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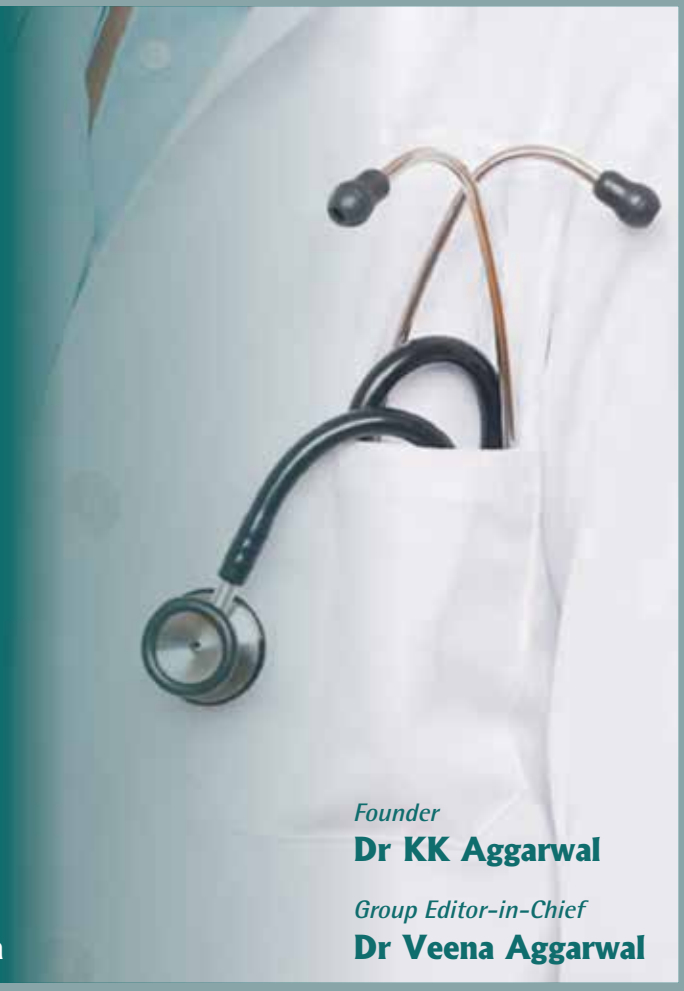

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Medicine Update

WHO REPORT HIGHLIGHTS SIGNIFICANT INCREASE IN CURABLE STIS

A new World Health Organization (WHO) report has highlighted a significant increase in sexually transmitted infections (STIs) worldwide. Syphilis, chlamydia, gonorrhea, and trichomoniasis, which are curable, account for more than 1 million daily. Cases of new human immunodeficiency virus (HIV) decline, albeit only marginally, from 1.5 million in 2020 to 1.3 million in 2022. Viral hepatitis deaths increased from 1.1 million in 2019 to 1.3 million in 2022… (*Source: WHO News. May 21, 2024*).

THE FIRST ARTIFICIAL PANCREAS FOR TYPE 1 DIABETES

CamAPS FX, the artificial pancreas developed by researchers at the University of Cambridge has received approval from the US Food and Drug Administration (FDA). This device is designed for individuals with type 1 diabetes and is approved for use in patients aged 2 years and older, including pregnant women. It is an Android app, which links compatible continuous glucose monitors and insulin pumps into an artificial pancreas system… (*Source: Cambridge University. May 24, 2024*).

PREVALENCE OF COLORECTAL CASES RISING AMONG AMERICAN TEENS

Although low, the rate of colorectal cancer has increased threefold among teenagers in the United States over the past two decades, according to an analysis of the Centers for Disease Control and Prevention (CDC) Wonder Database. Among children, aged 10 to 14 years, the annual colorectal cancer rates increased by 500% from 1999 to 2020; among teenagers, aged 15 to 19 years, the rates increased by 333%; and by 185% among adults, ages 20 to 24 years… (*Source: Medpage Today. May 26, 2024*).

STUDY SUGGESTS ANTINEPHRIN AUTOANTIBODIES AS BIOMARKERS FOR RENAL DISEASE

High levels of circulating antinephrin autoantibodies are frequently detected in patients with minimal change disease or idiopathic nephrotic syndrome and may be regarded as markers of disease activity. Over half of the children with idiopathic nephrotic syndrome (94/182) had detectable antinephrin autoantibodies. Among 105 adults with minimal change disease, antinephrin autoantibodies were detected in 46 (44%)… (*Source: NEJM. May 25, 2024*).

