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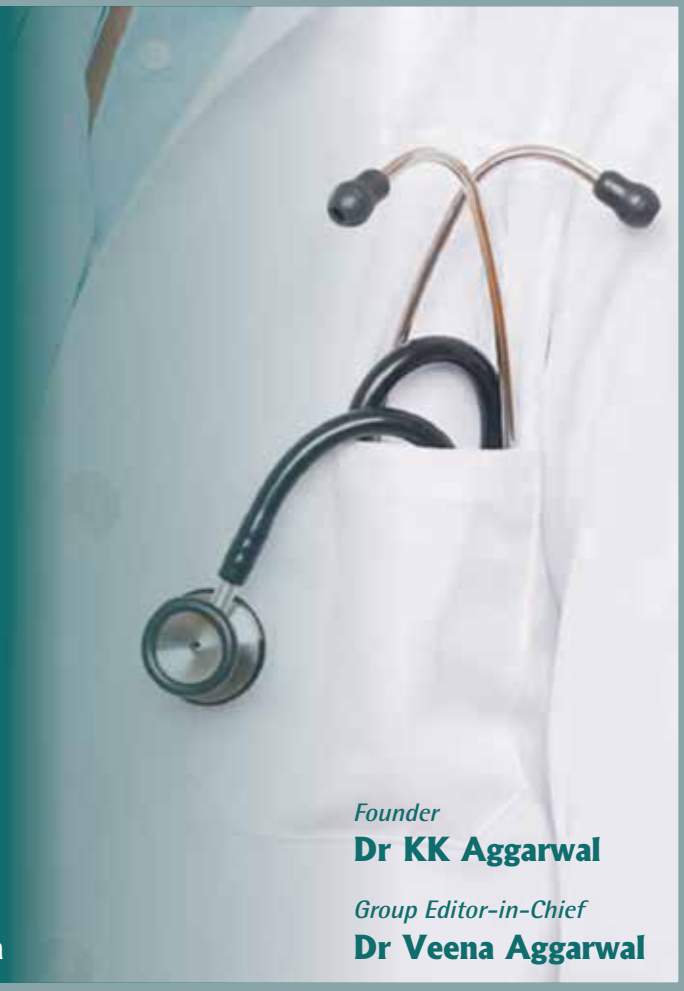

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Medicine Update

FOUR STAGES OF MYOCARDIAL INJURY IN HEART ATTACK

An expert consensus statement from the Canadian Cardiovascular Society has classified four stages of an acute atherothrombotic myocardial infarction (MI) based on the severity of myocardial injury as follows:

- "Aborted MI (no or minimal myocardial necrosis).
- MI with significant cardiomyocyte necrosis but without microvascular injury.
- Cardiomyocyte necrosis and microvascular dysfunction leading to microvascular obstruction ('no-reflow').
- Cardiomyocyte and microvascular necrosis leading to reperfusion hemorrhage."

(*Source: Canadian Journal of Cardiology. Oct. 28, 2023*)

CRISPR GENE EDITING APPROVED FOR TREATMENT OF BLOOD DISORDERS FOR THE FIRST TIME

UK's Medicines and Healthcare products Regulatory Agency (MHRA) has for the first time approved Casgevy, a therapy that utilizes the CRISPR gene editing tool for treatment of sickle cell disease and β-thalassemia… (*Source: Nature. Nov. 16, 2023*).

BENEFITS OF INTENSIVE BP-LOWERING: ESPRIT

In the ESPRIT trial, intensive lowering of systolic blood pressure (BP) to a target of <120 mmHg (vs. target of <140 mmHg) reduced cardiovascular (CV) events by 12% in high-risk persons including those with diabetes and history of stroke. Death due to CV causes decreased by 39% and death due to any cause reduced by 21%… (*Source: Medscape. Nov. 16, 2023*).

INADEQUATE SLEEP: A NOVEL RISK FACTOR FOR TYPE 2 DIABETES IN WOMEN?

Limiting sleep to 6.2 hours or less for 6 weeks, a reduction of only 1.5 hours each night, resulted in nearly 15% rise in insulin resistance in otherwise healthy women, both pre- and postmenopausal. The effects were more pronounced in postmenopausal women with almost 20% increase in insulin resistance… (*Source: NIH. Nov. 14, 2023*).

IBS PATIENTS COMMONLY DEVELOP FIBROMYALGIA

Patients with irritable bowel syndrome (IBS) are 5 times more likely to develop fibromyalgia and chronic fatigue syndrome (CFS) with adjusted odds ratio (aOR) of 5.33 and 5.4, respectively. Those with IBS-C were at greater risk compared to those with IBS-D. Older persons were at higher risk with aOR of 1.02. Women were also 11 times at greater risk (aOR 11.2)… (*Source: Biomedicines. Sept. 22, 2023*).

FDA APPROVES CAPIVASERTIB + FULVESTRANT FOR HR$^+$ AND HER$^-$ BREAST CANCER

The Food and Drug Administration (FDA) has approved the use of capivasertib to be used in combination with for adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. These patients have ≥1 PIK3CA/AKT1/PTEN-alterations and in whom the disease progression occurred on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy… (*Source: US FDA. Nov. 16, 2023*).

RECENT SURGE IN RESPIRATORY ILLNESS IN CHINA DUE TO SEASONAL INFECTIONS, SAYS CHINA: WHO

Chinese health authorities attribute the sharp increase in the number of cases of children with respiratory diseases including pneumonia in Northern China to known pathogens such as influenza, *Mycoplasma pneumoniae*, respiratory syncytial virus (RSV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as well as the advent of winter, says the World Health Organization (WHO). The organization is "closely monitoring the situation and is in close contact with national authorities in China"… (*Source: WHO. Nov. 23, 2023*).

THE PROFID EHRA TRIAL ENROLLS ITS FIRST PATIENT

The first clinical trial to examine the benefits of defibrillator implantation along with drug treatment vis-a-vis medical treatment alone in post-MI patients with symptomatic heart failure and left ventricular ejection fraction of ≤35% has started with enrollment of the first patient from Germany. Some of the outcomes to be examined in the trial include all-cause death and sudden cardiac death. The PROFID EHRA noninferiority trial will be conducted in 13 countries with around 3,505 patients. Results are expected in early 2027… (*Source: ESC. Nov. 21, 2023*).

AGA PUBLISHES UPDATED GUIDELINE FOR USE OF BIOMARKERS IN CROHN'S DISEASE

The American Gastroenterological Association (AGA) recommends use of serum C-reactive protein (CRP) and fecal calprotectin to monitor patients with asymptomatic or symptomatic Crohn's disease rather than relying on symptoms alone. It advocates a cut-off of <150 μg/g for fecal calprotectin and/or <5 mg/L for CRP to exclude active inflammation in patients with symptomatic and endoscopic remission, whereas patients with symptomatic but not endoscopic remission should undergo endoscopy to exclude active inflammation… (*Source: Gastroenterology. Dec. 2023*).

LEBRIKIZUMAB APPROVED IN EUROPE FOR MODERATE TO SEVERE ATOPIC DERMATITIS

Atopic dermatitis patients who have not responded to topical therapies can now be treated with lebrikizumab, a monoclonal antibody, which inhibits interleukin-13. It has been approved by the European Commission for the treatment of patients aged ≥12 years with moderate to severe atopic dermatitis… (*Source: Medscape. Nov. 20, 2023*).

UPPER GI ENDOSCOPY ENABLES DIAGNOSIS OF IRON DEFICIENCY ANEMIA ETIOLOGY IN CHILDREN

The use of upper gastrointestinal endoscopy enabled identification of the cause of iron deficiency anemia in ≥70% of children with severe unexplained iron deficiency anemia. Sixty-eight percent were found to have polyps, gastronodularity or erosions, while 12% had duodenitis or ulcers. Histopathology revealed gastritis in 72% and *Helicobacter pylori* in 50% of children… (*Source: HCPLive. Oct. 23, 2023*)

A CATHETER LOCK SOLUTION FOR RENAL FAILURE PATIENTS ON CHRONIC HEMODIALYSIS

A catheter lock solution, Defencath (taurolidine and heparin) has been approved by the US FDA to prevent catheter-related bloodstream infections in patients with renal failure on chronic hemodialysis via a central venous catheter. It is available in single dose 3 mL and 5 mL vials and is to be used only as a catheter lock solution. The product carries a warning about heparin-induced thrombocytopenia… (*Source: US FDA. Nov. 15, 2023*).

STUDY LINKS HIPPOCAMPAL ATROPHY TO COGNITIVE DECLINE

Decrease in the volume of the hippocampus is associated with cognitive impairment. The Harvard Aging Brain Study reported that the faster the atrophy of the hippocampus occurred, faster was the cognitive decline. These observations were independent of amyloid-beta (Aβ) and tau levels… (*Source: AAN. Nov. 15, 2023*)

THE FIRST HOME DIAGNOSTIC TEST FOR COMMON STIS

LetsGetChecked's Simple 2 Test has been accorded marketing approval as the first diagnostic test for two common sexually transmitted infections Chlamydia and gonorrhea for patients aged ≥18 years. It is available over-the-counter and the sample can be collected at home… (*Source: US FDA. Nov. 15, 2023*).

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Metabolic Mentorship

ABSTRACT

In this editorial, we propose metabolic mentorship as an umbrella term, which includes all activities that are undertaken in order to achieve and maintain metabolic health. Metabolic mentorship includes not only conventional medical prescription, but also education, counseling and support for effective self-management. Metabolic mentorship facilitates value-added therapy (VAT), i.e, the nonpharmacological and pharmacological interventions that help ensure optimal therapeutic outcomes. From a pedagogic perspective, metabolic mentorship implies the learning that health care professionals can gain by interacting and sharing experiences with each other. We suggest that endocrinologists take the responsibility of spearheading metabolic mentorship within, and beyond, the health care sciences.

Keywords: Diabetes, insulin, metabolic health, public health

Mentorship is the guidance provided by a mentor, especially an experienced person.[1] The word 'mentor' is used to describe an advisor who is experienced and trusted.[2] While mentorship is a noun, the term mentor can be used as a noun as well as verb.

The concepts of reverse mentoring, mutual mentoring and group mentoring are well known in education as well as business management. In reverse or mutual mentoring, colleagues or individuals "pair up", regardless of status or seniority, to learn from each other. Group mentoring suggests that a single expert takes charge of a group of mentees to help them in their cares. A similar framework operates in health and medicine, especially in the field of chronic and noncommunicable disease.

METABOLIC MENTORSHIP: A FRAMEWORK TO ACHIEVE OPTIMAL METABOLIC CARE

We propose metabolic mentorship as a framework for guidance to ensure optimal metabolic care and health. Metabolic mentorship is an umbrella term, which includes all activities that are undertaken in order to achieve and maintain metabolic health. It includes not only conventional medical prescription, but also education, counseling and support for effective self-management. Metabolic mentorship facilitates value-added therapy (VAT), i.e., the nonpharmacological and pharmacological interventions that help ensure optimal therapeutic outcomes.[3]

SCOPE AND SPECTRUM

Metabolic mentorship can be mutual. The treating physician learns from, and benefits from, the knowledge and experience of colleagues from other specialties and disciplines, including diabetes educators, nurses, physiotherapists and psychologists. A significant amount of mutual metabolic mentorship occurs between the person living with metabolic disease, e.g., diabetes, and the health care professional. An effective two-way

Table 1. Metabolic Mentorship: Scope and Spectrum

Mega level

- Metabolic health advocacy to policymakers, health planners and public

Meso level

- Continuing medical education
- Continuing nursing education
- Paramedical education

Micro level

- Therapeutic patient education
- Counseling and support

conversation, engaging caregivers and family members as well, allows for healthy exchange of ideas and information.[4]

We, for example, have learnt best practices related to nutrition, exercise, self-care and medication administration from our patients.

The use of the word mentorship reinforces the importance of education, experience and erudition in metabolic medicine. Reverse mentorship and mutual mentorship also reminds us of the importance of person-centered care, offered in the spirit of team work.

SOUTH ASIAN FOCUS

The South Asian Federation of Endocrine Societies (SAFES) has chosen metabolic mentorship as a focus area for the year 2023-24. This includes enhancing awareness about the targets set by the World Health Organization (WHO) for 2030,[5] spearheading advocacy regarding the need to accomplish these goals, and stimulating action on the ground, in order to do so. From a glucocentric perspective, metabolic mentorship includes the rubric of glycemic guardianship,[6] i.e., the activities carried out by the health care team and health care system, to ensure optimal care of the person or group of people, living with diabetes. Glycemic guardianship can be operational at a macro-(country/regional), meso-(health care system) or micro-(individual) levels. Metabolic mentorship, too, is required at all these levels (Table 1).

Metabolic mentorship includes the important concept of glucometric guardianship as well.[7]

RIGHT AND RESPONSIBILITY

Metabolic mentorship is every stakeholder's right, and every stakeholder's responsibility. As endocrinologists, however, we take up the responsibility of leading the call for metabolic health. Our work includes both public health and clinical, both preventative and curative, and both nonpharmacological and pharmacological aspects of metabolic health care. Through this communication, we invite all interested individuals, and organizations, to join us. Our aim is to achieve the goals laid down by the WHO[5] and to better them.

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REVIEW ARTICLE

Role of Linagliptin in Type 2 Diabetes Mellitus Therapy: An Indian Perspective

RAKESH SAHAY*, GANAPATHI BANTWAL†, SHUBHANKAR CHOWDHARY‡

ABSTRACT

Given the rising prevalence and significant health and economic burdens associated with type 2 diabetes mellitus (T2DM) globally, especially in low- and middle-income countries, exploring effective treatment options is crucial. In this review, we have reviewed the role of linagliptin therapy in managing T2DM in the Indian context. The review specifically delves into the pharmacokinetic and pharmacodynamic properties of linagliptin, emphasizing its potential benefits in the context of the unique characteristics of Asian T2DM patients. The study provides valuable insights into the strategic use of linagliptin in the treatment landscape of T2DM, offering a comprehensive and all-encompassing approach to its clinical implications in various patient settings.

Keywords: Linagliptin, DPP-4 inhibitors, type 2 diabetes mellitus, gliptins

As per the International Diabetes Federation (IDF) Atlas 10th edition, 537 million adults (20-79 years) are living with diabetes. Over 3 in 4 adults with type 2 diabetes mellitus (T2DM) live in low- and middle-income countries. In South-East Asia, 1 in 11 adults are living with diabetes, which is expected to rise to 113 million by 2030 and 151 million by 2045. India accounts for 1 in 7 of all adults living with diabetes worldwide.[1] As per the Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study published in July 2023, the overall weighted prevalence of diabetes was 11.4%. Prediabetes 15.3% and generalized obesity 28.6%. All metabolic noncommunicable diseases (NCDs), including diabetes, were reported to be more frequent in urban than rural areas.[2]

T2DM is a chronic condition in which inadequate glycemic control is associated with several macro- and microvascular complications, including renal impairment, increased risk of coronary artery disease, stroke, high levels of low-density lipoprotein cholesterol and peripheral vascular disease.[3] Microvascular complications of diabetes may also include end-stage renal disease (ESRD) and retinopathy. Considering the prevalence and severity of complications associated with inadequate glycemic control, attaining tight glycemic control is an important step in diabetes management.[4] With India topping the list of individuals living with diabetes, health care costs associated with diabetes are high in terms of direct costs as well as loss of productivity related to chronic disability and premature mortality.[4]

Various pharmacological approaches are in use to improve glucose homeostasis through different modes of action, including sulfonylureas, biguanides, alpha-glucosidase inhibitors, thiazolidinediones, sodium-glucose co-transporter 2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors.[5] DPP-4 inhibitors are a class of oral antidiabetic drugs (OADs) that increase the levels of glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP), which maintains glucose homeostasis by increasing insulin secretion in the pancreas, in turn reducing postprandial and fasting hyperglycemia.[6] Currently, there are five DPP-4 inhibitors, including sitagliptin, saxagliptin, linagliptin, alogliptin, teneligliptin, evogliptin and vildagliptin. Despite the same mode of action and efficacy in terms of optimizing blood glucose levels, the various gliptins have differences in their pharmacodynamic and pharmacokinetic properties, which make them clinically relevant for different groups of patients.

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Linagliptin is a DPP-4 inhibitor with several actions, including insulin secretion, reduced glucagon production, delayed gastric emptying, promotes satiety and decreased appetite.[7] It is one of the most extensively studied OADs and has been extensively evaluated in a clinical trial program comprising more than 8,500 patients from different races and/or ethnic backgrounds.[8]

This article is an expert consensus on the place of linagliptin therapy in the T2DM treatment and management landscape in Indian experts.

GLYCEMIC EFFICACY OF LINAGLIPTIN

Asian T2DM patients are characterized by early age of diagnosis, long duration of disease, a high-risk for renal dysfunction and a beta-cell insufficiency. Hence, DPP-4 inhibitors are known to possess a therapeutic advantage over other drug classes in these patients, including those with low body mass index (BMI). Linagliptin enhances prandial insulin secretion and suppresses glucagon with a low risk of hypoglycemia.[9]

In a study by Kawamori et al (2012) assessing the efficacy of linagliptin versus placebo, a 1.2% change in glycated hemoglobin (HbA1c) was reported in the linagliptin group.[10]

In another study, linagliptin displayed superior glucose-lowering activity compared to placebo and alpha-glucosidase inhibitors such as voglibose.[11] Figure 1 shows the comparative glucose-lowering efficacy of DPP-4 inhibitors.[12]

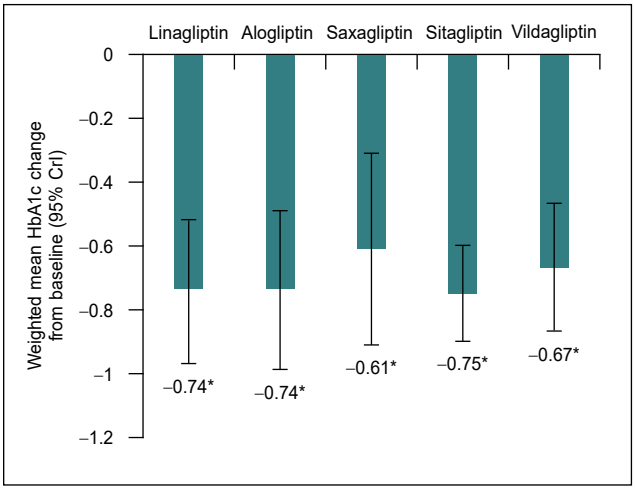

Figure 1. Glucose-lowering efficacy of DPP-4 inhibitors.[12]

*Statistically significant versus comparator: monotherapy versus placebo, DPP-4i plus metformin versus metformin, DPP-4i plus SU versus SU, DPP-4i plus metformin plus SU versus metformin plus SU, DPP-4i plus pioglitazone versus pioglitazone, DPP-4i plus insulin versus insulin, pioglitazone versus pioglitazone, DPP-4i plus insulin versus insulin.

CrI = Credible interval; DPP-4i = Dipeptidyl peptidase-4 inhibitor; SU = Sulfonylurea.

