.

LESSON: The researchers have demonstrated that regular practice of yogasanas and pranayama helps in stabilizing blood glucose levels and has a positive impact on cognitive performance in patients with T2DM.

Natl J Physiol Pharm Pharmacol. 2017;7(3):232-5.

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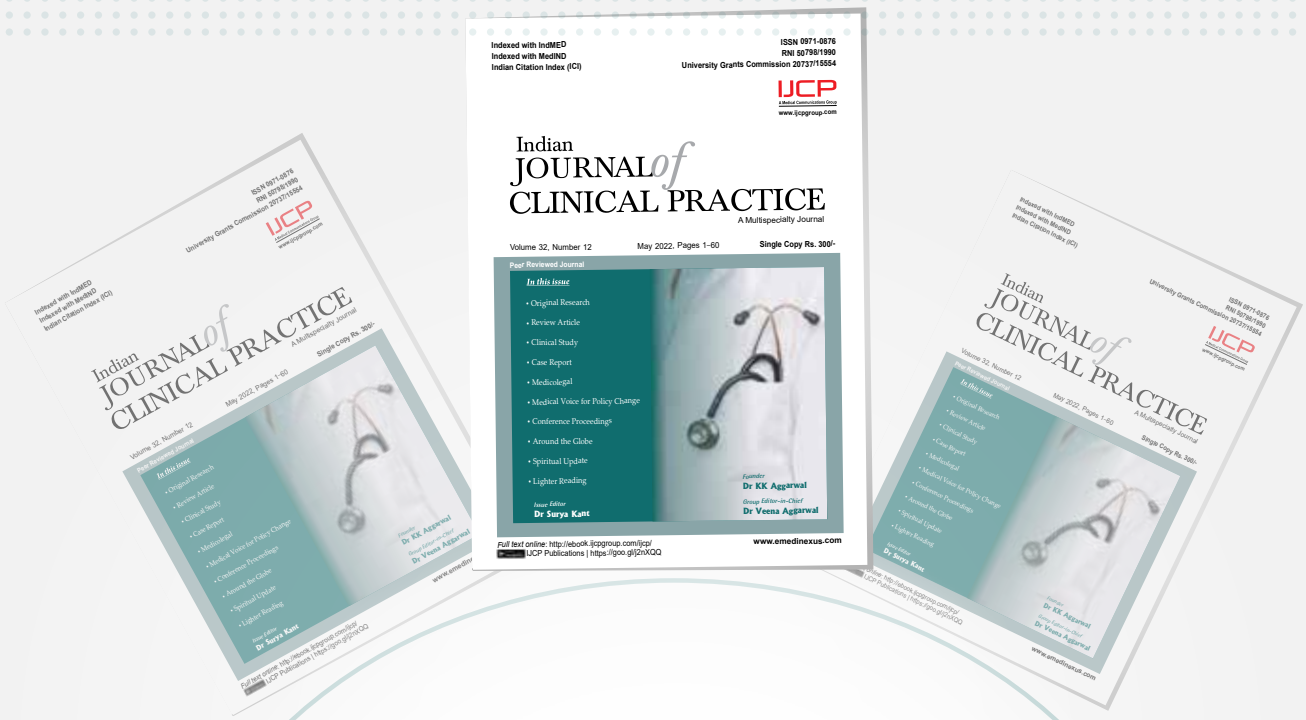

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Paintal AS. Impulses in vagal afferent fibres from specific pulmonary deflation receptors. The response of those receptors to phenylguanide, potato S-hydroxytryptamine and their role in respiratory and cardiovascular reflexes. Q. J. Expt. Physiol.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

Books

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

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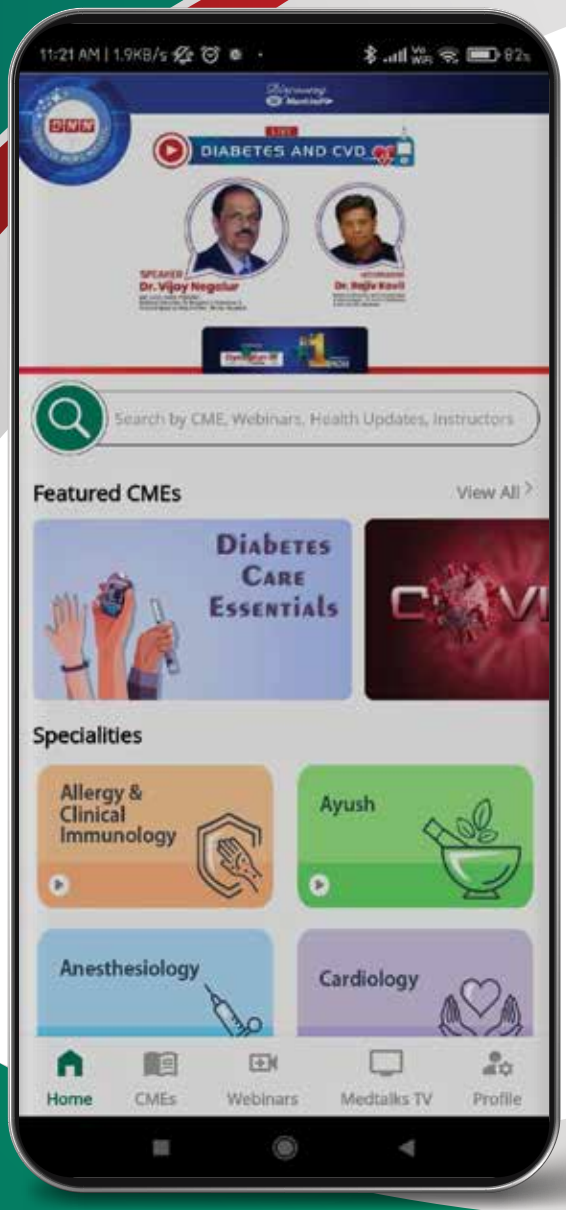

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