A NONINVASIVE mt-sRNA TEST FOR COLORECTAL CANCER SCREENING

The US FDA has given the go-ahead to ColoSense, a noninvasive multi-target stool RNA (mt-sRNA) test, for colorectal cancer screening in adult patients aged 45 years or older who are considered to be at average risk for developing colorectal cancer… (*Source: HCPLive. May 7, 2024*).

ASSOCIATION OF ANTIHYPERTENSIVE DRUGS WITH RISK OF ECZEMA

Analysis of medical records of 1,561,358 older adults in the UK has demonstrated an association between antihypertensive drugs and risk of eczema with hazard ratio (HR) of 1.29 versus those who were not taking

antihypertensives. The highest association was observed for diuretics (HR 1.21) followed by calcium channel blockers (HR 1.16), angiotensin receptor blockers (HR 1.12) and alpha-blockers (HR 1.08). The risk was least for angiotensin-converting enzyme inhibitors (HR 1.02) and beta-blockers (HR 1.04)… (*Source: Medscape. May 27, 2024*).

ONYCHOPAPILLOMA MAY BE AN INDICATOR OF BAP1 TUMOR PREDISPOSITION SYNDROME

Onychopapilloma, a rare benign tumor of the nail may be an indicator of BAP1 tumor predisposition syndrome, which is a genetic condition characterized by cancerous tumors of the skin, eyes, kidneys, and the mesothelium. Onychopapilloma can be diagnosed by the presence of a colored band along the length of the nail and thickening at the distal end of the nail. In patients with diagnosed BAP1 tumor predisposition syndrome, 88% were found to have onychopapillomas… (*Source: NIH. May 17, 2024*).

THE FIRST mRNA RSV VACCINE FOR OLDER ADULTS

The first-ever mRNA-1345 vaccine (mRESVIA) for respiratory syncytial virus (RSV) manufactured by Moderna has been accorded US FDA approval. The vaccine, to be available in a prefilled syringe, is intended to protect against lower respiratory tract disease in individuals aged ≥60 years… (*Source: MedPage Today. May 31, 2024*).

PRESENTING SIGNS AND SYMPTOMS OF EARLY-ONSET COLORECTAL CANCER

Early-onset colorectal cancer, which is diagnosed before 50 years of age most frequently presents with hematochezia and abdominal pain. The other most common symptoms were altered bowel habits and unexplained weight loss. The time period from the onset of these signs/symptoms to diagnosis of colorectal cancer ranged between 4 and 6 months… (*Source: JAMA Network Open. May 24, 2024*).

STUDY SUGGESTS NIGHTTIME HEAT AS A CRITICAL TRIGGER OF STROKES

Warm nights increase the incidence of strokes by 7%, especially for older women. Analysis of data from Germany's Augsburg Hospital across a 15-year period revealed 11,037 cases of strokes between 2006 and 2020, from May through October, when temperatures are at their highest. Over 80% of the strokes were minor or of moderate-severity. Incidence of ischemic strokes was highest followed by transient ischemic attacks and hemorrhagic strokes… (*Source: European Heart Journal. May 21, 2024*).

CDC REPORTS THIRD CASE OF H5N1 BIRD FLU IN THE US

CDC has reported the third human case of H5N1 (highly pathogenic avian influenza) following exposure to infected dairy cows in a dairy farm worker from the state of Michigan in the US. Unlike the other 2 cases, which reported only conjunctivitis, this patient has reported upper respiratory tract symptoms, cough without fever, and eye discomfort with watery discharge… (*Source: CDC. May 30, 2024*).

EMA APPROVES DASIGLUCAGON TO TREAT SEVERE HYPOGLYCEMIA IN PATIENTS WITH DIABETES

The European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) has granted marketing authorization for dasiglucagon for the treatment of children aged ≥6 years, adolescents and adults with diabetes mellitus. Available by the name of Zegalogue, dasiglucagon is a glycogenolytic hormone that raises blood sugar levels by increasing the glycogen breakdown and encouraging the liver to release glucose by activating hepatic glucagon receptors… (*Source: EMA. May 30, 2024*).