PLACE IN THERAPY: INITIATION

In a randomized controlled trial by Del Prato et al, linagliptin reduced HbA1c by 1.01% ($p < 0.0001$) in patients with baseline HbA1c ≥9.0%. In the same study, it was suggested that patients who underwent treatment for 24 weeks attained a reduction in HbA1c of ≥0.5%. These results prove that monotherapy with linagliptin has produced significant, clinically meaningful results in glycemic control and sustained effects accompanied by enhanced parameters of the beta-cell function.[13]

Studies on Asian subjects with T2DM and suboptimal glycemic control with metformin therapy showed that the mean change in HbA1c after 24 weeks of treatment with linagliptin was –0.79%, with similar adverse event profiles in the linagliptin and placebo group.[14,15]

PLACE IN THERAPY: INTERCHANGE

In patients who are unable to take metformin, linagliptin has proven to be a valuable alternative option. Linagliptin can improve glycemic control, especially in cases where metformin is inappropriate. It was seen in several randomized, controlled clinical trials in T2DM patients with inadequate glycemic control in whom metformin was inappropriate; monotherapy with linagliptin for 18 weeks led to a clinically meaningful lowering of HbA1c and fasting plasma glucose (FPG).[16-18]

PLACE IN THERAPY: INTENSIFICATION

Linagliptin as Second-line Therapy

As a second-line therapy, linagliptin leads to clinically relevant glycemic control when given to individuals with T2DM who had inadequate glycemic control (HbA1c ≥7.5% to ≤10%) with metformin alone. Forst et al, in a 2010 study, showed that linagliptin 5 mg led to a 0.73% (± 0.14) lowering in HbA1c.[19]

For patients inadequately controlled on metformin alone, linagliptin 5 mg once daily over 24 weeks brings a significant and clinically relevant improvement in glycemic control as seen through pre- and postprandial glucose levels and HbA1c levels. Linagliptin 5 mg leads to a 25% change in 2-hour postprandial glucose, a significant change as postprandial glucose state in patients with T2DM is related to endothelial dysfunction and hence the risk of cardiovascular complications.[20]

Inagaki et al (2013) evaluated once-daily linagliptin 5 mg as add-on therapy to an OAD (biguanide, glinide, glitazones, sulfonylurea or alpha-glucosidase inhibitors), the decline in HbA1c levels was seen throughout the

study period for the background therapy groups receiving linagliptin. This suggests that linagliptin is a safe and tolerable alternative as second-line therapy over other OADs.[21] Even though sulfonylureas have good glycemic-lowering ability, they are also associated with hypoglycemic events. In comparison, DPP-4 inhibitors like linagliptin with good glucose-lowering efficacy without hypoglycemic side effects, making it a clinically stable choice for second-line therapy.[22]

In T2DM management, acute hypoglycemic events and the OAD's effect on body weight are two important things to consider. Linagliptin has a low propensity for acute hypoglycemic events and a neutral effect on body weight. Linagliptin is an effective, well-tolerated and logical choice for patients with T2DM who are inadequately treated with metformin alone.

Linagliptin Compared to Combination Therapy

Linagliptin has been shown to be an important treatment option for individuals with inadequate glycemic control despite ongoing combination therapy. Owens et al (2011) showed in a randomized study that when linagliptin was administered to T2DM patients on therapy with metformin and sulfonylurea, it led to a reduction in HbA1c (29.2% vs. 8.1% placebo, $p < 0.0001$), FPG and improvements in homeostasis model assessment of beta-cell function.[23]

Results from Phase III studies on Asian patients, including Japanese, have exhibited clinically relevant improvements in glycemic control, improved beta-cell function,[19,24] and a good safety profile with linagliptin 5 mg as monotherapy or in combination with other OADs.[15,20,23,25] In the double-blind active comparator-controlled study by Kawamori et al (2012), linagliptin demonstrated superior glucose-lowering efficacy and comparable safety and tolerability to both placebo and voglibose.[10]

Linagliptin is also beneficial as triple combination therapy with empagliflozin and metformin in patients with type 2 diabetes. Studies have shown that 24 weeks of treatment with the triple combination reduced the HbA1c significantly.[26,27]

Linagliptin Combination with Other Oral Antidiabetics

In view of various challenges posed by the complex pathophysiology of T2DM, the involvement of multiple organs, including the heart, blood vessels, nerves, eyes and kidneys, and the deterioration of beta-cell function, the T2DM management is shifting towards a more proactive and aggressive treatment approach, which involves the initiation of combination pharmacotherapy immediately following diagnosis. It has been shown that initial combination therapy with linagliptin and metformin was superior to metformin monotherapy in improving glycemic control, with a similar safety and tolerability profile, no weight gain and a low risk of hypoglycemia. It was also seen that initial combination treatment with linagliptin and metformin combination produced a more rapid improvement in glycemic control compared to the stepwise approach from metformin monotherapy to linagliptin and metformin combination therapy.[18]

An early, aggressive reduction of hypoglycemia in newly diagnosed patients can elicit sustained disease remission. In the 10-year follow-up of the United Kingdom Prospective Diabetes Study (UKPDS) by von Eynatten et al, early, intensive pharmacotherapy led to long-term benefits in reducing the incidence of microvascular complications and cardiovascular events.[28] In a study by Mu et al, linagliptin and metformin combination significantly improved glycemic control in treatment-naïve Asian patients with T2DM and inadequate glycemic control.[29]

Linagliptin can be safely given as an add-on treatment to glimepiride to improve glycemic variability and control without enhancing the risk of hypoglycemia in patients with hepatocyte nuclear factor 1α (HNF-1α) or maturity-onset diabetes of the young type 3.[30]

Treatment with linagliptin led to noninferior glycemic control and considerably reduced risk of hypoglycemia compared to insulin glargine in long-term care and individuals with long-term diabetes.[31]Additionally, linagliptin can be safely added to basal insulin therapy to lead to considerable improvement in glycemic control compared to placebo without increasing hypoglycemia or body weight.[32]

The addition of linagliptin to insulin early in the therapy led to a reduction in the daily insulin dose along with improved glycemic control and sustained effect over the long duration of therapy.[33]

Linagliptin vs. Other DPP-4 Inhibitors

A direct comparison revealed that all DPP-4 inhibitors were significantly more effective compared to placebo in attaining a greater mean reduction from baseline in HbA1c, and a higher proportion of individuals met the target of HbA1c <7%.[12] Table 1 depicts the difference in HbA1c, hypoglycemic events and weight gain among different DPP-4 inhibitors.[34]

Table 1. Difference in Diabetes Efficacy and Safety Parameters among DPP-4 Inhibitors

	Sitagliptin	Vildagliptin	Saxagliptin	Linagliptin
HbA1c lowering	WMD –0.74%	WMD –0.60%	WMD –0.57%	WMD –0.68%
Weight gain	WMD 0.22 kg	WMD 0.26 kg	WMD 0.14 kg	WMD 0.15 kg
Hypoglycemia	OR 2.94	OR 0.85	OR 1.19	OR 0.93
The mean reduction in HbA1c in patients with severe renal insufficiency[35]	-	0.5% at week 12 and 0.7% at week 52	0.45% and 0.32% at weeks 12 and 52, respectively	–0.60% at week 12 and –0.72% at week 52

WMD = Weighted mean difference; OR = Odds ratio.

The results of a Bayesian network meta-analysis of 58 randomized controlled trials showed that amongst all the doses, linagliptin 5 mg reduced the levels of 5 mg most, compared to linagliptin 10 mg and 0.5 mg. It has been proven that 5 mg/day of linagliptin for 12 to 24 weeks significantly reduced FPG.[36] Furthermore, in a network meta-analysis of randomized clinical trials comparing sitagliptin with linagliptin, the proportion of patients achieving HbA1c <7% was higher in the linagliptin group.[37]

Patients treated with either sitagliptin or vildagliptin resulted in a clinically meaningful increase in mean body weight compared to placebo of 0.70 kg and 0.83 kg, respectively. However, there was no significant difference in mean change in body weight for alogliptin or linagliptin versus placebo (Fig. 2). Linagliptin is the only DPP-4 inhibitor with a statistically significant lesser chance of patients having a hypoglycemic event compared with placebo.[12]

The results of the study by DeFronzo et al showed that after a 24-week treatment with the combination, the reduction with SGLT2 inhibitor/DPP-4 inhibitor was superior to those with SGLT2 inhibitor or DPP-4 inhibitor individually as add-on to metformin.[38]

DPP-4 inhibitor and SGLT2 inhibitor combination are safe, effective, tolerable and rationale cost-effective in patients with uncontrolled blood glucose on therapy with metformin alone, intolerance to metformin, increased baseline HbA1c, overweight or obesity and diabetic hypertensive, congestive heart failure, atherosclerotic cardiovascular disease (CVD), and renal dysfunction patients.[39]

LINAGLIPTIN IN PATIENTS WITH VASCULAR COMPLICATIONS

The presence of clinical features such as micro-albuminuria and hypertension is the key to assessing the risk of cardiovascular and renal outcomes. Vascular complications are a primary challenge in the management

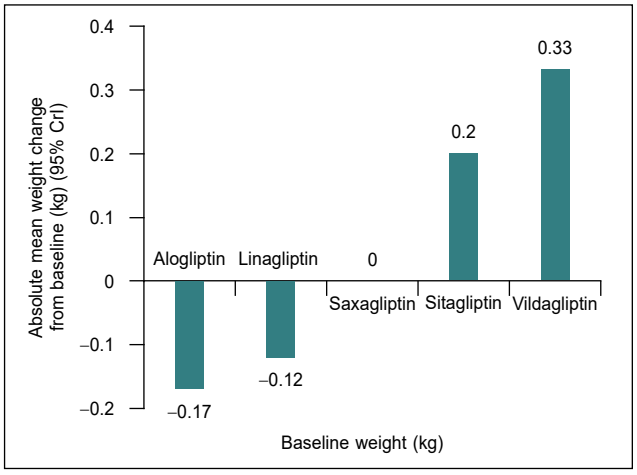

Figure 2. Absolute treatment effect mixed treatment comparisons-Absolute mean weight change from baseline (following 54 weeks of treatment), kg (95% credible interval CrI).

(Data sourced from Craddy P, et al. Diabetes Ther. 2014;5(1):1-41.[12])

of T2DM. It was seen in the UKPDS trial that one-fourth of the study population developed microalbuminuria within 10 years of being diagnosed with T2DM. The American Diabetes Association (ADA) guidelines and the Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines[40,41] for diabetes and chronic kidney disease (CKD) on T2DM management recommend reducing the risk or delaying the progression of kidney diseases through strict normalization of glycemic control. Renal impairment acts as a challenge in the selection of appropriate OADs in managing T2DM.[28]

According to a study, linagliptin can improve endothelial and neurovascular microvascular function and is related to reduced markers of inflammation in patients with type 2 diabetes.[42]

Managing Patients with Renal Impairment

A characteristic feature of linagliptin is that the primary route of elimination is via the nonrenal route, with 5% of the dose being excreted via the kidneys (Fig. 3). Further,

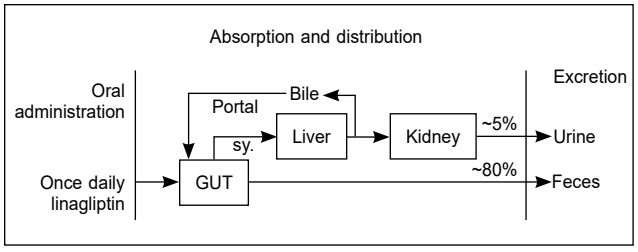

Figure 3. Elimination of linagliptin.

linagliptin requires no dose adjustment when given to patients with renal issues. In comparison, all other DPP-4 inhibitors are predominantly cleared by renal excretion as well as dose adjustment is required, especially in the case of creatinine clearance <50 mL/min and those with ESRD requiring dialysis. A study by McGill et al (2013) showed that in patients with type 2 diabetes and severe renal impairment, after 1-year treatment period, only a few patients experienced severe hypoglycemia in linagliptin and placebo groups. The linagliptin group showed superior mean HbA1c and FPG at week 12, and patients undergoing changes in 1 or more daily glucose-lowering background therapy was similar between linagliptin and placebo. No significant change was seen in the rate of adverse events, and no change was seen in the average estimated glomerular filtration rate (eGFR) values by clinically meaningful relevance.[43]

Von Eynatten et al, in a study on 512 patients with T2DM at high renal and vascular risk, linagliptin demonstrated a significant and clinically meaningful reduction in HbA1c and FPG compared to placebo. Linagliptin treatment also leads to minor alterations in urine albumin-creatinine ratio.[28] Linagliptin, when given across three renal function categories, achieved a consistent reduction in HbA1c levels; normal (–0.63%; $p < 0.0001$), mild renal impairment (–0.67%; $p < 0.0001$) and moderate renal impairment (–0.53%; $p < 0.01$). The efficacy of linagliptin remained stable across all groups, and it proved to be an effective, well-tolerated, and convenient treatment in individuals with T2DM and mild to moderate renal impairment.[44]

The CARMELINA cohort comprised patients with T2DM and CVD, and/or CKD, contradictory to the restricted renal risk population of other cardiovascular outcomes (CVOTs). It is the first DPP-4 inhibitor CVOT in a substantial proportion of patients with renal dysfunction and/or characterized microalbuminuria at baseline. Table 2 depicts the renal safety of DPP-4 inhibitors as shown across different CVOTs. CARMELINA CVOT identified and utilized the opportunity to include a significant number of patients with CKD along with patients with CVD, as these patients will remain apt for linagliptin at a single dose, irrespective of the decline in renal function (Table 2).[45]

Table 2. Renal Safety of DPP-4 Inhibitors

	Sitagliptin	Saxagliptin	Alogliptin	Linagliptin
Renal safety composite	Studies not reported			
Renal function	Studies show moderately increased risk		Neutral	
Albuminuria	Studies show modest benefit		Studies not reported	Studies show modest benefit

Managing Patients with Cardiovascular Disorders

A comparison with other DPP-4 inhibitors has shown that linagliptin has a modest effect on blood pressure while others, such as saxagliptin and sitagliptin, have small to neutral effects on blood pressure.[28] Further, linagliptin was well tolerated and effective when added to the treatment regimen of patients with T2DM and coronary artery disease. It was not related to an increased incidence of cardiac adverse events. The CARMELINA trial was a cardiovascular event-driven, placebo-controlled, double-blind, randomized clinical trial conducted between August 2013 and January 2018 in 27 countries across Asia, Europe, Latin America and North America. In the CARMELINA trial, it was seen that linagliptin did not raise the risk of cardiovascular events or hypoglycemia in older patients with T2DM and established CVD. Linagliptin did not cause the risk of hospitalization for heart failure across all age groups.[46]

Compared to CARMELINA, TECOS was a global clinical trial performed in a usual care setting among patients with type 2 diabetes and established CVD; the DPP-4 inhibitor did not affect rates of major atherosclerotic cardiovascular events. However, the study enrolled patients with moderate hyperglycemia and excluded those with renal insufficiency.[47]

Linagliptin in Patients with Liver Disease

Liver disease has a high prevalence in people with T2DM. Linagliptin has been noted to be effective and well-tolerated in people with T2DM and liver disease. Linagliptin brought about a change in HbA1c from baseline in individuals with hepatic disorders, –0.75% compared to –0.20% with placebo.[21] Dose adjustment

Table 3. Linagliptin Use Across Different Patient Profiles with T2DM

Patient category	Glucose-lowering efficacy	Safety	Benefits
Elderly patients (≥65 years)	The mean change in HbA1c was –0.64% (241 patients)[16]	Well-tolerated No risk of hypoglycemia or other drug-related side effects.[49,50]	Achieve individualized glycemic targets with the least chance of risk. Improves glucose control in patients on stable insulin therapy.[51]
Treatment-naïve patients	Significant and clinically meaningful improvement of glycemic control.[52]	Excellent safety profile[52]	Improves parameters of β-cell function.[52]
Pediatric patients	Dose-dependent reduction in mean HbA1c of 0.48% and 0.63% with linagliptin 1 and 5 mg, respectively; linked to a corresponding lowering in mean FPG of 5.6 and 34.2 mg/dL.[53]	Well-tolerated[53]	Dose-dependent DPP-4 inhibition accompanied by a corresponding lowering of HbA1c and FPG levels.[53]
Hospitalized surgical patients	Effective in patients undergoing noncardiac surgery with mild to moderate hyperglycemia (blood glucose <11.1 mmol/L).[54]	Safe[55] Fewer hypoglycemic events compared to basal-bolus insulin.[54]	Safe and effective choice as an alternative to multi-dose insulin therapy.[54]

with linagliptin is not needed in patients with hepatic impairment.[48]

SPECIAL SITUATIONS

Linagliptin effectively lowered hyperglycemia in Asian patients with uncontrolled T2DM, irrespective of age, BMI, renal function or ethnic subgroups and was well-tolerated[9] (Table 3[16,49-55]).

CLINICAL SAFETY OF LINAGLIPTIN

The clinical safety of linagliptin has been evaluated in more than 4,000 patients with type 2 diabetes. In a placebo-controlled clinical study, nasopharyngitis occurred in about 5% of the linagliptin group of patients; and more often in the linagliptin group compared to placebo. Other adverse events associated with linagliptin were hypersensitivity and myalgia.[55]

Hypoglycemic events are rare during treatment with linagliptin. In fact, in a study of linagliptin versus placebo, monotherapy led to hypoglycemic events occurring in 0.6% of the linagliptin group and 0.3% of the placebo group.[13] In another placebo-controlled study of linagliptin monotherapy, no episodes of hypoglycemia were reported in patients with type 2 diabetes.[56] DPP-4 inhibitors, in general, have a neutral effect on weight. It was reported in a study that weight loss of 0.15, 0.57 and 12.7 kg was seen with linagliptin 1 mg, 5 mg and 10 mg, respectively.[19] However, combination therapy with metformin led to a decrease in body weight in a 24-week study.[57] Linagliptin did not cause any significant changes in electrocardiographic parameters.

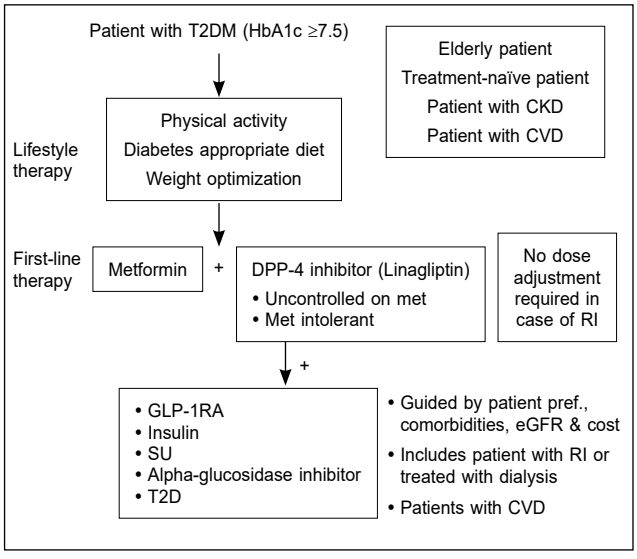

Figure 4. Algorithm for the place of linagliptin in T2DM management.

T2DM = Type 2 diabetes mellitus; HbA1c = Glycated hemoglobin; CKD = Chronic kidney disease; CVD = Cardiovascular disease; DPP-4 = Dipeptidyl peptidase-4; RI = Renal impairment; GLP-1RA = Glucagon-like peptide-1 receptor agonists; SU = Sulfonylurea; eGFR = Estimated glomerular filtration rate.

A randomized, placebo-controlled, double-blind, four-period crossover study showed that linagliptin had the ability to prolong the QT interval at therapeutic and subtherapeutic doses.[58] Linagliptin was well-tolerated, and no clinically meaningful electrocardiographic changes or relevant changes in other safety parameters were observed.

Figure 4 shows the treatment algorithm for managing type 2 diabetes patients with combination therapies.

CONCLUSION

In recent years, DPP-4 inhibitors have emerged as a promising option for the management of T2DM. Among them, linagliptin has a unique pharmacokinetic and pharmacodynamic profile featured by target-mediated nonlinear pharmacokinetics and a large safety window, more than 100 times the recommended daily dose. Linagliptin has shown clinically meaningful glucose-lowering efficacy and good tolerability as monotherapy or second-/third-line therapy across several race groups.

Numerous clinical trials have demonstrated the efficacy of linagliptin in reducing HbA1c levels and improving glycemic control, both as monotherapy and in combination with other oral antidiabetic agents. It has also shown a favorable effect on beta-cell function, making it particularly beneficial for Asian populations with beta-cell insufficiency. Another crucial advantage of linagliptin is its cardiovascular safety profile, as seen in the CARMELINA trial, setting it apart from other DPP-4 inhibitors, making it a favorable choice for patients with CVDs and/or kidney impairment.

Evidence suggests that the use of linagliptin in combination with other OADs, such as metformin, would prove to be a well-tolerated and effective treatment option for T2DM patients. Overall, it would provide a comprehensive approach to managing T2DM by addressing both CVD risk factors as well as hyperglycemia, ultimately improving patient outcomes and quality of life. The combination of DPP-4 inhibitors and SGLT2 inhibitors is also beneficial as second-line therapy in T2DM patients uncontrolled on metformin therapy.

EXPERT RECOMMENDATIONS

Place in Therapy: Initiation

- Linagliptin may be used as first-line therapy in persons in whom metformin is contraindicated.
- Linagliptin may be used as part of initial dual oral therapy in persons with HbA1c >7.5%.
- Linagliptin may be used as part of initial triple oral therapy if persons with HbA1c >8.5% at presentation.

Place in Therapy: Interchange

- Linagliptin may be used as monotherapy in persons in whom metformin is not tolerated.
- Linagliptin may be used to replace any other oral antidiabetic agents/injectable GLP-1RA if the drug is deemed unsafe or is not tolerated.

Place in Therapy: Intensification

- Linagliptin may be used as add-on therapy if pre-existing metformin monotherapy is inadequate in achieving desired HbA1c targets.
- Linagliptin may be used as add-on therapy if pre-existing dual therapy is inadequate in achieving desired HbA1c targets.
- Linagliptin may be co-prescribed with insulin to reduce insulin requirements to minimize glycemic variability and provide renoprotective benefits.

Special Situations

- Linagliptin is the preferred drug of choice in persons with renal impairment, including those on dialysis, irrespective of eGFR status.
- Linagliptin may be used in persons with moderate hepatic impairment.
- Linagliptin has been shown to have beneficial effects in persons with foot infections.
- Linagliptin may be used in persons with chronic heart disease, irrespective of ejection fraction.
- Linagliptin is the preferred drug of choice in persons at high risk of hypoglycemia.

Caveats and Considerations

- Linagliptin does not need any dose titration based on renal or hepatic status.
- Linagliptin can be safely prescribed to persons who are unable to undergo frequent investigations or follow-up regularly.
- Linagliptin can be co-prescribed with every glucose-lowering drug except other gliptins and GLP-1RA.

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CLINICAL REVIEW

Rational Renometrics

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ABSTRACT

The precise evaluation of renal function and structure is indispensable clinical medicine. This is required not only to screen, diagnose and monitor kidney disease, but also to allow accurate choice of drugs and their dosages while treating individuals. Traditional methods, exemplified by glomerular filtration rate (GFR) calculations and urinalysis, have long served as pillars of nephrology. However, their inherent limitations introduce diagnostic ambiguities, raising concerns for both health care providers and patients. This comprehensive review introduces the concept of "Rational Renometrics", a transformative approach that harmonizes various tests and factors to provide a holistic assessment of renal health. It focuses on correct urine sample collection, mitigates false positives in urinalysis and embraces the concept of permissive hypercreatinemia. The evidence-based, data-driven perspective of rational renometrics empowers health care providers and patients, leading to more accurate diagnoses, individualized treatment strategies and improved therapeutic outcomes. Rational renometrics allows accurate risk assessment and institution of preventive interventions, reinforcing its pivotal role in preserving renal health and optimizing patient care. We describe the principles, advantages, challenges and potential clinical applications of rational renometrics, emphasizing the need for continued research and validation of this concept.

Keywords: Renal function assessment, transformative, permissive hypercreatinemia, risk assessment

Renal function assessment is a cornerstone of clinical medicine, providing critical insights for the diagnosis and management of kidney diseases.[1] It also helps ensure appropriate choice and accurate dosage of drugs for management of disease.[2] However, the conventional methodologies employed for renal evaluation, such as glomerular filtration rate (GFR) calculations and urinalysis, are not immune to inherent limitations.[3-6] These limitations often result in ambiguous interpretation of results, and erroneous decisions based on them. We propose the concept of "Rational Renometrics" to offer a comprehensive and data-driven perspective on renal function assessment, potential to significantly enhance the quality of care provided to patients with renal conditions.

Rational renometrics, as a systematic framework, mandates consideration of a multitude of factors and ancillary tests to contextualize clinical data. For patients, this translates into a more precise evaluation of their renal health status, potentially allaying unwarranted apprehensions and facilitating a more individualized approach to medical care. Consider, for example, a patient presenting with marginally elevated creatinine levels but concomitant radiological assessments demonstrating unremarkable renal structures and urinalysis results indicating no evidence of kidney dysfunction. The traditional interpretation of isolated elevated creatinine levels in routine blood tests may often precipitate anxiety and concerns related to underlying renal dysfunction.[7] However, it is imperative to acknowledge that creatinine levels are subject to various nonrenal determinants, including age, muscle mass and dietary factors. In such instances, an isolated elevation in creatinine may not necessarily signify inherent renal pathology.[3,4,8] In this scenario, rational renometrics would provide a more grounded and rational perspective, reducing unjustified anxiety and enabling health care providers to make informed decisions.

By providing a concordant view of both renal function and structure, rational renometrics empowers patients to engage in data-driven discussions with their health care providers. It ensures that treatment decisions, lifestyle modifications and further diagnostic tests are founded on precise and rational assessments, thereby fostering enhanced patient confidence in the health care delivery system. In this review, we will expound upon the

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principles, advantages, challenges and potential clinical applications of rational renometrics. Additionally, we will discuss the necessity for research and validation to establish this approach as a standard practice in nephrology, as well as explore future directions for the field. Through this review, we aim to underscore the transformative potential of rational renometrics for health care providers and patients, culminating in more accurate diagnoses, individualized treatment strategies and improved patient outcomes.

RENAL FUNCTION ASSESSMENT

Renal function assessment is a critical aspect of clinical medicine, providing essential insights into the health and performance of the kidneys.[1] The two primary pillars of this assessment have traditionally been the estimated glomerular filtration rate (eGFR) and urinalysis.[4,5] While these methods have played a pivotal role in nephrology, it is important to acknowledge their inherent limitations.

Urinalysis, particularly albumin or red blood cells (RBCs) in urine, is a fundamental tool used in renal assessment.[5] Despite its wide usage, urinalysis is not without significant limitations. Albuminuria is a critical marker for kidney disease.[9,10]

However, it is important to recognize that albuminuria is not always indicative of underlying renal pathology. Urinary albumin levels can be influenced by factors unrelated to kidney health, such as systemic inflammation, exercise and urinary tract infections (UTIs).[1] This presents a challenge in interpreting urinalysis results, as false positives may lead to unwarranted concerns and potentially unnecessary follow-up procedures. Similarly, the presence of RBCs in urine may not always be indicative of intrinsic kidney disease. Nonrenal factors, such as strenuous exercise, menstruation and UTIs, can also lead to hematuria.[1] This complicates the interpretation of urinalysis results and raises the potential for misdiagnosis.

Estimation of GFR using creatinine measurements is a widely accepted and commonly used method for assessing renal function.[3,4] However, it relies heavily on the assumption that creatinine production and elimination are relatively stable within individuals. This assumption may not hold true for all patients, particularly those with conditions that can affect creatinine metabolism.[3,4] For example, individuals with varying muscle mass, age or diet may exhibit different creatinine production rates, leading to inaccurate GFR estimates.[1,3,4]

Serum creatinine levels can vary between different laboratories, and even within the same laboratory over time, due to differences in assay methodologies and equipment calibration. These variations can result in discrepancies in GFR estimations when using creatinine-based equations. This inconsistency can be a source of diagnostic uncertainty, and patients may be misclassified as having kidney dysfunction when they do not.[4,11]

The concept of "permissive hypercreatinemia" refers to the phenomenon where elevated creatinine levels within a certain range do not necessarily indicate kidney dysfunction.[12-14] In some cases, creatinine levels may be chronically elevated but stable, and patients may have normal renal function. Using creatinine-based GFR estimation alone may lead to incorrect diagnoses of renal impairment or disease progression in such cases, causing unnecessary concern and medical interventions. Certain medications, such as cimetidine, trimethoprim and some antibiotics, can interfere with creatinine secretion and reabsorption in the renal tubules. This can lead to inaccuracies in GFR estimations based on creatinine levels, potentially causing overestimation of renal function.[3,4,11] Creatinine-based GFR estimations may be less accurate in specific populations, such as elderly individuals, pediatric patients or individuals with extremes in muscle mass. In these cases, the limitations of creatinine-based GFR calculations become more pronounced.

To address these shortcomings and improve the accuracy of renal function assessment, the rational renometrics approach emphasizes the need for a more comprehensive evaluation. It incorporates a range of tests, accounts for confounding factors and considers the broader clinical context to provide a more accurate and rational assessment of renal health. Furthermore, rational renometrics underscores the importance of collecting urine samples correctly and accounting for various confounding factors to reduce the incidence of false positives. This approach helps reduce diagnostic uncertainties, unnecessary concern and the potential for misclassification of kidney function.

RATIONAL RENOMETRICS FRAMEWORK

Rational renometrics seeks to provide a holistic and rational approach to the assessment of renal function and structure.

- **Investigations and their interpretation**
  - **Integration of radiological and nuclear tests:** The framework incorporates radiological and nuclear imaging alongside traditional assessments to provide a more comprehensive view of renal health.

- **Addressing false positives:** The approach accounts for potential false positives, such as albuminuria in the presence of UTIs, in urinalysis interpretation.
- **Creatinine variation consideration:** Rational renometrics acknowledges variations in creatinine levels between different laboratories or at different times and seeks to account for these fluctuations.
- **Permissive hypercreatinemia concept:** The framework recognizes that elevated creatinine levels within a certain range may not necessarily indicate kidney dysfunction and takes a more nuanced approach to interpretation.

➲ **Clinical evaluation and approach**

- **Comprehensive patient evaluation:** Rational renometrics aims to provide a comprehensive and individualized assessment, tailoring the evaluation to each patient's unique clinical context.
- **Improved diagnostic accuracy**: By considering a wider range of parameters and addressing nuances, rational renometrics enhances the accuracy and reliability of renal health diagnoses.
- **Informed treatment decisions:** The approach empowers physicians and patients to make more informed decisions about treatment, lifestyle changes and further diagnostic tests based on a rational and comprehensive assessment.
- **Research and validation**: To establish rational renometrics as a standard practice in nephrology, research and validation studies are necessary, encompassing various patient populations and clinical settings.

POINT OF CARE TESTING

The availability of accurate point of care testing (POCT) devices for the measurement of urine albumin-to-creatinine ratio (UACR) has helped improve the efficiency of clinical decision making and health care delivery. Availability of test reports within minutes allows rapid titration of therapy and improves patient's satisfaction with health care.

CHALLENGES AND CAVEATS

Rational renometrics is not without its challenges. The complexity of integrating various tests and the need for standardized protocols pose logistical hurdles.

Table 1. Challenges and Caveats Related to Rational Renometrics

Challenges	Comments
Complex Integration	Integrating various tests, including radiological and nuclear imaging, in a systematic manner can be logistically challenging, requiring standardization and coordination among health care providers.
Interpretation Complexity	The interpretation of test results, especially when variations exist across different laboratories or time points, demands meticulous attention to detail, introducing potential sources of error.
Change in Diagnostic Workflow	Implementing rational renometrics in clinical practice necessitates changes in traditional diagnostic workflows and may require health care providers to adapt to a new paradigm of assessment.
Data-Driven Approach	Rational renometrics relies heavily on data-driven decision-making, which requires accurate and consistent data collection, storage and analysis.
Point of Care Services	Point of care testing facilities are required to help optimize usage and benefits of renometrics in clinical decision-making.
Standardization Challenges	The development of standardized protocols for implementation of rational renometrics across diverse health care settings can be complex task.
Validation Requirements	The establishment of rational renometrics as standard practice in nephrology requires extensive research and validation studies, which can be resource-intensive and time-consuming.
Patient Education	Patients must be educated about rational renometrics nuances to understand rationale behind assessment and its potential impact on their decisions.
Collaboration	Successful implementation of rational renometrics requires interdisciplinary collaboration among pathologists, radiologists and other health care providers.
Integration with Electronic Health Records	Rational renometrics may necessitate integration of new data points and test results into electronic health records and electronic medical record systems, posing technical and administrative challenges.

Table 2. Various Advantages of Rational Renometrics

Challenges	Comments
Accurate Diagnoses	Rational renometrics provides more reliable assessment of renal function and structure, reducing potential for misdiagnosis and unnecessary concern.
Tailored Treatment Strategies	The comprehensive evaluation empowers health care providers to design individualized treatment plans, optimizing patient care and outcomes.
Reduced Diagnostic Uncertainty	By accounting for variations in test results and incorporating wider range of parameters, rational renometrics reduces diagnostic uncertainties and ensures more confident clinical decision-making.
Early Disease Detection	The approach offers improved sensitivity for detecting early stages of kidney disease, enabling timely intervention and preventive measures.
Data-Driven Discussions	Rational renometrics encourages data-driven discussions between health care providers and patients, fostering patient engagement and informed decision-making.
Patient Confidence	Patients benefit from a more rational and nuanced assessment of their renal health, leading to reduced anxiety and enhanced confidence in their health care providers.
Monitoring Disease Progression	Rational renometrics is effective for monitoring disease progression and treatment response, allowing health care providers to make timely adjustments to the management plan.
Improved Risk Assessment	The approach aids in the identification of patients at risk of developing chronic kidney disease, facilitating targeted interventions to mitigate risks.
Enhanced Patient Outcomes	Rational renometrics ultimately contributes to improved patient outcomes by ensuring that clinical decisions are grounded in accurate and comprehensive data.
Potential for Preventive Medicine	By identifying early signs of renal dysfunction and addressing modifiable risk factors, rational renometrics supports preventive medicine and the preservation of renal health.

Interpreting test results, particularly when variations exist across different laboratories, requires meticulous attention. Additionally, addressing the practical implementation of rational renometrics in clinical practice presents challenges, as it necessitates changes in diagnostic workflows and requires interdisciplinary cooperation. The challenges and caveats related to rational renometrics have been depicted in Table 1.

Overcoming these challenges and addressing the associated caveats is essential to successfully implementing rational renometrics and realizing its potential benefits in clinical practice.

ADVANTAGES AND CLINICAL APPLICATIONS

The advantages of rational renometrics are promising. This approach can lead to more accurate diagnoses, improved monitoring of kidney health and better-informed treatment decisions. The various advantages of rational renometrics have been depicted in Table 2.

The advantages and clinical applications of rational renometrics hold the potential to revolutionize the assessment of renal function and structure, leading to more accurate diagnoses, tailored treatment strategies and improved patient outcomes.

CONCLUSION

In conclusion, rational renometrics emerges as a transformative approach to renal health assessment, effectively addressing the limitations of traditional methods. By providing a more comprehensive, data-driven evaluation of renal function and structure, it empowers health care providers and patients to make informed decisions, allaying uncertainties and fostering individualized care.

While challenges and standardization remain key considerations, the potential for more accurate diagnoses, personalized treatment strategies, and improved patient outcomes highlights the significance of rational renometrics in modern nephrology. Its evolving role in risk assessment and preventive medicine positions it as a pivotal tool in the preservation of renal health and the optimization of patient care.

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Effect of Symptom Burden on Physical Activity in Persons with COPD

There is an inverse association between moderate-to-vigorous physical activity and severity of symptoms in patients with chronic obstructive pulmonary disease (COPD), as per a new research published in the journal *Chronic Obstructive Pulmonary Diseases*.[1]

A total of 1,558 COPD patients, ≥40 years, from the Canadian Cohort Obstructive Lung Disease study (CanCOLD) were enrolled for this multicenter cross-sectional study to examine the association between physical activity of moderate-to-vigorous intensity and COPD symptoms. The selected participants were grouped into four categories: 474 individuals at-risk for COPD (ever-smokers and normal spirometry), 406 participants with mild COPD (GOLD 1 stage), 287 with moderate COPD (GOLD 2 stage) and 347 healthy subjects (never-smokers and normal spirometry). The study excluded patients with GOLD stage 3 and 4. Moderate-to-vigorous intensity physical activity, measured as energy expenditure (kcal/week) was the primary endpoint of the study.

Significant associations were observed between lower moderate-to-vigorous intensity physical activity levels and high symptom burden overall and in patients with moderate COPD ($\beta = -717.09$). Seventy-two percent of patients had never been diagnosed with COPD ($\beta = -694.1$) prior to their recruitment in this study. These undiagnosed subjects had significantly higher moderate-to-vigorous intensity physical activity vis-à-vis those with physician-diagnosed COPD ($\beta = -592.41$).

Shortness of breath or dyspnea, especially during physical activity, is a characteristic symptom of COPD, which is a deterrent for physical activities. In this study of patients with newly diagnosed COPD of mild to moderate severity, moderate-to-vigorous intensity physical activity was inversely associated with greater severity of symptoms. Therefore, evaluation of symptom burden enables identification of patients with lower moderate-to-vigorous intensity physical activity, especially in those with moderate disease severity as well as relatively inactive patients with mild COPD. These patients should be encouraged to engage in relatively less strenuous exercises such as gentle yoga at a slower pace and walking, under supervision, to improve their quality of life.

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CASE REPORT

An Unusual Case of Liver Abscess Caused by Trematodes

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ABSTRACT

Liver abscess caused by trematodes is considered highly unusual. Here we present a case of an elderly female with no known comorbidities, who presented with fever and right upper quadrant pain. Upon evaluation, she was found to have features of liver abscess on abdominal ultrasound and 640-slice computed tomography (CT) of the abdomen. Ultrasound-guided needle biopsy of the liver showed features of trematode. Patient was treated with oral nitazoxanide. Patient's fever and abdominal pain subsided after the treatment.

Keywords: Liver flukes, rare, right upper quadrant pain, ultrasound-guided needle biopsy

Liver abscess is a pus-filled collection in the liver. It is one of the most common forms of visceral abscess. It can develop either from an intra-abdominal infective source disseminated through portal circulation or following an injury. Majority of them are caused by bacteria or amoeba while rarely caused by fungi and parasites.[1] Approximately 91 species of trematodes or flatworms, called flukes are known to affect humans worldwide.[2] Rarely, liver abscess formation may occur secondary to hepatic inflammation or cholangitis. Some authors argue that tolerance instead of the immunity is the preferred immunological response of liver, which offers a favorable environment for the parasites.[3] The common liver flukes include *Fasciola hepatica*, *Fasciola gigantica*, *Opisthorchis viverrini*, *Opisthorchis felineus* and *Clonorchis sinensis*. Liver abscess caused by trematodes is considered highly unusual. A definitive diagnosis of trematode-induced liver abscess can be made based on detection of eggs in stool, tissue samples or based on serological tests. Nonspecific and asymptomatic clinical presentation often hampers the diagnosis.[3] Cholangiocarcinoma is the most dreaded complication of *C. sinensis* and *O. viverrini*, which needs early evaluation and treatment.[4]

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CASE REPORT

A 72-year-old female presented with chief complaints of intermittent fever and generalized weakness for 2 years. She had a history of open drainage, debridement and peritoneal lavage for a liver abscess (involving the 7th segment) 2 years back. She also had right-sided abdominal pain and loss of appetite since then. She denied any history of abdominal distension, jaundice, loss of weight or bowel and bladder disturbances.