NEUROPSYCHIATRIC SYMPTOMS IN AUTOIMMUNE DISEASES

Results from the INSPIRE study show that neuropsychiatric symptoms such as nightmares and hallucinations may be a presentation feature of systemic lupus erythematosus and other systemic autoimmune rheumatic diseases at any stage during the course of the disease. More than half of the patients who reported hallucinations developed these symptoms more than 1 year after the onset of disease… (*Source: eClinicalMedicine. May 20, 2024*).

USE OF ULTRASOUND TO DIAGNOSE MENISCAL INJURIES IN PRIMARY CARE

Supplementing history and physical examination with point-of-care ultrasound (POCUS) may help primary care physicians to accurately diagnose meniscal injuries. Magnetic resonance imaging confirmed meniscal injuries in 6 of the 11 patients who underwent POCUS. These findings were presented at the 2024 Annual Meeting of the Society of General Internal Medicine held in Boston…. (*Source: Medscape. May 31, 2024*).

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Silver Stewardship

Humankind has been able, over the past century, to double its life expectancy[1]. This has increased not only our total population, but also the proportion of elderly persons in the population. Increasing longevity exposes individuals to the degenerative diseases of old age. These impact quality of life, and may lead to disability as well as dysfunction[2].

This situation calls for enhanced focus on geriatric care. While geriatric medicine offers preventive and curative services to elderly persons, longevity and antiaging medicine (LAM) works to promote and preserve health. Emphasizing both esthetic and functional youthfulness, LAM complements and supports geriatric medicine by aiming to reduce the need for secondary and tertiary geriatric care services. LAM may also be viewed as a primary and secondary prevention strategy, designed to promote health and prevent complications of aging[3].

The word stewardship has been used in multiple ways in medicine and health. Antibiotic stewardship, steroid stewardship, and insulin stewardship are notable examples[4-6]. The word silver, which alludes to 'silver-haired', denotes the elderly age group.

We use the term 'Silver Stewardship' to describe the practices and behaviors that help protect and promote health of elderly persons, while pre-empting and preventing disease and disability. Though there is no consensus on the age cut-off for geriatric and elderly persons, a threshold of 65 years is accepted by most researchers[7]. The physiological changes of aging, and their impact on health and function, however, begin much earlier. Silver stewardship, therefore, can be taken to mean care of all persons above the age of 40 years.

Silver stewardship is a multidimensional construct, which includes all aspects of health and happiness. These are listed in Table 1. The table also lists a few of the commonly encountered diseases that are the focus of silver stewardship.

Table 1. Domains of Silver Stewardship

Domain	Description	Common conditions
Musculoskeletal	Maintenance of bone, muscle, joint health	Osteoarthritis, osteoporosis, sarcopenia
Metabolic and endocrine	Management of metabolic/endocrine dysfunction	Diabetes, dyslipidemia, hypertension, obesity
Medical and surgical	Management of comorbid illness	Heart disease, kidney disease, urinary complaints
Mirror-related	Optimization of dermatologic health, including hair nails, and esthetics	Hairloss, skin aging
Macho/maiden health	Optimization of genital gonadal and sexual health	Late-onset hypogonadism in men, menopause in women
Mitogenic	Early detection, management and prevention of cancer	Common cancers
Mental	Mental emotional and cognitive health	Depression, dementia
Multi-personal (social health)	Ensurance and strengthening of social connections	Social withdrawal
Monetary	Financial autonomy and stewardship	Financial ill health

As the world's population ages, the need for silver stewardship is bound to increase. A multifaceted concept, silver stewardship should be practiced by policymakers and planners, physicians and paramedical staff, pharmaceutical researchers, and members of the public alike. Within the medical fraternity, geriatric medicine, along with longevity and antiaging medicine, as well as endocrinology and metabolism, should take the lead in strengthening and supporting silver stewardship.

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■■■■

Hypothyroidism Gestational and Pregnancy Outcomes

Hypothyroidism during pregnancy poses significant risks to pregnancy outcomes and is influenced by various factors such as maternal age, parity, gravidity, and thyroid hormone levels, suggests a case-control study from China published in the journal *Endocrine Practice*[1].