On examination, patient was conscious and oriented. Her vital data were within normal limits. Systemic examination revealed tenderness in the right hypochondrium. Her baseline blood investigations showed anemia (Table 1).[1] Chest X-ray was normal. Ultrasonogram (USG) of the abdomen showed mild hepatomegaly with a cystic space-occupying lesion.

A differential diagnosis of resolving liver abscess or pancreatic pathology was considered. Further evaluation with 640-slice computed tomography (CT) abdomen showed multiple peripherally enhancing lobulated lesions with internal calcifications involving segments 6, 7 and 8 of right hepatic lobe (Fig. 1 a-f). Few lesions appeared tubular/serpiginous and were located in the subcapsular region (Fig. 2). Imaging was in favor of liver trematodes as the cause of liver abscess. A liver biopsy was done and histopathology of the tissue showed necrotic liver parenchyma with degenerated parts of parasite, likely a trematode (Fig. 3 a and b). Gram stain, acid-fast stain, fungal stain, Xpert *Mycobacterium tuberculosis* and tissue culture and sensitivity of the sample were negative. Since liver

Table 1. Baseline Parameters of the Patient

Parameters	Patient's value	Normal value
Hemoglobin	10.6 g/dL	12-16 g/dL
White cell count	5.81 × 10/mm^3	4-11 × 10/mm^3
Neutrophils	62	40-80
Lymphocytes	22	20-40
Eosinophils	9	1-6
Monocytes	6	2-10
Platelet count	155 × 10/mm^3	150-450 × 10/mm^3
Serum creatinine	0.5 mg/dL	0.7-1.3 mg/ dL
Alanine transaminase (ALT)	34 U/L	<34 U/L
Aspartate transaminase (AST)	38 U/L	<31 U/L
Alkaline phosphatase (ALP)	97 U/L	<141 U/L
Gamma-glutamyl transpeptidase (GGTP)	17 U/L	<38 U/L
Total bilirubin	1.3 mg/dL	0.0-1.3 mg/dL
Direct bilirubin	0.4 mg/dL	0.0-0.5 mg/dL
Indirect bilirubin	0.9 mg/dL	0-1.2 mg/dL
Serum albumin	4.0 g/dL	3.5-1.2 g/dL
Serum globulin	2.9 g/dL	2.0-3.5 g/dL

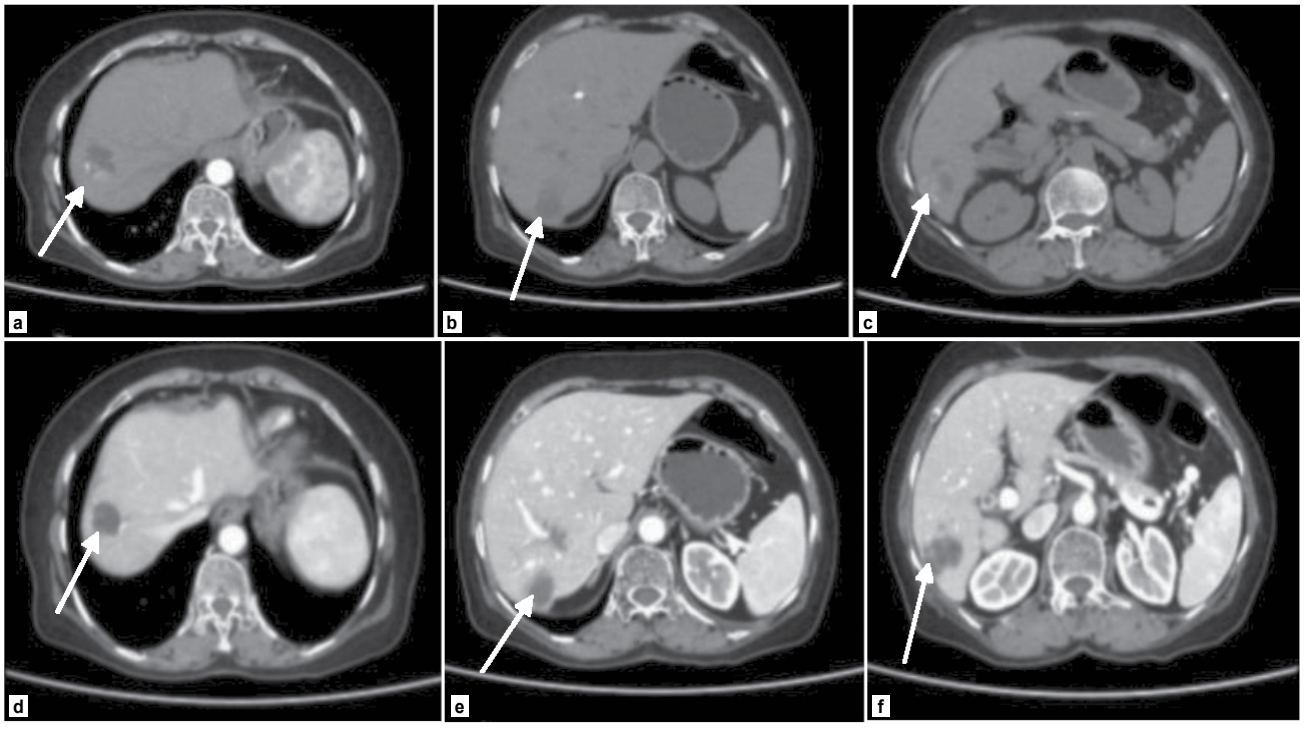

Figure 1 (a-f). CT images of liver showing multiple peripherally enhancing lobulated lesions in the right lobe of liver. Few lesions in the subcapsular region can be seen.

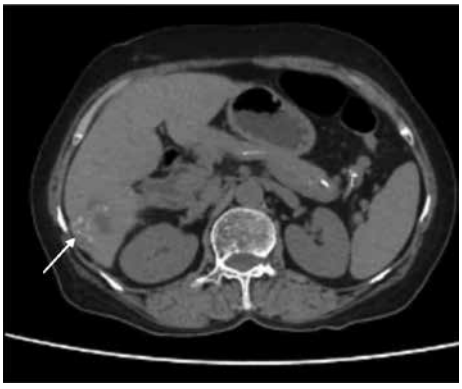

Figure 2. Serpiginous lesion in the subcapsular region.

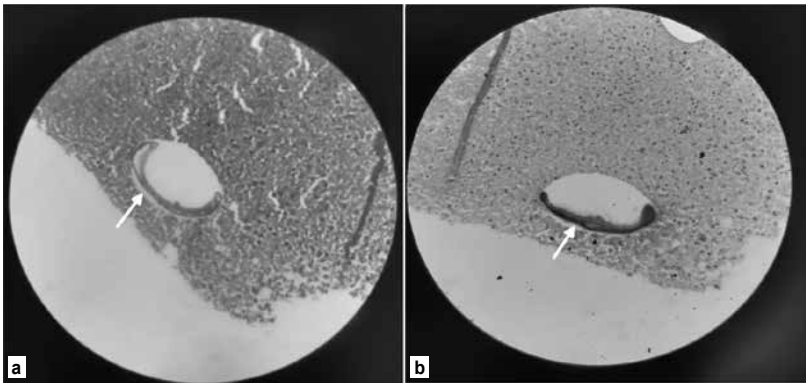

Figure 3 a and b. Histopathology of the liver showing a trematode.

Table 2. Comparative Analysis of Common Liver Flukes

	Opisthorchis	***C. sinensis***	***Fasciola***
Epidemiology	*Viverrini*: Northeastern Thailand, Laos and Cambodia[6]	Asia including Korea, Taiwan, China, Vietnam and Japan[8]	Hepatica: More than 50 countries in all continents except Antarctica
	Felineus: Europe and Asia[7]		Gigantica: Less widespread
Definitive host	Humans[6]	Humans[8]	Sheep, goats, cattle and humans
First intermediate host	Snail[6]	Snail[8]	Snail
Second intermediate host	Freshwater fish[6]	Freshwater fish[8]	Aquatic plants
Infective form	Metacercariae[6]	Metacercariae[8]	Metacercariae
Clinical features	***Viverrini***	**Acute**	**Migratory phase** (1-4 weeks):
	Acute: Asymptomatic or hepatitis like features[6]	<100 flukes: Innocuous infection[8]	Fever, liver tenderness, urticarial (increased eosinophils) and weight loss[9]
	Chronic: Recurrent cholangitis, cholelithiasis, periductal fibrosis and cholangiocarcinoma[6]	>20,000 flukes: Acute cholangitis, jaundice, right upper quadrant pain, nausea, vomiting, anorexia, malaise and fever[8]	**Complications:** Subcapsular hematomas and prolonged febrile illness[3]
	Felineus		**Chronic phase:** Cholestatic jaundice, recurrent cholangitis, cholelithiasis, fibrosis of biliary duct[9]
	Acute: Fever, abdominal pain, headache, arthralgia, diarrhea, nausea and eosinophilia[7]	**Chronic**	
	Chronic: Recurrent cholangitis, hepatic abscess, acute pancreatitis and biliary peritonitis[7]	Cholelithiasis, pancreatitis, liver abscess and cholangiocarcinoma[8]	**Complications:** Liver abscess, liver fibrosis, cirrhosis, weight loss and anemia[9]
Imaging	USG: Diffuse to mild intrahepatic biliary duct dilation with intraductal sludge and stones. Sparing of large bile ducts with common bile duct often in normal caliber is seen[10]	USG: Subcapsular ill-defined hypoechoic mass in parenchymal phase, features of cholangitis in biliary phase[10]	
	CT: Mild to moderate intrahepatic biliary ductal dilation, predominantly peripheral involvement. Intrahepatic sludge and stones can also be seen[10]	CT: Capsular thickening, hyperenhancement with peripheral nodular and tortuous lesions corresponding to migratory tract[10]	
Treatment	Praziquantel 25 mg/kg in 3 divided doses per day × 2-3 days[6]	Praziquantel 25 mg/kg in 3 divided doses per day × 2-3 days	Triclabendazole 2 doses of 10 mg/kg per dose × 12-24 hours
			Nitazoxanide 500 mg twice daily × 1 week[11]

function tests were normal, endoscopic retrograde cholangiopancreatography (ERCP) was deferred and a decision to start medical management was taken. Patient was started on oral nitazoxanide 500 mg 3 times a day for 3 weeks. During follow-up, the patient was found to have no further fever spikes and her right upper quadrant pain had significantly reduced.

DISCUSSION

Trematodes are unsegmented helminths. They are flat and broad and resemble the leaf of a tree or a flat fish; hence, the name fluke.[5] Table 2 describes the comparative analysis of the common liver flukes.[6-11]

Risk factors include travel to endemic areas, consumption of raw or uncooked fish and low socioeconomic status. Most of the patients present with fever, right upper quadrant pain, eosinophilia and anemia.[9] As our patient had fever, right upper quadrant pain, loss of appetite, and generalized weakness with serpiginous pattern in CT and liver biopsy showed trematode, a diagnosis of liver abscess due to trematodes was confirmed. Based on the review of existing evidence from several clinical and experimental studies *O. viverrini* is found to be a definite cause of bile duct carcinoma, while *C. sinensis* is considered as a probable cause of carcinoma. *O. felineus*, on the other hand, has not been studied sufficiently.[12] Clonorchis and Opisthorchis are associated with recurrent pyogenic cholangitis and pigment stones.[13]

CONCLUSION

This case report underscores the importance of increasing awareness regarding liver abscess caused by trematodes as a potential differential diagnosis in patients with fever, abdominal pain and eosinophilia. It also highlights the need for high index of suspicion to diagnose this rare entity.

Declaration

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CASE REPORT

Sturge-Weber Syndrome Associated with Bilateral Angle-closure Glaucoma in a Young Adult

PARAALI SHAH*, AJITA SASIDHARAN*, MITHUN THULASIDAS*

ABSTRACT

Sturge-Weber syndrome (SWS) is a phakomatosis involving the eyelids, conjunctiva, choroid and retina. The mechanism of glaucoma in SWS involves developmental anomaly of the anterior chamber angle and elevated episcleral venous pressure. Here, we present a case of Roach's type II SWS with bilateral angle-closure glaucoma (ACG) in a young adult, which to the best of our knowledge, is the first-of-its-kind report in the literature. Though unusual, ACG may occur in young adults too. However, the underlying causes that make them develop the ACG are poorly understood. We also highlight the importance of comprehensive clinical examination and appropriate investigations for early detection and proper treatment of such young patients with ACG.

Keywords: Sturge-Weber syndrome, Roach's type II variant, glaucoma, angle-closure glaucoma, young adult, laser peripheral iridotomy

Sturge-Weber syndrome (SWS) is a neurocutaneous disorder characterized by unilateral facial cutaneous venous dilation (port-wine stain), leptomeningeal capillary-venous malformation and vascular abnormalities of the eye. Vascular abnormalities can affect any portion of the eye, including the eyelid, orbit, conjunctiva, episclera, ciliary body, retina and choroid. Glaucoma occurs in 30% to 70% of individuals of SWS, is usually unilateral and often diagnosed in infancy, though it can also develop later.[1] Theories regarding the mechanism of glaucoma in eyes with SWS are developmental anomalies of the anterior chamber angle and elevated episcleral venous pressure, each leading to aqueous outflow obstruction.[2] The Roach scale is often used for the classification of SWS.[3]

Angle-closure glaucoma (ACG) is rare in young adults. The current knowledge of ACG in young patients needs to be improved. Young patients presenting with ACG are likely to have different etiologies, which are not very well understood.[4]

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Here we report an unusual case of bilateral ACG in a 24-year-old man with unilateral Roach's type II SWS.

CASE PRESENTATION

A 24-year-old man presented to us with headache, and decreased vision in his left eye (LE) for 6 months. He was on four antiglaucoma medications (bimatoprost 0.03%, timolol maleate 0.5%, brimonidine tartrate 0.2% and brinzolamide 1%) in his right eye (RE) for 6 months. He had undergone a diode laser cyclophotocoagulation in his LE 5 years ago elsewhere. He had no family history of glaucoma. He had a capillary hemangioma on the left half of his face involving the fifth nerve dermatome, which had been present since birth (Fig. 1). The patient had no history of seizures or paretic episodes and was not on systemic medications. He also provided reports of a magnetic resonance imaging (MRI) of the brain, which did not reveal any leptomeningeal involvement.

On examination, the corrected distance visual acuity was 20/20 in RE with no perception of light in LE. The intraocular pressure (IOP) was 23 mmHg and 19 mmHg on the Goldmann applanation tonometer in RE and LE, respectively. Anterior segment examination of RE revealed a clear cornea, shallow anterior chamber (Van Herick Grade 1), round reacting pupil and a clear crystalline lens (Fig. 2a). LE showed dilated tortuous episcleral vessels, clear cornea, shallow anterior chamber, relative afferent pupillary defect and a clear crystalline lens (Fig. 2b). Gonioscopy revealed Shaffer

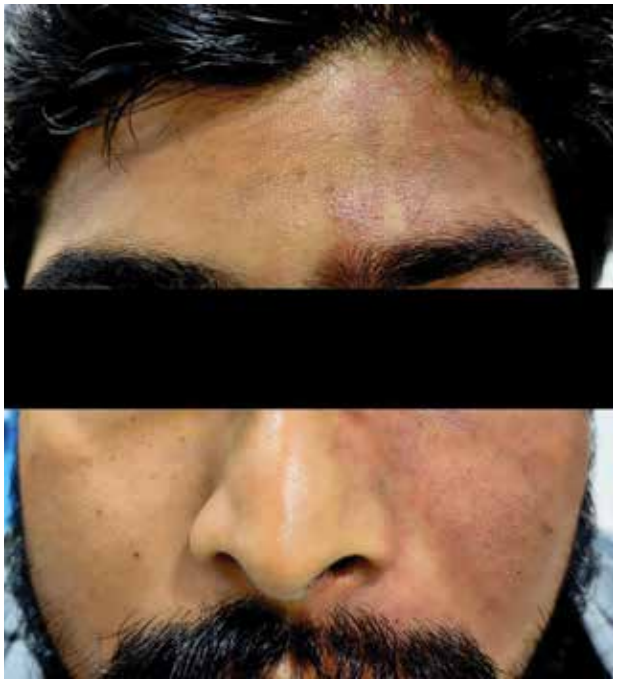

Figure 1. Port-wine stain on the left half of the face.

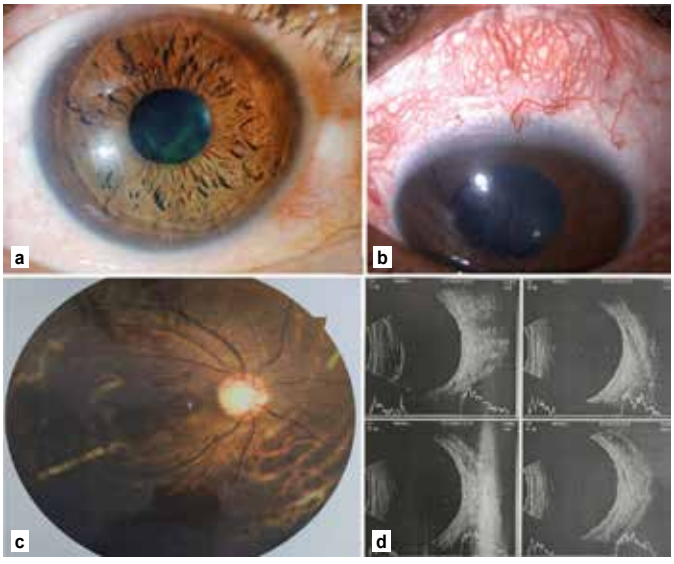

Figure 2. (a) Slit-lamp photograph of right eye; **(b)** Slit-lamp photograph of left eye showing dilated tortuous episcleral vessels; **(c)** Fundus photograph of right eye showing a cup-disk ratio of 0.7 with no localized areas of neuroretinal rim loss and normal macula and **(d)** B-scan ultrasonography within normal limits.

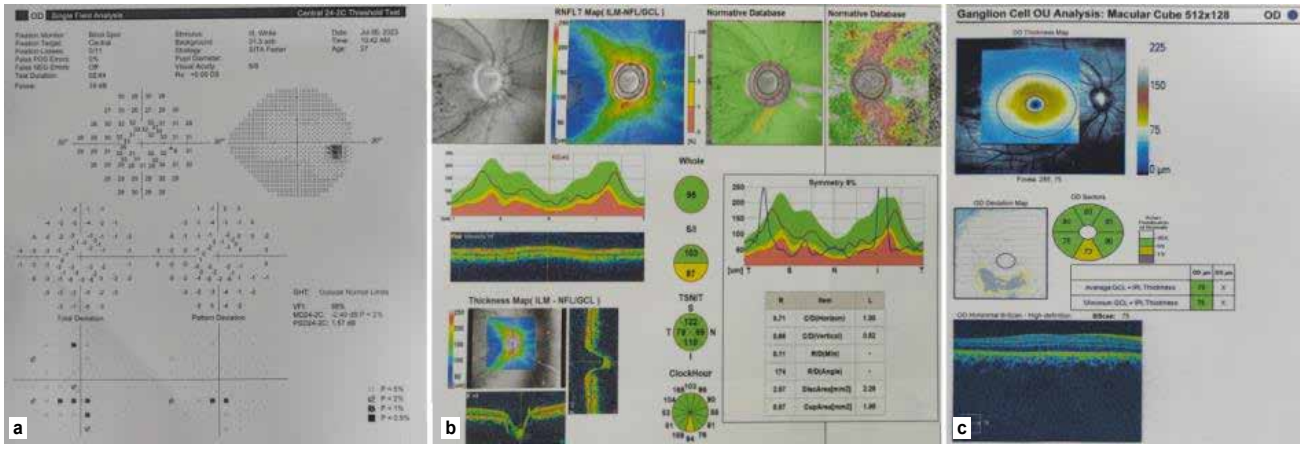

Figure 3. Right eye **(a)** Swedish Interactive Threshold Algorithm 24-2C program revealing a scotoma in the paracentral area; **(b)** OCT showing retinal nerve fiber layer thickness in different quadrants and **(c)** Ganglion cell complex thinning in the inferior quadrant.

grade with 180 degrees synechial angle closure in RE and total synechial angle closure in LE. Undilated fundus examination showed a cup-disk ratio of 0.7 with no localized areas of neuroretinal rim loss and normal macula in RE (Fig. 2c) and glaucomatous optic atrophy in LE. The central corneal thickness was 481 μm and 478 μm in RE and LE, respectively. B-scan ultrasonography of both eyes was within normal limits (Fig. 2d). The axial length was 21.80 mm and 21.92 mm in RE and LE, respectively. Ultrasound biomicroscopy of BE showed no signs of a forward shift of the lens-iris diaphragm, anterior rotation of the ciliary process, choroidal effusion or ciliary body swelling.

A provisional diagnosis of Roach's type II SWS with bilateral ACG was made based on clinical findings. A neodymium-doped yttrium aluminum garnet (Nd:YAG) laser peripheral iridotomy (LPI) was performed in RE to relieve the pupillary block. One hour later, the IOP came down to 18 mmHg in RE. At 1 week follow-up, the IOP was 17 mmHg in RE, and the LPI was patent.

The RE visual field test was performed using Humphrey Field Analyzer (HFA), Swedish Interactive Threshold Algorithm (SITA) 24-2C program, which revealed a scotoma in the paracentral area (Fig. 3a). A dilated fundus examination revealed no additional findings.

Optical coherence tomography (OCT) of RE showed a retinal nerve fiber layer thickness of 95 μm (average), 103 μm (superior quadrant) and 87 μm (inferior quadrant) (Fig. 3b). The ganglion cell complex also showed thinning inferiorly (Fig. 3c). The investigations established the diagnosis of unilateral SWS (Roach's type II variant) with ACG, and the patient was continued on two antiglaucoma medications.

DISCUSSION

Glaucoma in SWS is typically congenital, with buphthalmos related to chamber angle malformation, as in other types of congenital glaucoma. In juvenile and adult SWS, the alteration of trabecular meshwork Schlemm canal complex and persistence of Streeter primordial vascular plexus, leading to episcleral venous pressure increase, has been described as the cause of glaucoma development.[2]

ACG is a rare presentation in SWS, which has been reported as a consequence of ectopia lentis, posterior scleritis, chronic uveitis and alteration of the ciliary body configuration secondary to diffuse choroidal hemangioma.[5-9] However, unlike our case, all these case reports had a unilateral secondary angle closure mechanism associated with SWS. In the present case, the patient had ACG in the contralateral eye, too and all possibilities of a secondary angle closure mechanism were ruled out with the help of investigations. The undiagnosed angle closure component superimposed with elevated episcleral venous pressure might in fact have been responsible for development of glaucomatous optic atrophy in the LE.

Another unique feature of this case report is the presentation of ACG in a young patient. There are limited studies about the etiologies of angle closure in young patients. Most of them were scattered cases except the ones by Gao et al and Ritch et al.[4,10] Primary ACG, uveitis and anterior segment dysgenesis were the common three etiologies of ACG in the study by Gao et al, which accounted for 32.6%, 20.3% and 15.1% of the total patients (463 eyes), respectively. Other known etiologies included iridocorneal endothelial syndrome, neovascular glaucoma, nanophthalmos, retinitis pigmentosa, spherophakia, bestrophinopathy, persistent fetal vasculature, iridociliary cysts, congenital retinoschisis, Marfan's syndrome, retinopathy of prematurity, familial exudative vitreoretinopathy, congenital retinal folds, Coat's disease and neurofibromatosis.[4] In our case, we carried out a comprehensive clinical examination and investigated systematically to rule out the known secondary etiologies of ACG.

CONCLUSION

To the best of our knowledge, this is the first report of a case of SWS associated with bilateral ACG in a young patient. A comprehensive clinical examination and appropriate investigations can identify most of the etiologies of ACG in young patients, which helps in early detection and timely treatment.

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The manuscript has been read and approved by all the authors, the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

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BRIEF COMMUNICATION

Optimizing Finerenone Therapy: A Comprehensive Review Using the "Finerenone Pentad"

SOURABH SHARMA*, SANJAY KALRA†

ABSTRACT

Chronic kidney disease (CKD) is a pressing global health concern, often intertwined with comorbid conditions such as type 2 diabetes mellitus (T2DM) and cardiovascular complications. Managing CKD in T2DM patients requires a multifaceted approach, and emerging therapeutic options are increasingly essential. Finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, has shown considerable promise in addressing the intricate cardiorenal needs of these patients. To maximize the effectiveness of this therapy, we propose the approach of "Finerenone Pentad" which can be utilized as a checklist while starting and subsequently monitoring the finerenone therapy. This structured approach offers guidance on patient selection, monitoring and outcome evaluation, ensuring a holistic approach to the care of individuals with T2DM and CKD.

Keywords: Chronic kidney disease, type 2 diabetes, selective nonsteroidal mineralocorticoid receptor antagonist

Chronic kidney disease (CKD), often exacerbated by the presence of type 2 diabetes mellitus (T2DM), represents a challenging medical condition, both for patients and health care providers.[1] In the search for therapeutic solutions, finerenone has emerged as a promising option.[2-4] This selective nonsteroidal mineralocorticoid receptor antagonist (MRA) addresses the cardiovascular and renal complications frequently encountered in T2DM patients with CKD.[2] The concept of "Finerenone Pentad" framework provides a comprehensive strategy for optimizing patient selection, monitoring and outcome assessment, with the ultimate aim of enhancing patient care (Table 1 and Fig. 1).

THE PATIENT SELECTION PENTAD

In the first component of the "Finerenone Pentad", the focus is on selecting the most suitable patients for finerenone therapy. To qualify for this treatment, individuals should present a combination of specific inclusion and exclusion criteria.

- **Inclusion criteria:** These encompass five crucial points, including a diagnosis of T2DM with CKD, potassium levels ≤5 mmol/L, estimated glomerular filtration rate (eGFR) ≥25 mL/min/1.73 m², a urine albumin-to-creatinine ratio (UACR) of ≥30 mg/g and men and women above ≥18 years.[2-4] These criteria ensure that the therapy is directed toward patients who stand to benefit the most from finerenone's cardiorenal protective effects.
- **Exclusion criteria:** Five specific factors necessitate the exclusion of certain patients. These encompass those already receiving spironolactone or eplerenone, concomitant use with strong CYP3A4 inhibitors, pregnant or lactating patients, those with severe hepatic impairment (Child-Pugh C), and those diagnosed with adrenal insufficiency.[2-5] These exclusions help prevent potential complications and ensure patient safety.
- **Universal nondiscriminatory criteria:** Apart from the defined inclusion and exclusion criteria, there is no requirement for additional considerations when prescribing finerenone. The medication can be administered irrespective of the patient's glucophenotype (including glycated hemoglobin [HbA1c] levels and T2D duration),[6] barophenotype,[7] concomitant therapy for diabetes (sodium-glucose cotransporter-2 inhibitor [SGLT2i]/insulin/glucagon-like peptide-1 receptor agonist [GLP-1RA]),[6,8,9] atherosclerotic cardiovascular

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Table 1. The Pentad of Finerenone

Selection Pentad		
5 points for inclusion	**5 points for exclusion**	**5 points regardless**
• T2DM with CKD	• With spironolactone/eplerenone	• Glucophenotype
• Potassium ≤5 mmol/L	• Strong CYP3A4 inhibitors	• LVH and HF status
• eGFR ≥25 mL/min/1.73 m^2	• Pregnancy/Lactation	• Concomitant therapy for diabetes: SGLT2i/insulin therapy/GLP-1RA
• UACR ≥30 mg/g	• Severe hepatic impairment (Child-Pugh C)	• ASCVD status
• Men and women ≥18 years	• Adrenal insufficiency	• Barophenotype
Monitoring Pentad	**Outcome Pentad**	
• Serum potassium	• Reduced risk of ESKD by 1/5	
• UACR	• Reduced risk of HHF by >1/5	
• eGFR	• Reduced UACR by 32%	
• Blood pressure	• Reduced cardiovascular mortality risk by 12%	
• Serum creatinine	• Low clinical impact of hyperkalemia with incidence rate of permanent discontinuation at 1.7%	

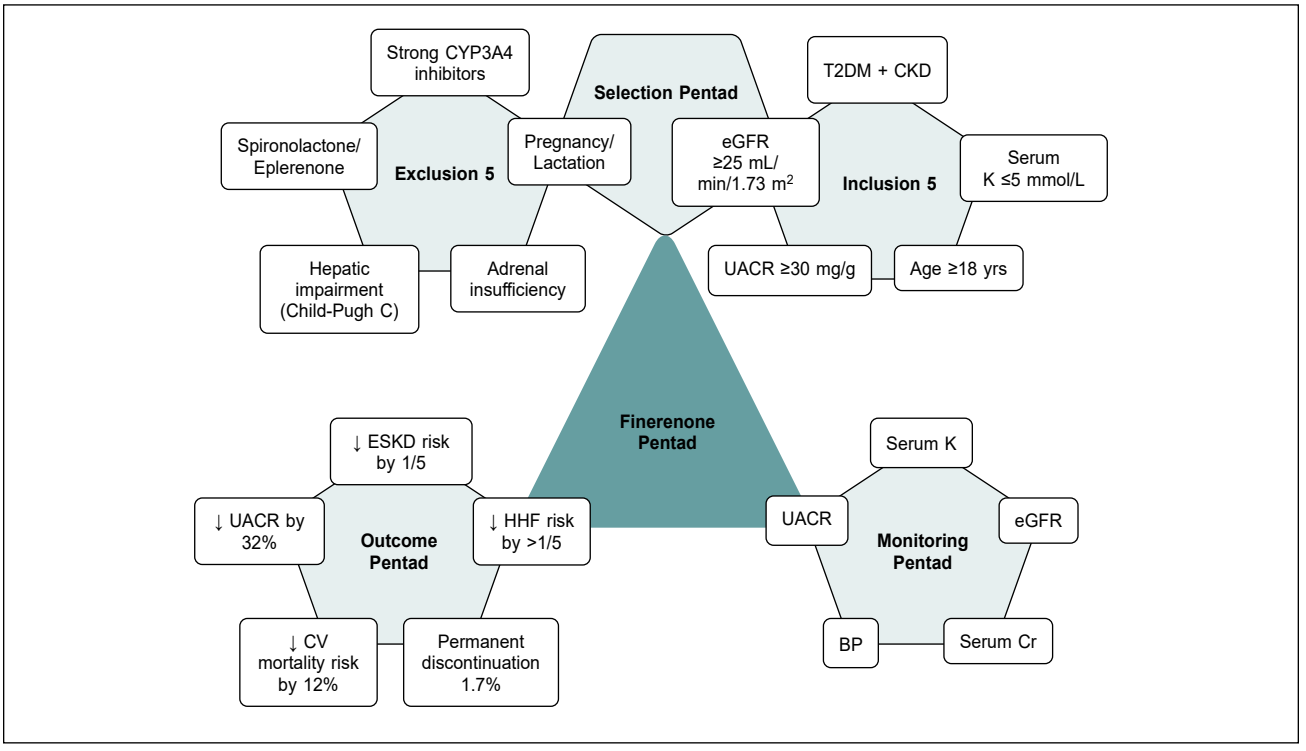

Figure 1. Finerenone Pentad.

disease (ASCVD),[10] left ventricular hypertrophy (LVH) and heart failure (HF) status.[11,12]

THE MONITORING PENTAD

Upon selecting patients for finerenone therapy, the monitoring phase incorporates consideration of a few specific parameters. The following aspect of the framework delineates five essential factors that health care professionals should observe during the treatment course to assess and monitor the prognostic outcomes of the patients.

- **Serum potassium:** Due to its distinct structure and mode of action (MoA), the rates and intensity of hyperkalemia is significantly lower compared to steroidal MRA (Spironolactone) as noted in Phase II clinical trials and Amber like post hoc subanalysis.[13,14] However, regular monitoring is imperative to mitigate potential adverse events.

The proposed potassium monitoring protocol suggests an initial assessment after 1 month of drug initiation to allow for optimal stabilization. Subsequent evaluations, following the standard protocol, are recommended every 4 months if the patient remains stable. In the event of potassium levels going beyond 5.5 mmol/L, it is advised to withhold the drug for a minimum of 72 hours and reintroducing it when levels fall below 5 mmol/L.[2-4]

- **Blood pressure:** Hypertension is a common concern in CKD patients. Regular blood pressure monitoring is essential to maintain optimal cardiovascular health, as well as to monitor the control of hypertension.[15] Finerenone is noted to cause a mild reduction in blood pressure levels to the tune of 3-4 mmHg in the doses recommended for CKD with T2DM[3] as opposed to steroidal MRAs[13] and is not a primary therapeutic objective, which hinges primarily on its anti-inflammatory and antifibrotic properties.
- **UACR:** It offers valuable insights into kidney function and the progression of kidney disease.[16] Regular assessments enable health care providers to gauge the effectiveness of finerenone therapy in slowing the deterioration of renal function.
- **eGFR:** eGFR is a critical parameter for assessing kidney function.[16,17] Continuous monitoring helps clinicians make necessary adjustments to therapy and ensures that the treatment aligns with the patient's renal status.
- **Serum creatinine:** Regular assessments of serum creatinine levels provide crucial information about kidney function and the impact of therapy.[18] This parameter aids health care professionals in gauging the patient's renal health over time.

eGFR and serum creatinine are important parameters for assessment of renal function alongside UACR.[16-18] The use of finerenone demonstrates a potential reduction in the decline of eGFR within 12 months. However, a mild initial eGFR decline of 3-4 mL may occur in the first 1-4 months of finerenone initiation, this typically remains within 30% mirroring the pattern seen with many renal protective drugs. There have been no increased incidences of acute kidney injury noted with finerenone in the Phase III clinical trials.[2,4]

The transient decline in GFR noted with many reno-protective drugs such as angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) or SGLT2i is a pharmacological effect leading to a new physiological renal function set point.[19]

Patient education plays a really crucial role here so as to prevent undue alarm, as this initial dip aligns with the drug's long-term renal stabilization effect.

THE OUTCOME PENTAD

The final component of the "Finerenone Pentad" outlines specific outcomes that therapy aims to achieve or evaluate during the treatment process. These outcomes are quintessential in assessing the success of finerenone therapy.

- **Reduced risk of ESKD:** A primary objective of finerenone therapy is to slow down the progression of kidney disease and subsequently the risk of end-stage kidney disease (ESKD), which has been seen to be reduced by 20%.[2,3] ESKD poses significant challenges for patients and is often associated with a reduced quality of life.[20] The reduction in ESKD risk represents a major benefit for individuals receiving this treatment.
- **Reduced risk of HHF**: Hospitalization for heart failure (HHF) is a critical concern in patients with T2DM and CKD.[21] Therapy aims to reduce the risk of HHF by more than 20%,[2,3] further improving the patient's quality of life and reducing the burden on health care resources.
- **Reduced UACR:** Another key outcome is the reduction in UACR by 32%,[3] and this change is seen within 1-4 months of initiation with finerenone and is sustained. This decrease signifies an improvement in kidney function and a slowing of kidney disease progression as well as provides significant cardiovascular risk benefit.
- **Reduced cardiovascular mortality**: In addition to renal benefits, finerenone therapy aims to lower cardiovascular mortality risk by 12%[22] and sudden cardiac death by 25%.[22] Cardiovascular events are a major cause of morbidity and mortality in this patient population,[23] and this reduction represents a significant improvement in overall patient outcomes.
- **Low clinical impact of hyperkalemia**: Managing hyperkalemia is a common concern with MRAs.[2] Despite a hyperkalemia incidence rate of 14% compared to placebo in FIDELITY analysis, clinical impact rates were minimal, with a specific incidence rate of permanent discontinuation set at 1.7%.[3] With an average increase of 0.2 mmol,

only 4.5% of the patients exceeded a potassium level of 6 mmol/L.[24] This ensures the safety and tolerability of the treatment.

RECOMMENDED POSITIONING OF FINERENONE FOR CARDIORENAL PROTECTION

Over the past few years, there has been a notable paradigm shift in the management of patients, from an organ-specific strategy to a more holistic patient-centric approach, with guidelines recommending regular routine screening of individuals with T2D using UACR and eGFR for early diagnosis of CKD and cardiovascular risk, along with a multifactorial approach towards management. In addition to the traditional standard of care including lifestyle modifications, glycemic control, blood pressure regulation and lipid management, which form the cornerstone/foundation of therapy, agents conferring cardiovascular and kidney benefits such as ACEIs/ARBs, SGLT2i and finerenone have firmly established themselves as the "three pillars" of therapy for slowing kidney disease progression and reducing development of heart failure and risk of cardiovascular death in patients with CKD in T2D, with a Level A recommendation for these drugs.[25-28] Nonsteroidal MRAs like finerenone are now recommended along with other medications for cardiovascular and kidney protection rather than as alternatives when other treatments have not been effective.[26]

A proposed approach recommends optimizing the dose of ACEI/ARB to a maximally tolerated level initially and subsequently introducing the other two drugs, i.e., Finerenone and SGLT2i with at least a week's interval in between to allow for equilibration of kidney function before the addition of the next agent.[28] Early initiation of combination therapy with this triad is advocated due to their distinct yet complementary MoA facilitating a more comprehensive disease management approach.[29]

CONCLUSIONS

The "Finerenone Pentad" is a comprehensive, patient-centric framework that empowers health care professionals to provide high-quality care for individuals with T2DM and CKD. By following the selection, monitoring and outcome criteria, clinicians can offer a well-rounded approach to address the complex cardiorenal needs of these patients.

In conclusion, this framework allows for the effective optimization of finerenone therapy. The structured approach empowers health care providers to make data-driven decisions, targeting the reduction of ESKD, HHF, cardiovascular mortality and other complications while ensuring the safe and effective management of hyperkalemia.

Author Contributions

All authors contributed substantially to the article concept and were accountable for the accuracy of the information contained in the article.

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Data Availability

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Competing Interests

Pravin Manjrekar, Aparajita Praharaj and Amaninder Mann are employees of Bayer.

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Medicolegal Insight

SURGERY PERFORMED ON THE WRONG PATIENT IS A 'NEVER EVENT'

A patient who was hospitalized in a dedicated Trauma Centre run by the Delhi government with head and face injuries that he sustained in an accident, instead underwent surgery under general anesthesia for a fractured leg, as reported in TOI. The surgeon mistook him for another patient admitted in the same ward who had a leg fracture. A small hole was drilled into the patient's right leg to put a pin. As the procedure had been done under general anesthesia, the patient could not realize or object to it. However, the pin was removed within hours following a corrective surgery after it was brought to the attention of the authorities. A committee examined the case found merit in the allegations and a disciplinary action was initiated against the doctor, a senior resident, who has been barred from conducting surgeries without supervision with immediate effect.

Res ipsa loquitur is a Latin term, which literally translates as "the thing speaks for itself". The doctrine of *res ipsa loquitur* is a rule of evidence in cases of medical negligence. It infers negligence from the very nature of an accident or injury in the absence of direct evidence on how any defendant behaved. *Res ipsa loquitur* is not applicable when determining the liability for criminal negligence; it applies only in cases of civil negligence.

To prove medical negligence, usually three components have to be established:

- There was an element of duty to be performed
- There was breach of duty
- Resultant damage.

If the patient is not harmed by the physician's error, then the patient cannot recover damages arising out of the error.

This case answers 'yes' to all the three components of medical negligence: there was a duty of care, there was a breach in the duty of care and the patient did suffer damage as a direct result of the breach.

In *res ipsa loquitur*, these three components of medical negligence elements are inferred from an injury that does not ordinarily occur without negligence, i.e., negligence is evident and the complainant does not have to prove anything as the "thing proves itself" as also in this case.

This is a medical error and can be classified as a 'never event', i.e., event that should never occur under any circumstance. Never events are defined as adverse events that are serious, largely preventable, and of concern to both the public and health care providers for the purpose of public accountability. They are usually a direct result of a negligent action and no trial of expert's evidence is necessary

The US National Quality Forum has defined 29 never events segregated into seven categories: surgical, product or device, patient protection, care management, environmental, radiologic and criminal.

"Surgery or other invasive procedure performed on the wrong patient" is included in list of surgical never events along with "surgery or other invasive procedure performed on the wrong body part, wrong surgical or other invasive procedure performed on a patient, unintended retention of a foreign object in a patient after surgery or other procedure".

The World Health Organization (WHO) has developed a Surgical Safety Checklist, *to be read out loud*, to decrease errors and adverse events for use in any operating theatre environment. The checklist has three phases as below:

"Sign In": Before induction of anesthesia

- Has the patient confirmed his/her identity, site, procedure and consent?
- Is the surgical site marked?
- Is the anesthesia machine and medication check complete?
- Does the patient have a: Known allergy, Difficult airway/aspiration risk or Risk of >500 mL blood loss (7 mL/kg in children)?

"Time Out": Before start of surgical intervention

- Have all team members introduced themselves by name and role?
- Surgeon, Anesthetist and Registered Practitioner verbally confirm: What is the patient's name? What procedure, site and position are planned?
- Anticipated critical events (surgeon, nurse, anesthetist)
- Has the surgical site infection (SSI) bundle been undertaken? Antibiotic prophylaxis within the

last 60 minutes • Patient warming • Hair removal • Glycemic control

- Has venous thromboembolism (VTE) prophylaxis been undertaken?
- Is essential imaging displayed?

"Sign Out": Before any member of the team leaves the OR

- Registered Practitioner verbally confirms with the team:
  - Has the name of the procedure been recorded?
  - Has it been confirmed that instruments, swabs and sharps counts are complete (or not applicable)?
  - Have the specimens been labeled (including patient name)?
  - Have any equipment problems been identified that need to be addressed?
- Surgeon, Anesthetist and Registered Practitioner: What are the key concerns for recovery and management of this patient?

However, when deciding the quantum of punishment, the mitigating circumstances need to be considered.

Does the hospital have a protocol in place to avoid such mistakes? Generally, a minimum of two ID marks are required to be checked at the time of surgery. More than 1 patient can have the same name; room numbers may not be reliable as an identification mark. Matching of HUID no. is important.

Being overworked, lack of resources and infrastructure, insufficient staff, etc. is no excuse for not following such a checklist.

There should be guidelines and/or protocols in place, which should be strictly implemented. If there are no guidelines, then there is an urgent need to develop them as per requirements. The checklist must be completed for each patient who undergoes a surgery, including under LA. It also must be documented in the patient chart.

By following these few but crucial steps, such errors can be minimized. It also ensures effective team work.

This mistake is not just that of the doctor alone. It is also a result of system failure and administration error.

SOME COMMON MISTAKES IN TAKING MEDICINES

- **Prescribing liquid medications in teaspoons and tablespoons:** A teaspoon (tsp) can be confused with a tablespoon (tbsp). Their sizes may vary. Hence, all liquid medications should be prescribed in milliliters (mL) and they should be taken with a dosing device such as a small cup which should have mL markings.
- **Pill splitting:** Tablets that are not scored should not be split into two. They can crumble or are divided into unequal halves affecting the dose strength. Sustained or extended-release tablets and enteric- or film-coated tablets are generally not considered appropriate for tablet splitting. Film coating masks taste; therefore, splitting film-coated tablets may unmask the taste.
- **Sound-alike drugs can cause confusion** e.g. a hypertensive patient called up his family physician who asked him to take Amlopress AT but the patient took amlopress 80 mg. After sometime, he developed dizziness, flushing, palpitation, nausea, abdominal pain. Another example of sound-alike drugs is the patient received Isoprin IV in place of Isoptin and nearly died.
- **Misinterpreting decimal points**: *Using a trailing zero after a decimal point*, e.g., do not write 5.0 mg. There are chances that the patient may get 50 mg; 5.0 mistaken as 50 mg if the decimal point is not seen. *Lack of a leading zero before the decimal point*, if the dose of a drug is less than one, may cause a decimal point to be missed. E.g., writing .25 mg may result in the patient taking 25 mg instead, so write 0.25 mg.
- **Mistaking "U" as zero**. Do not write 'U' for units; always write the complete word 'units'. E.g. 4U insulin may be mistaken to be 40 units of insulin when the doctor meant 4 U (4 units).
- **8-2-8 mistake:** The time interval should be written more clearly as 8 am 2 pm 8 pm. Or, the patient may consider it to be the number of tablets to be taken 8 in the morning, 2 in the afternoon and again 8 at night.
- **Taking medicines with inadequate quantity of water or lying down immediately after taking the drug** can cause pill esophagitis by direct esophageal mucosal injury. It is commonly seen with drugs such as nonsteroidal anti-inflammatories (NSAIDs), tetracycline, doxycycline, alendronate, antiviral drugs, iron supplements.
- **Some medicines need to be taken "before meals" or "on an empty stomach"** because food

can prevent absorption of some medicines and reduce their effectiveness. E.g., Levothyroxine and rifampicin should be taken on an empty stomach.

- **Taking medicines with fruit juices:** Grapefruit, orange, and apple juices decrease the absorption of many drugs such as fexofenadine, cancer chemotherapy (etoposide), antibiotics (ciprofloxacin, levofloxacin), itraconazole, antihypertensives (atenolol), immunosuppressant (cyclosporine)
- **Skipping doses:** This may be dangerous especially with antiepileptic drugs or anticoagulants.

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Severe Maternal Morbidity and Risk of Recurrence

Women who develop severe morbidity during the first pregnancy are at significant risk of experiencing a recurrence of morbidity in a subsequent pregnancy, suggests a new study of over 8,00,000 women from Quebac, Canada published in the *American Journal of Obstetrics & Gynecology*.[1,2] Women with cardiac complications or uterine rupture at first delivery were particularly at risk.

Women who had at least two hospital-based singleton childbirths between 1989 and 2021 were included in this study. These women had experienced a complicated first delivery with severe maternal morbidity from 20 weeks of gestation up to 42 days postpartum. The aim of this study was to determine the impact of severe maternal morbidity in the first pregnancy on the risk of severe maternal morbidity in the second delivery. Various types of severe maternal morbidity examined included severe pre-eclampsia or eclampsia, uterine rupture, severe obstetrical hemorrhage, acute heart failure, acute renal failure or dialysis, cerebrovascular accidents, shock, embolism, sepsis, disseminated intravascular coagulation, assisted ventilation, surgical complications, intensive care unit admission and other grave disorders.

A total of 8,19,375 participants were included in the study and 43,501 (3.2%) had suffered severe morbidity at the time of the first delivery. Among these, the recurrence rate of severe maternal morbidity, which was the primary study outcome, was 65.2 per 1,000 deliveries in women with severe maternal morbidity in the earlier delivery compared to 20.3 per 1,000 deliveries in women with no history of severe morbidity. The adjusted relative risk (aRR) was 3.11. The aRR for recurrence was 2.94 with one type of severe maternal morbidity, 4.06 with two types of maternal morbidity. Women who had experienced 3 or more types of severe maternal morbidity were at the highest aRR of experiencing a severe maternal morbidity in the subsequent delivery compared to women who did not have any maternal morbidity. The aRR was 5.50. History of cardiac complications in the first delivery was associated with the highest risk of severe maternal morbidity in the next delivery with aRR of 5.06. Those who had severe pre-eclampsia or eclampsia were also at similar elevated risk with aRR of 5.85. The aRR was highest for cardiac arrest at 7.27 with uterine rupture following (aRR 6.22).

Women with severe maternal morbidity in the first delivery were 3 times more likely to experience acute renal failure, severe hemorrhage, embolism, shock and disseminated intravascular coagulation, and need for intensive care in the next delivery. Those who had needed intensive care or assisted ventilation in the earlier pregnancy were 4 times more likely to experience severe maternal morbidity again in a subsequent pregnancy.

This study showed that the occurrence of severe maternal morbidity in a previous pregnancy increased the risk of severe maternal morbidity recurrence in the next pregnancy. Women with cardiac complications or uterine rupture at first delivery were most likely to experience a recurrence. It has also determined the association of different types of morbidities with the risk of recurrence. These findings highlight the need for pre-pregnancy counseling for informed decision making about future pregnancies. Monitoring of maternal health in such cases must be continuous and not stop at childbirth or postpartum period. Also, they must be kept under close observation in their subsequent pregnancy.

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HCFI Dr KK Aggarwal Research Fund

Minutes of an International Weekly Meeting on "Men's Health, the New Superspecialty"

Dr Raman Tanwar, *MBBS, MS, FMAS, MCh (Urology), National Expert in Andrology, Urology, and Men's Health*

September 9, 2023 (Saturday, 9.30-10.45 am)

- The X chromosome has 3,000 genes, while the Y chromosome has 50 genes. It is said that the Y chromosome is dwindling. There will only be women with male characters. This could happen in 1,000 years from now.
- Humans could face extinction as sperm counts decline. The average sperm count of men in 1973 was 101 million sperms per mL of semen. This has declined to 49 million sperms per mL of semen in 2018.
- There is a gap between men and women. In India, men are dying 2 to 3 years earlier than women. This is the same globally.
- When we talk about gender equality, we should also talk of gender equity. Women empowerment has been pushed to the forefront. But men also need to be supported. Only then, we will have an equitable society. In Russia, there is a 10- to 12-year gap in longevity between men and women.
- Men have enjoyed privileged health status in ancient times, which was a patriarchal society. Health of men was correlated with strength of the nation. Woman was regarded as an inferior immature version of man.
- Male needs are different in terms of health. Men have a higher threshold. They usually do not go the hospital till the problem becomes more severe. They are more self-reliant and fear sharing as it is linked to livelihood. Substance abuse leads men to a downward spiral.
- They battle loneliness, work stress, family responsibility. They rarely tell and the reason for this is who can they talk to.
- Women interact with health care at several points in their lives. But there are no other checkpoints for men aside from childhood visits and if they develop any disease later on in life.
- There are too many misconceptions and judgementalism even by misguided professionals. Sexual health and hygiene has to start from an early age and misconceptions and taboos broken.
- The triggers to interaction with health care for men are unable to work or sexual problems.
- In a survey of more than 500 men, they were asked who is a doctor for men; 92% did not know whom to meet, while most knew that doctors for women are gynecologists. Eighty-four percent felt that men's health means sexual health, 76% needed someone to treat them and 21% had already been to a quack.
- When men do not know whom to visit, then they do not get the right treatment and the result is incomplete cure.
- There is a direct implication of men's health on the family. Poor health leads to financial problems, which affect the resources as they are diverted in health care. This affects children and their education. There are other problems such as substance abuse, domestic abuse; smoking affects other family members (passive smoking).
- Men face occupational hazards. Early deaths or disabilities would leave many families unsupported.
- Men's health is not just andrology or sexology. It also caters to specific disease of organs present in men such as prostate, testes and other common diseases such as stroke, heart disease, metabolic syndrome.
- Men's health is a subspecialty of medicine related to the study and management of diseases, behaviors and social conditions specific and more common in men. The definition is still evolving.
- There is a need to create a strategy for men's health. Every visit is important as men do not visit health care very often. It is a golden opportunity and the risk factors should not be missed. It goes beyond health. It is a nation-building exercise so that men remain healthy. Men will not go to different doctors. So, the strategy should be to provide a one-stop shop (holistic therapy), which provides a comfortable experience.
- Men's health is a continuum through comorbidities. Lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) are a part of the bigger picture. ED is bothersome, but endothelial dysfunction is hidden and can be fatal. ED can be used to detect endothelial dysfunction.

- Sexual dysfunction is a part of metabolic syndrome. Patients will come very early if they have ED. But they will come very late for problems like diabetes mellitus (DM), hypertension (HT), insulin resistance (IR), dyslipidemia.
- A men's health expert can evaluate men for sexual health issues. Treat every problem of men holistically and provide basic management of ED (Lifestyle, medication, refer/learn, regular follow-up and spread awareness) and establish a men's health clinic.
- Assess sexual history, do a focused examination (general, androgenization, local, multisystemic), laboratory tests (random blood sugar, testosterone, lipid profile), do an oral sildenafil test/audio-visual sexual stimulation (AVSS) response.
- Do a cardiovascular examination. Simple questions like "are you able to climb two flights of stairs?" can help assess the cardiovascular health.
- Re-emphasize lifestyle changes. Make men aware of exercise, weight reduction, quality of diet, smoking cessation, alcohol control, stress reduction. Start with motivation. Prescribing phosphodiesterase-5 inhibitor (PDE5i) on first visit will help. Don't wait for discovering the etiology. Prepare for cerebrovascular accidents.
- Understand the cause of ED. Start with PDE5i/L-arginine/nerve tonics. They can be combined or given as SOS therapy. If they do not work well, then intracavernosal injections can be given. If these do not work, then implants (malleable/inflatable). Lifestyle changes (exercise/low-fat diet) and manage the primary disease.
- The medical management of ED entails consideration of correct patient (age/requirement/marital status/comorbidites/suitability/past usage/degree of ED/economic status/associated sexual dysfunction), which drug (nutraceuticals/sildenafil/tadalafil/vardenafil/udenafil/selective estrogen receptor modulators [SERMs]/testosterone/combination/others), what dose (chronic low/on demand/highest/higher than permitted) and what formulation (pill/strip/mouth dissolving).
- Concomitant use of PDE5i with nitrates is absolutely contraindicated as they potentiate the hypotensive effects of nitrates.
- Concomitant medications that potentially require lower doses of PDE5i include ketoconazole, itraconazole, erythromycin, clarithromycin, human immunodeficiency virus (HIV) protease inhibitors (ritonavir, indinavir), grapefruit juice, cimetidine and antacids.
- Concomitant medications potentially require higher doses of PDE5i include rifampin, phenobarbital, phenytoin and carbamazepine.
- Nitrates should be avoided for 24 hours and 48 hours after an individual has taken sildenafil or tadalafil.
- PDE5i have an additive nitric oxide pathway. With nitrates, they may produce life-threatening hypotension.
- Support the patient with fluid resuscitation and alpha-adrenergic agonists.
- For recurrent angina after sildenafil use, other non-nitrate antianginal agents, such as beta-blockers should be available.
- Sildenafil (100 mg) has also been shown to potentiate the hypotensive effect of amlodipine (5/10 mg) and doxazosin (4 mg).
- Vardenafil (10/20 mg) when concomitantly administered with alpha-blockers (terazosin, tamsulosin) and with nifedipine to healthy volunteers resulted in some subjects experiencing hypotension.
- Any alpha-adrenergic antagonist other than 0.4 mg once-daily tamsulosin is contraindicated as tadalafil (20 mg) significantly enhanced the blood pressure (BP)-lowering effect of doxazosin.
- Lower starting doses are recommended for older men (25 mg for sildenafil and 5 mg for vardenafil. No adjustments for elderly men taking tadalafil.
- If the patient needs more than just the basic evaluation and management, it is best to refer e.g., post-traumatic, post surgery, psychiatric illness, major uncontrolled comorbidity, altered orientation, spinal cord injury, hormonal disturbances (hypogonadism).
- Every men's health specialist has to have a circle of colleagues whom they can refer the patient to for different problems.
- Men should be able to get holistic health when they come to a men's health specialist.
- Men's health is also important for older men.
- Issues related to sexuality and sexual health should be discussed without anxiety or discomfort.
- There is a need to adopt strategies, which create environments that are more supportive of sexuality.
- Health centers should be equipped to handle men's health. They should at least offer screening, if not

treatment. The objective is to cover up the gaps in health care.

- It is easy to start with new checkpoints such as premarital check-up (20-35 years age), executive check-up (30-50 years age) and geriatric (>50 years) recheck-up.
- There should be posters in clinics to encourage men to speak up about their problems. Make the clinics more men's health-friendly places.
- Enlist the services offered such as mental health consult, wellness check-ups, sexual health consult, premarital counseling, lifestyle disease management and executive check-up.
- Educational intervention with involvement of partner helps to improve men's intention to screen and increased screening uptake.
- Men usually do not come forward because men in general have poorer health knowledge than women. They avoid showing weakness to women. They regard screen in as a waste of time. Also, screening facilities are usually cumbersome.
- To increase screening, develop mobile health apps or websites on health screening to reach out to men. More male-sensitive interventions need to be developed, which address male-specific behaviors, interests. Framing of messages is important. Involving partners can help to increase screening. Do screening in a fun way with mainly male workforce.
- Screening should be made a part of policy, which forces men to go for screening.
- To change practice to men's health, understand what is men's health and how is it different. Equip yourself properly with guidelines, resources and peer support. Reform your facility by providing screening opportunities and outpatient sensitization. Associate with men's health for a social cause.
- Strategies to initiate a continuum through ages include establishing points of intervention (entry check-ups and at parenthood), making health an important performance indicator and making health accessible and friendly. It is easy to start small. Offer basic diagnostics (uroflowmetry, ECG). Evening clinic (part time practice) is the easiest way.
- It is important to upgrade to maintain gender ratio (F:M 1:1 and not 10:1). There should be a central National program for men's health similar to mother and child health programs.
- Men's health is yet to make a comeback. There are only a few centers offering this specialized service and very few trained experts. There is ample avenue for training.
- We need to change the way we look at men's health. We have to look at them as a weaker sex and understand that they are not going to come to the clinic again and again (precious visit). See the problem differently, i.e., the problem is only a presentation. Holistic treatment is needed. Provide men friendly facilities.
- Men's health is an opportunity waiting to be taken up. It can be a huge financial success.
- Giving a little time to men's health practice is one way to contribute to this. This entails organizing screening camps, celebrate special days (e.g., November is Prostate Health Awareness month), corporate programs, allocate a budget to men's health, holding camps, include men's health in national and state level programs and introduce checkpoints for interaction with health.
- Awareness is key.
- Future directions include encouraging research and talking more about men's health.

Participants: Dr Akhtar Hussain, South Africa; Dr Ashraf Nizami, Pakistan; Dr Wonchat Subhachaturas, Thailand

Invitees: Dr Monica Vasudev, USA; Dr Mulazim Hussain Bukhari, Pakistan; Dr Colin Goldberg; Dr Asima Rashid; Dr Hamid Manzoor; Dr Zameer Naqvi; Dr Joher Hassan; Dr Milind Joshi; Dr DR Rai; Dr Deepak Jumani; Dr Arun Jamkar; Dr A Muruganathan; Dr Mahadev Harani; Dr Sanchita Sharma, Editor-IJCP Group

Moderator: Mr Saurabh Aggarwal

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

ENDOSCOPIC DRAINAGE AND ABLATIVE OPTIONS FOR PANCREATOBILIARY TUMORS

Dr Randhir Sud, Gurugram

- Endoscopic biliary drainage with a self-expandable metal stent (SEMS) is the standard of care today.
- More than 50% of liver volume must be drained to effectively palliate and avoid atrophic lobe drainage in multifocal hepatic steatosis (MHS).
- Two or more uncovered SEMS are preferred in high-grade hilar tumors. It is important to prevent contamination of segments that have not been drained.
- Endoscopic ultrasound-guided choledochoduodenostomy (EUS-CDS) is preferred if endoscopic retrograde cholangiopancreatography (ERCP) drainage fails or is incomplete.
- Percutaneous transhepatic biliary drainage (PTBD) is a valid option if ERCP fails or in altered anatomy. It is associated with a high success rate (87-100%).
- Intraductal photodynamic therapy (PDT) and possibly endobiliary radiofrequency ablation (eRFA) improve survival.
- Asia Pacific Consensus 2013 advises SEMS for palliation of high-grade MHS if the expected survival of the patient is more than 3 months.
- ESGE Guidelines 2018 recommends uncovered SEMS as a choice of the stent in MHS for palliative drainage. ERCP is the first choice for lower-end and Bismuth I and II. However, there is controversy in the route of drainage (ERCP or PTBD) of the advanced MHS.

CONVENTIONAL TRANSARTERIAL CHEMOEMBOLIZATION FOR HEPATOCELLULAR CARCINOMA

Dr Naveen Kalra, Chandigarh

Surgery is the gold standard for treating hepatocellular carcinoma (HCC). But 70% to 90% of the patients are unsuitable for resection due to extensive intrahepatic tumor involvement, extrahepatic disease and poor liver reserve. In these patients, conventional transarterial chemoembolization (TACE) is considered one of the standard treatment options for patients with HCC. TACE is the blockade of tumorous arterial flow through embolic material, which carries chemotherapeutic drugs.

In this method, the catheter/microcatheter is selectively placed in the hepatic artery via the common femoral artery to visualize the blood vessels supplying the tumor and identify the tumor-feeding arteries. This is followed by infusing a chemotherapeutic drug, such as doxorubicin, emulsified with lipiodol, a carrier of a chemotoxic drug. The viscosity of lipiodol creates a temporary vascular embolization effect. Lastly, particulate agents are injected.

The rationale behind using TACE for such patients are: Tumor-fed primarily from hepatic arteries; intro-arterial injection of anticancer drugs; higher intratumoral concentration; minimize systemic side effects; relatively inexpensive compared to other endovascular techniques.

THE EMERGING ROLE OF SSM AND OTHER NONINVASIVE MODALITIES IN THE DIAGNOSIS AND MANAGEMENT OF PORTAL HYPERTENSION

Dr Shiv K Sarin, New Delhi

- Portal hypertension (PHT) can be accessed via invasive or noninvasive tests.
- Noninvasive tests are promising in predicting the presence of clinically significant portal hypertension (CSPH) and excluding patients not needing endoscopy. Current invasive measures for identifying patients at high risk of CSPH and decompensation include biopsy and hepatic venous pressure gradient (HVPG).
- Developing noninvasive measures for the identification of patients at high risk of CSPH and decompensation includes plasma biomarkers (vWF-AG, APRI, ELF, ICG-r15), liver stiffness measurement (LSM) and spleen stiffness measurement (SSM).
- SSM <21 kPa rules out CSPH, while SSM >50 kPa rules-in CSPH.
- For the assessment of PHT-HVPG is the gold standard; vWF is promising; spleen stiffness is reliable, and machine learning is promising.
- SSM/LSM are promising noninvasive tests for knowing the response to beta-blockers.

MANAGEMENT OF POST LIVER TRANSPLANT BILIARY STRICTURES: ENDOSCOPIC INTERVENTIONS

Dr Manoj K Sahu, Bhubaneswar

- Biliary anastomosis has long been considered the Achilles heel of orthotopic liver transplantation (OLT).
- Biliary strictures are the most frequently described complication, affecting 4% to 15% of patients after liver transplant. It can be anastomotic (85%) or nonanastomotic.
- Anastomotic strictures appear more often in living donor liver transplantation (LDLT) than in deceased donor liver transplant (DDLT), in the percentage of 13% to 36% and 5% to 15%, respectively.
- Prompt and systematic evaluation of abnormal liver enzymes after liver transplant surgery is crucial to identify biliary strictures at an early stage.
- Clinicians are advised to retain a high index of suspicion, especially in the first year after the transplant, and investigate all liver function abnormalities with a magnetic resonance cholangiopancreatography (MRCP) to allow early recognition.
- Endoscopic retrograde cholangiopancreatography should be used as the initial therapy for biliary strictures. Endoscopist must ascertain the full operative details of the biliary and liver anatomy.
- The rendezvous method, magnetic compression anastomosis and peroral cholangioscopy, endoscopic ultrasound guided-biliary drainage (EUS-BD) are options in difficult scenarios.

EUS-GUIDED LIVER BIOPSY AND PORTAL PRESSURE GRADIENT MEASUREMENT

Dr Arka De, Chandigarh

Endoscopic ultrasound-guided liver biopsy (EUS-LB) is a safe alternative to percutaneous and transjugular routes with comparable diagnostic yields. It is very suitable for the biopsy of both the hepatic lobe and can be used to assess the portal pressure gradient (PPG) simultaneously.

The basic steps performed in the EUS-LB technique are:

- Localize avascular path in the liver using gastric cardia in the left hepatic lobe or from D1 in the right hepatic lobe.
- Puncture through gastric or duodenal wall liver using a quick stroke.
- After entering the liver parenchyma, turn on the suction by turning the stop-clock.
- Take around three actuations with the to-and-fro movement of the needle.
- Needle travel: 3 cm course of the needle travels sufficient, but a longer needle can be used if the condition permits.
- Turn off the suction before removing the needle from the liver.

EUS-PPG is found to have a good correlation with the hepatic venous pressure gradient. Mathematically, it can be defined as **"Portal pressure gradient (PPG) = Portal venous pressure - Free hepatic venous pressure."**

Some important tips to remember while performing the EUS-PPG technique are:

- Sedative agents are the Achilles heel of EUS-PPG as they can affect the portal hemodynamic.
- Low doses of midazolam are preferred if needed.
- Entry site of the vessel should be surrounded by adequate liver parenchyma for tamponade.
- When the needle is passed into the hepatic vein, flush the needle with hep-saline before recording the pressure reading.
- Take at least three pressure readings.
- Re-flush the needle before taking the readings.

RADIOLOGICAL INTERVENTIONS IN POST-TRANSPLANT BILIARY STRICTURES

Dr Deepashree T, Chennai

Post-transplant biliary strictures are a known complication after liver transplantation. Following a liver transplant, they occur when there is a narrowing or obstruction in the bile ducts that connect the liver to the small intestine (common bile duct and its branches). These strictures can lead to bile flow impairment, causing symptoms such as jaundice, itching and cholangitis (infection of the bile ducts). Few tips to avoid this complication are avoiding this complication are: RHD not to be clamped to avoid crushing injury back table. Graft to be flushed with the University of Wisconsin or histidine-tryptophan-ketoglutarate solution. A small amount of liver tissue should be left around the right hepatic duct to prevent devascularization, and the complete right hilar plate should be encircled. Also, it has been seen that preventing bile leaks has the potential to reduce the incidence of biliary strictures, apart from the reduction in biliary and fungal sepsis. Using the bile leak test with saline, propofol or intralipid can be beneficial in reducing strictures and sepsis, particularly in the early stage of a program or when biliary reconstruction is complicated.

News and Views

Should Combination Therapy be the First-line of Treatment in Type 2 Diabetes?

Combined therapy with sodium-glucose cotransporter-2 inhibitors (SGLT2i) or glucagon-like peptide-1 receptor agonists (GLP-1RA), compared to either drug alone, is associated with reduced risk of all-cause mortality and cardiovascular disease (CVD), according to a new study published in the journal *Diabetes, Obesity and Metabolism*.[1]

This study retrospectively analyzed data of people with type 2 diabetes receiving insulin to examine the risk of all-cause mortality, hospitalization and cardiovascular outcomes at 5 years following monotherapy with either SGLT2i or GLP-1RA alone or their combination (SGLT2i + GLP-1RA). Out of the 2.2 million patients included, 143,600 received SGLT2i, 186,841 received GLP-1RA, while 108,504 were treated with the combination. The controls received neither SGLT2i nor GLP-1RA.

The risk of all-cause mortality was found to be decreased in all three intervention groups over a period of 5 years with hazard ratios (HR) of SGLT2i 0.49, GLP-1RA 0.47 and combination 0.25.

Similarly, the risks of hospitalization (HR 0.73, 0.69, 0.60) and myocardial infarction (HR 0.75, 0.70, 0.63) were also reduced in SGLT2i arm, GLP-1RA arm and the combination arm, respectively.

At 5 years, treatment with SGLT2i (vs. controls) reduced the risk of all-cause mortality with HR of 0.49. SGLT2i also reduce the risk of hospitalization (HR 0.73), myocardial infarction (HR 0.75), unstable angina (HR 0.79), heart failure (HR 0.73), atrial fibrillation (HR 0.74), stroke (HR 0.75), peripheral vascular disease or PVD (HR 0.79), lower limb amputation (HR 0.69) and chronic kidney disease or CKD (HR 0.79).

Similar trend was noted with GLP-1RA monotherapy (vs. controls) at 5 years with reduction in the risk of all-cause mortality (HR 0.47), hospitalization (HR 0.69), acute myocardial infarction (HR 0.70), unstable angina (HR 0.73), ischemic heart disease or IHD (HR 0.85), heart failure (HR 0.73), atrial fibrillation (HR 0.77), stroke (HR 0.77), PVD (HR 0.89), lower limb amputation (HR 0.66) and CKD (HR 0.90).

Treatment with combination therapy (SGLT2i + GLP-1RA) also reduced the risk of all-cause mortality (HR 0.25), of hospitalization (HR 0.60), acute myocardial infarction (HR 0.63), unstable angina (HR 0.75), IHD (HR 0.84), heart failure (HR 0.60), atrial fibrillation (HR 0.65), stroke (HR 0.69), PVD (HR 0.84), lower limb amputation (HR 0.59) and CKD (HR 0.72) vs. controls.

This study demonstrates that the risk of all-cause mortality and CVD in patients with type 2 diabetes was reduced in all the three intervention arms when compared to the control group. However, the greatest reduction in risk for all-cause mortality was seen with combination therapy. Similarly, the probability of hospital admission was lowest with combination therapy, which also conferred greater cardiovascular protection. Optimal timely glycemic control prevents or delays the onset of diabetes-related macro- and microvascular complications. The antidiabetic drugs should address the "ominous octet" of factors implicated in pathophysiology of type 2 diabetes. They should also be cardioprotective and renoprotective and not just lower blood glucose. SGLT2i and GLP-1RAs are relatively newer antidiabetic drugs, which have also shown extra-glycemic benefits with improvements in cardiovascular and renal outcomes, besides effective glucose-lowering effects in patients with type 2 diabetes, with cardiovascular risk factors or underlying heart disease. Hence, they are game changers in diabetes care. Their combination might potentially provide superior control of blood glucose with low hypoglycemic risk along with cumulative cardiovascular and renal protection.

Reference

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Simple Blood Test for Bipolar Disorder: Study

Researchers at the University of Cambridge created a straightforward blood test to improve the precision of bipolar illness diagnoses, according to a study published in *JAMA Psychiatry*. This test was found to be very helpful when used in conjunction with a digital mental health assessment. It can identify up to 30% of bipolar individuals with accuracy.

Bipolar disorder and major depressive disorder are diseases that have similar symptoms but require

distinct pharmacological treatments; biomarker testing may help physicians differentiate between them.

This study's findings suggest that the blood test can complement existing psychiatric diagnostic methods while shedding light on the biological underpinnings of mental health disorders. Notably, around 1% of the population experiences bipolar disorder, yet nearly 40% of those affected receive a misdiagnosis of major depressive disorder. The researchers utilized samples and data from the Delta study conducted in the UK from 2018 to 2020. The data included information of individuals previously diagnosed with major depressive disorder within the last 5 years, and who were currently displaying depressive symptoms.

The study identified a distinct biomarker signal for bipolar disorder, even after adjusting for confounding factors like medication. The combination of patient-reported information and the biomarker test significantly enhanced diagnostic accuracy for individuals with bipolar disorder, particularly in cases where the diagnosis was less evident.

(*Source: https://www.tribuneindia.com/news/health/simple-blood-test-can-help-diagnose-bipolar-disorder-accurately-study-557857*)

Study: Extreme Heat Linked to More Cardiovascular Death

A study published in *Circulation* suggests that extreme heat will drive an increase in cardiovascular-related fatalities in the US between 2036 and 2065. The impact of underlying health issues and socioeconomic challenges will be disproportionately felt by vulnerable groups, particularly those 65 years of age and older and persons of color. The study projects an increase in summer days with temperatures reaching at least 90 degrees, as indicated by the heat index, which takes humidity into account. As a result, this tendency is anticipated to change. Although extreme heat currently contributes to less than 1% of cardiovascular deaths, the modeling analysis forecasts a change in this pattern. While most individuals can adapt to extreme heat through mechanisms like perspiration, those with underlying health issues, including diabetes and heart disease, face heightened risks of heart attacks, irregular heart rhythms or strokes.

The study's predictions were generated by evaluating county-level data from 48 states between May and September in the years 2008-2019, during which more than 12 million cardiovascular-related deaths occurred. Environmental modeling estimates indicated that the heat index exceeded 90 degrees approximately 54 times each summer. Researchers linked these extreme temperatures to an average of 1,651 annual cardiovascular deaths nationally. Further modeling analyses, incorporating environmental and population changes, anticipate that between 2036 and 2065, there will be about 71 to 80 days each summer with temperatures feeling 90 degrees or hotter. The general population is expected to experience a 2.6-fold increase in heat-related cardiovascular deaths, requiring minimal greenhouse gas emissions. If these emissions increase and are not controlled, then extreme heat would potentially triple the fatality.

(*Source: https://www.daijiworld.com/news/newsDisplay?newsID=1135159*)

Research Reveals Mobile Phone Use Linked to Lower Semen Quality

A University of Geneva study published in *Fertility & Sterility* revealed that frequent mobile phone usage can reduce sperm concentration and total count. However, it found no connection between mobile phone use and sperm motility and morphology.

The study analyzed data from 2,886 Swiss men aged 18 to 22 (recruited between 2005 and 2018) and found a significant decrease of 21% in sperm concentration for those who used their phones more than 20 times a day compared to those who used them less than once a week. Sperm quality is evaluated based on parameters including sperm concentration, total count, motility and morphology. Over the past half-century, numerous studies have reported a decline in semen quality, with sperm count dropping from an average of 99 million per milliliter to 47 million per milliliter. This decrease is believed to result from a combination of environmental factors like endocrine disruptors, pesticides and radiation, as well as lifestyle factors such as diet, alcohol consumption, stress and smoking. Notably, the study did not find a correlation between the position of the phone, such as being in a trouser pocket, and lower semen parameters.

(*Source: https://www.daijiworld.com/news/newsDisplay?newsID=1135820*)

Impact of Surgical Treatment of Endometriosis

Women who undergo surgical treatment for endometriosis had significant improvement in their quality of life on several domains, according to a study published in the journal *Revista da Associação Médica Brasileira*.[1,2]

A total of 102 women with pelvic pain and endometriosis were included in this observational, longitudinal and

prospective analytical study. Their condition had not improved with clinical treatment. These participants, with mean age of 35.96 years, underwent surgical treatment from September 2020 to May 2022. Through this study, the researchers aimed to examine their pre- and post-surgery (3 months and 6 months) quality of life, which was assessed with the help of the Endometriosis Health Profile-30 (EHP-30) questionnaire. The score ranged from 0 to 100; lower scores denoted better quality of life.

Based on the revised endometriosis classification of the American Society of Reproductive Medicine (rASRM), 9 women were categorized has having minimal endometriosis, 18 (17.6%) with mild endometriosis, 35 (34.3%) moderate endometriosis, while 40 (39.3%) women had severe endometriosis. The different surgical procedures adopted were: excision of only endometriotic lesions (20.5%), excision + myomectomy (29.5%), excision + hysterectomy (22.6%), excision + rectosigmoidectomy + hysterectomy (22.5%), excision + myomectomy + rectosigmoidectomy (~5%).

Comparison of the EHP-30 scores before and after the surgery showed that the scores reduced 3 and 6 months after surgery in the central questionnaire (Part 1) and in Sections A, B, C, E and F. Compared to 3 months after the surgery, the scores further reduced 6 months post-surgery.

The mean quality of life score in the central questionnaire (Part 1) before the surgery was 46.67, which reduced to 16.25 at 3 months after surgery and 7.5 at 6 months after the surgery. The scores in Section A (work) before the surgery and 3 and 6 months after the surgery were 35, 10 and 0. Section B (relationship with children) scores reduced to 0 at 3- and 6-months post-surgery compared to the score of 50 before the procedure. The scores in Sections C (Sexual Relations; 15 and 0 vs. 50), E (Treatment; 16.6 and 0 vs. 41.6) and F (Infertility; 25 and 6.25 vs. 50) were found to reduce at 3 and 6 months after surgery compared with before surgery, respectively. Reduction in scores for Section D (Relationship with Physician) was observed 6 months after surgery compared to before surgery.

The severity of endometriosis had no correlation with the EHP-30 quality of life scores before and after surgery. Quality of life is an integral and critical component of management of endometriosis. This study highlights the good prognosis in women who undergo surgery for endometriosis in terms of improved quality of life. The study group comprised of women with "all forms of endometriosis", who underwent different types of procedures. Hence, women who do not respond to medical treatment should be offered surgical treatment to reduce their symptoms thereby improving their quality of life.

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Study: No Increased Miscarriage Risk with Pre-pregnancy COVID Vaccine

A study featured in *Human Reproduction* has confirmed that receiving a coronavirus disease 2019 (COVID-19) vaccine prior to conceiving does not elevate the risk of early or late miscarriage. This study was conducted by Boston University School of Public Health (BUSPH) researchers and is the first to assess the risk of early miscarriage (before 8 weeks' gestation) following COVID-19 vaccination.

The research analyzed COVID-19 vaccination and miscarriage data from 1,815 female participants in the BUSPH-based Pregnancy Study Online (PRESTO). Notably, 75% of these participants had already been given at least one dose of a COVID-19 vaccine before pregnancy. Approximately a quarter of pregnancies ended in miscarriage, with 75% occurring prior to 8 weeks' gestation. However, the study found no increased risk of miscarriage. The risk percentages were as follows: 26.6% for unvaccinated participants, 23.9% for those who received one vaccine dose before conception, and 24.5% for those who completed the full primary vaccine series before conception. For those who completed the vaccine series 3 months before conception, the risk was 22.1%, and for those who received only one dose of a two-dose vaccine before conception, it was 21.1%.

(*Source: https://health.economictimes.indiatimes.com/news/industry/research-shows-covid-vaccination-before-pregnancy-doesnt-increase-risk-of-miscarriage/104886474*)

Benefits of High-flow Nasal Cannula in COPD Patients with Chronic Hypercapnia

Use of home high-flow nasal cannula (HFNC) for chronic hypercapnic respiratory failure in patients with chronic obstructive pulmonary disease (COPD) may reduce acute exacerbations and hospital admissions, according to a recent study published in the journal *Respiratory Medicine*.[1,2]

This study, which was a systematic review and meta-analysis, was conducted by researchers from University of Toronto, McMaster University and Dalhousie University in Canada to investigate if HFNC versus standard care was effective in COPD patients with chronic hypercapnia. Four randomized controlled trials involving 440 adults with stable COPD (no exacerbations in the preceding month) who had started HFNC for at least 1 month were included in the meta-analysis after a comprehensive search of Cochrane CENTRAL, SCOPUS, MEDLINE, EMBASE and Clinicaltrials.gov databases. Acute COPD exacerbations, hospitalizations and change in St. George Respiratory Questionnaire (SGRQ) scores and all-cause mortality were selected as the primary study endpoints. The duration of follow-up ranged from 12 months to 15 months in the studies included. The forced expiratory volume in 1 second (FEV1) percent predicted at the start of the study was 26% to 45%. The highest CO_2 level at baseline was 51.9 mmHg and the lowest was 48.3 mmHg.

Analysis showed that compared to standard care, the risk of acute exacerbations was probably reduced by HFNC with relative risk (RR) of 0.77 (moderate certainty), suggesting that there were 69 fewer acute exacerbations per 1,000 patients. Use of HFNC (vs. standard care) was also likely associated with reduced risk of hospitalization (RR 0.87; low certainty) suggesting that there were 20 fewer hospitalizations per 1,000 patients. The researchers also found that the SGRQ score may also decline with mean difference –8.12 units suggesting an improvement in quality of life of the patients. But, no effect on mortality (RR 1.22) was noted with HFNC versus standard care.

These results suggest that home HFNC may be effective for patients with COPD and chronic hypercapnia. Although its effect on mortality was debatable, use of HFNC might lead to fewer acute exacerbations and hospital admissions in COPD patients with chronic hypercapnia resulting in better quality of life as shown in this study. The authors conclude by recommending further studies "with longer follow-up periods to provide more robust evidence on the efficacy of HFNC" and its comparative efficacy with noninvasive ventilation in patients with COPD.

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Research Shows Positive Outlook Reduces Aging Anxiety

In a recent study, the researchers have discovered that maintaining a positive attitude towards physical activity is linked to reduced anxiety related to the aging process.

Given the aging demographic, it becomes crucial to promote health-enhancing behaviors and emphasize preventive measures for chronic diseases. The anxiety surrounding aging encompasses concerns about losing independence, relationships, physical and psychological changes, as well as discomfort or dissatisfaction with interactions among older individuals.

While factors like gender, age, marital status and financial status influence one's perceptions of exercise and aging, a shift in how these topics are presented can encourage healthier behaviors.

A multi-state study involving 1,250 participants from Washington, DC, and six states revealed that African-American individuals were more interested in health-related programs. The most prominent aging-related concern was the fear of loss, particularly pronounced among those with lower incomes and individuals living alone. Women aged 40 to 49 expressed more anxiety about changes in their physical appearance compared to their male counterparts and older age groups.

A positive attitude towards physical activity correlates with reduced aging-related anxiety, likely due to the holistic benefits of staying physically, mentally and socially active, leading to an improved perception of the aging process and a subsequent reduction in anxiety associated with growing older.

These study findings can guide the development of educational workshops addressing aging-related anxiety while highlighting the health advantages of engaging in physical activity.

(*Source: https://www.hindustantimes.com/lifestyle/health/positive-attitude-towards-physical-activity-may-be-associated-with-less-anxiety-about-ageing-research-101698983902369.html*)

Study: COVID-19 has no Impact on MS Activity

A study discovered that the COVID-19 virus does not elevate the likelihood of clinical and magnetic resonance imaging (MRI) disease progression or motor and cognitive decline in multiple sclerosis (MS) patients.

The study compared 136 individuals with MS, both with and without a history of COVID-19. It encompassed regular neurologic check-ups, brain MRI scans, neuro-psychological assessments, and evaluations of fatigue,

depression, anxiety, sleep and psychological impacts related to COVID-19.

Over the 18 to 24 months following a COVID infection, there were no noteworthy distinctions between the groups in terms of EDSS (Expanded Disability Status Scale) worsening, the percentage of patients experiencing relapses, the need to alter disease-modifying therapies, the appearance of new or enlarged brain lesions visible on T2-weighted MRI scans, and gadolinium-enhancing lesions. Upon follow-up, 22% of MS patients with a history of COVID and 23% of those without COVID history displayed cognitive impairment. However, there were no substantial variations in overall cognitive functions, verbal and visual memory, and information processing speed, attention and verbal fluency.

Scores in assessments for the Modified Fatigue Impact Scale (MFIS), Hospital Anxiety and Depression Scale (HADS) for anxiety and depression, Pittsburgh Sleep Quality Index (PSQI), and Impact of Event Scale-Revised (IES-R), as well as tests for cellular immune responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), did not exhibit significant differences. In light of these findings, the authors propose that individuals with MS may gradually resume their everyday lives. Nevertheless, they emphasize the importance of maintaining good hygiene practices, as the virus can still pose a threat, and the potential emergence of new variants may present a different range of neurological symptoms.

(*Source: https://www.medscape.com/viewarticle/998044?src=*)

Impact of Early Testosterone on Mental Health in Transgender and Gender-Diverse Adults

Prompt initiation of testosterone in transgender and gender-diverse individuals significantly reduces gender dysphoria, depression and suicidality compared to starting testosterone after waiting for 3 months, according to new research published in *JAMA Network Open*.[1]

This 3-month study included 64 transgender and gender-diverse adults, aged 18 to 70 years, seeking initiation of testosterone therapy. The median age of the participants was 22.5 years. They attended the endocrinology OPDs and primary care clinics that specialized in transgender and gender-diverse health in Melbourne, Australia between November 2021 to July 2022. None of the selected participants had been treated with testosterone earlier. The selected subjects were randomized to immediate intervention with testosterone or to standard care with testosterone started after the usual wait period of 3 months. Testosterone was administered via intramuscular or transdermal routes, based on the preference of the participant. Gender dysphoria measured by the Gender Preoccupation and Stability Questionnaire (GPSQ) was the primary outcome of the study. The secondary outcomes were depression and suicidal ideation. Depression was assessed with the Patient Health Questionnaire-9 (PHQ-9) and suicidal ideation was evaluated with the help of the Suicidal Ideation Attributes Scale (SIDAS) at baseline and at 3 months. In the immediate intervention group, 74% had depression and 65% had anxiety. In the standard care group, 58% had depression and 65% had anxiety. At baseline, the mean testosterone levels in the immediate treatment group was 37.5 ng/L; in the standard treatment group, the mean testosterone levels were 25.9 ng/dL. After 3 months, the mean testosterone levels were ~392 ng/dL.

Participants in whom testosterone was started immediately showed substantial reduction in gender dysphoria compared to those receiving standard care with a 7.2 point decrease in GPSQ score. There was a clinically significant reduction in depression with a mean difference of −5.6 points in the PHQ-9 score as well as a significant decrease in suicidality with a mean difference of −6.5 points in SIDAS score was also seen. In over half (52%), the suicidal ideation was resolved as per the PHQ-9 item 9 following immediate intervention with testosterone compared to just one (5%) in the standard care group. Adverse effects with intramuscular testosterone undecanoate included injection site pain or discomfort and transient headache lasting for a day. None developed polycythemia.

Gender dysphoria due to incongruency of gender identify is a cause of significant distress and can cause depression affecting day to day life and may even lead to suicidal ideation. This trial has for the first time included a "transgender and gender-diverse control group randomized to no treatment" as controls, who started testosterone after 3 months. It is the first trial to demonstrate the benefits of early initiation of testosterone in transgender and gender-diverse adults who desired testosterone therapy on their mental health. Marked reduction in gender dysphoria, depression and suicidality was seen. "These findings have critical implications for service access and delivery to ensure timely access to gender-affirming hormone therapy", concluded the researchers.

Reference

1. Nolan BJ, et al. Early access to testosterone therapy in transgender and gender-diverse adults seeking masculinization: a randomized clinical trial. JAMA Netw Open. 2023;6(9):e2331919.

Entertainment vs. Ananda

All of us crave for and seek happiness. But do we know what true happiness actually is?

'Feel-good' movies, a tasty dish, a pleasant or delightful fragrance, a melodious song, a tender touch, seeing a beautiful thing – all these give pleasure and make us feel more upbeat. And, we often confuse or mistake these feelings as happiness.

But, these feelings are not true happiness; they fulfill or satisfy our worldly desires as they are at the level of the senses. This is entertainment, which is temporary or short-lived. A tasty meal will stay with you only until your next meal.

True bliss or happiness is Ananda, which is at the level of soul. For example, you watch a movie that stays with you for long after the movie is over. You keep on thinking about it for days to come. Or, you watch a dance drama and your expressions or emotions become one with those enacted on the stage. This is Ananda. You become one with the character. You lose track of time.

This is the Rasa theory of Natya Shastra, which establishes a relationship between the actor and the audience. The two are connected at the level of the soul.

According to the Rasa theory of the Natya Shastra, entertainment is a desired effect of performance arts but not the primary goal, and the primary goal is to transport the individual in the audience into another parallel reality, full of wonder and bliss, where he experiences the essence of his own consciousness, and reflects on spiritual and moral questions (Wikipedia).

This is the difference between Ananda and Entertainment.

Krishna has used the word 'Prasanna' in Bhagavad Gita, which is inner happiness and not just happiness.

Ananda can be achieved only if you live in the present and not in the past or the future.

Take 'Anand' in whatever you do; do your duty with devotion and discipline, which means, to be more productive, lose track of time…

■■■■

Study: Women Experience Severe Flu Shot Side Effects

According to research in the *Journal of Epidemiology & Community Health*, women may face a higher likelihood of experiencing both injection site and systemic reactions to seasonal flu vaccines, regardless of age or vaccine type. The study analyzed data from 18 clinical trials involving 34,343 adults from 2010 to 2018, examining sex-based differences by age.

The findings indicated that women had a greater risk of injection site reactions compared to men, with a 29% higher risk for younger participants and a 43% higher risk for older participants. Women also had an increased risk of systemic reactions, showing a 25% higher risk for younger participants and a 27% higher risk for older participants. The risk of severe reactions was twice as high in women as in men and approximately 50% higher for systemic reactions among younger participants. No notable differences were observed based on vaccine type. The study rated the quality of evidence as low for injection site reactions and moderate for systemic reactions.

Experts noted that most reactions following influenza vaccinations, as per data from randomized controlled trials, tend to be mild, self-limiting, and rarely severe. Nonetheless, addressing adverse events is crucial to minimize their impact on vaccination program success, particularly for the annual influenza vaccine. The researchers concluded that transparent communication about the increased risk for females could foster long-term trust in health authorities and vaccines.

(*Source: https://www.thestar.com.my/lifestyle/health/2023/11/03/women-tend-to-get-side-effects-from-flu-jabs*)

INSPIRATIONAL STORY

Two Monks and a Pretty Lady

Once upon a time a big monk and a little monk were traveling together. They came to the bank of a river and found the bridge was damaged. They had to wade across the river.

There was a pretty lady who was stuck at the damaged bridge and couldn't cross the river.

The big monk offered to carry her across the river on his back to which the lady accepted.

The little monk was shocked by the move of the big monk and was thinking "How can big brother carry a lady when we are supposed to avoid all intimacy with females?" But he kept quiet.

The big monk carried the lady across the river and the small monk followed unhappily. When they crossed the river, the big monk let the lady down and they parted ways with her.

All along the way for several miles, the little monk was very unhappy with the act of the big monk. He was making up all kinds of accusations about big monk in his head. This got him madder and madder. But he still kept quiet. And the big monk had no inclination to explain his situation.

Finally, at a rest point many hours later, the little monk could not stand it any further; he burst out angrily at the big monk. "How can you claim yourself a devout monk, when you seize the first opportunity to touch a female, especially when she is very pretty?"

All your teachings to me make you a big hypocrite.

The big monk looked surprised and said, "I had put down the pretty lady at the river bank many hours ago, how come you are still carrying her along?"

Moral: This very old Chinese Zen story reflects the thinking of many people today. We encounter many unpleasant things in our life, they irritate us and they make us angry. But like the little monk, we are not willing to let them go away. There is no point in remaining hurt by the unpleasant event after it is over. Learn to move on in life!

■■■■

Study: Consuming Strawberries Daily Reduce Dementia Risk in Youth

In a study published in *Nutrients,* researchers from the University of Cincinnati examined the potential of daily strawberry consumption to reduce dementia risk among middle-aged populations.

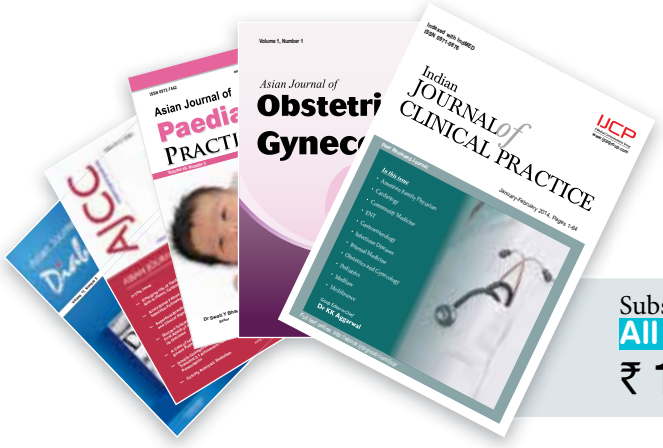
The study focused on 30 overweight individuals aged 50 to 65 with mild cognitive decline, a group at higher risk for late-life dementia and other common conditions. Over 12 weeks, participants were instructed to refrain from consuming berry fruits except for a daily supplement of strawberry powder. Half of the participants received strawberry powder, while the other half received a placebo.

Results showed that the group that received the strawberry treatment exhibited reduced memory interference, indicating an overall improvement in executive ability. Moreover, they also experienced a notable decrease in depressive symptoms, potentially attributable to enhanced executive function.

While further research is required, the cognitive benefits of strawberry consumption may be linked to reduced brain inflammation. Executive abilities tend to decline in midlife, and excess abdominal fat, associated with insulin resistance and obesity, can contribute to increased inflammation, including in the brain.

The study implies that the positive effects may result from moderate inflammation within the strawberry group, especially as executive abilities tend to decline in midlife, coinciding with an increase in abdominal fat-related inflammation.

(*Source: https://www.daijiworld.com/news/newsDisplay?newsID=1136098*)



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Lighter Side of Medicine

HUMOR

IDENTITY

A certain little girl, when asked her name, would reply, "I'm Mr Sugarbrown's daughter." Her mother told her this was wrong, she must say, "I'm Jane Sugarbrown." The Vicar spoke to her in Sunday school and said, "Aren't you Mr Sugarbrown's daughter?" She replied, "I thought I was, but mother says I'm not."

A GIRL WAS CRYING BITTERLY

Mom: What happened dear?

Daughter: Mom do I look like a wicked witch?

Mom: No!

Daughter: Are my eyes big as toad?

Mom: No!

Daughter: Is my nose flat?

Mom: No baby!

Daughter: Am I fat like a bulldog?

Mom: You have a fine physique, you are a Barbie Doll!

Daughter: Then why people tell me that you look like your mom?

COPY MACHINE HANDOUT

In most offices, the photocopier is out of order every now and then. One copy repairman had answered question after question for the employees. Finally one day, he just smiled and handed them this sheet.

The copier is out of order!

Yes, we have called the service man.

Yes, he will be in today.

No, we cannot fix it.

No, we do not know how long it will take.

No, we do not know what caused it.

No, we do not know who broke it.

Yes, we are keeping it.

No, we do not know what you are going to do now.

SPRING FEVER

Four high school boys afflicted with spring fever skipped morning classes. After lunch they reported to the teacher that they had a flat tire.

Much to their relief she smiled and said, "Well, you missed a test today so take seats apart from one another and take out a piece of paper."

Still smiling, she waited for them to sit down. Then she said: "First Question: Which tire was flat?"

A MATHEMATICIAN, A PHYSICIST AND AN ENGINEER

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

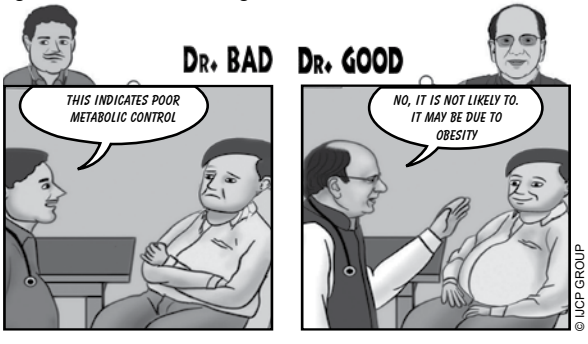
"Aha," says the engineer, "I see that Scottish sheep are black."

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

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

Dr. Good and Dr. Bad

SITUATION: An obese individual with T1DM was found to have high vascular endothelial growth factor.



LESSON: The researchers have shown that no connection exists between circulating plasma levels of vascular endothelial growth factor and present or historical metabolic control in long-standing T1DM. Moreover, these levels are not even affected by the presence of microvascular complications. Instead, they may correlate to insulin needs and BMI.

J Diabetes Res. 2017;2017:6192896.

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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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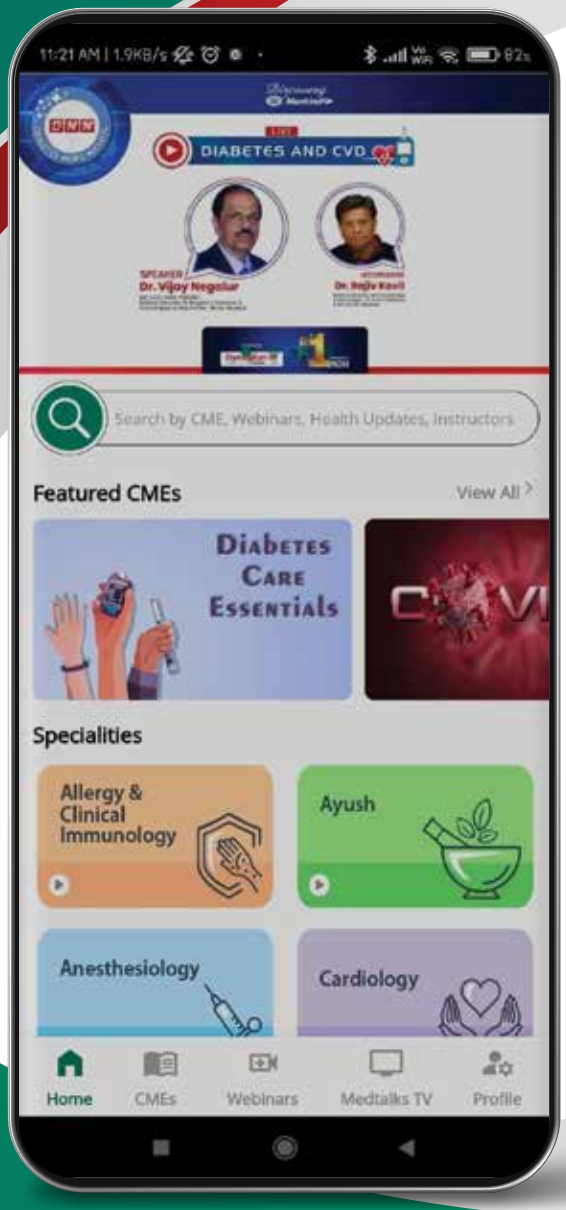

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