Our study revealed that the clinical features of patients with gestational hypothyroidism included age, gestational diabetes, gestational hypertension, gravidity, parity, spontaneous abortion, history of gestation, thyroid-stimulating hormone (TSH) levels, free triiodothyronine levels, thyroid peroxidase antibody (TPO-Ab) status, and free thyroxine levels. This study enrolled 298 hospitalized patients who had been diagnosed with gestational hypothyroidism between February 2021 and March 2023 as the study group. A group of 312 pregnant women without gestational hypothyroidism were randomly selected as controls. The clinical characteristics of the patients and risk factors associated with pregnancy outcomes were compared between the two groups.

The study found that several parameters differed significantly between the two groups of pregnant women, those with gestational hypothyroidism and those without. These parameters included age (≥30 years), gravidity (≥3), parity, spontaneous abortion, history of gestation (multiparity), gestational diabetes, gestational hypertension, thyroid hormones, TSH, and TPO-Ab.

Additionally, there were significant differences between the two groups in terms of pregnancy outcomes such as preterm delivery, premature rupture of membranes, placental abruption, postpartum hemorrhage, and pre-eclampsia.

Multivariate logistic regression analysis identified factors that had an impact on pregnancy outcomes in patients with gestational hypothyroidism. These were: Age (≥30 years), gestational diabetes, gestational hypertension, gravidity (≥3 times), spontaneous abortion, parity, history of gestation (multiparity), and positive TPO-Ab.

These findings highlight the importance of early detection and effective management of hypothyroidism in pregnancy. Regular monitoring and appropriate treatment based on thyroid function tests can mitigate the risks of adverse outcomes and ensure better health outcomes for both the mother and child.

Reference

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REVIEW ARTICLE

From Evidence to Practice: Denosumab in Osteoporosis and Joint Health

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ABSTRACT

Osteoporosis and osteopenia are prevalent conditions in India, particularly among postmenopausal women and the elderly, leading to increased fracture risks and morbidity. Denosumab, a monoclonal antibody, demonstrates superior efficacy over other treatments in reducing fracture risk and enhancing bone mineral density (BMD). Clinical trials highlight its effectiveness in preventing periprosthetic bone loss, improving implant stability, and mitigating femoral head collapse in various conditions; combination therapies involving denosumab further amplify BMD gains and reduce fracture risk. The article reviews the efficacy and safety of denosumab in managing osteoporosis, joint replacement therapy, and avascular necrosis based on a review of clinical evidence and studies. Denosumab emerges as a cornerstone therapy for osteoporosis management, offering multifaceted benefits in fracture prevention, joint replacement therapy, and avascular necrosis.

Keywords: Osteoporosis, osteopenia, fracture, denosumab, joint replacement therapy, avascular necrosis

Almost 1 out of 2 adults in India have osteopenia, and 1 out of 5 have osteoporosis. It is reported that osteoporosis prevalence is higher in women compared to the elderly. Almost 1 out of 3 women in postmenopausal age group have osteoporosis.

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The prevalence of osteoporosis is similar across the four zones of India[1]. Additionally, the prevalence of osteopenia was found to be higher in women (40.3%) than men (29.9%)[2].

In a study from Punjab, India, the prevalence of osteoporosis and osteopenia in postmenopausal women was seen to be 30.5% and 44.2%, respectively[3].

It has been suggested that hip fractures will increase to more than 1 million with a male-to-female ratio of 1:3[4]. Loss of bone leads to reduced compressive and/or torsional strength and increases the risk of fragility fractures, especially in the aging population. Considering this significant burden, early identification and management of osteopenia and osteoporosis are essential to reduce the burden of fracture[1]. Hence, this expert consensus statement is developed to provide a comprehensive review and synthesis of current clinical evidence and studies pertaining to the efficacy, safety, and practical applications of denosumab in the management of osteoporosis, joint replacement therapy, and avascular necrosis.

METHODOLOGY

The objective of the above consensus is to review denosumab's efficacy, safety, and practical applications and offer recommendations based on clinical evidence and consensus among the panelists.

In the first stage, a systematic literature review was conducted, including articles on denosumab's efficacy and safety from January 2005 to January 2024. The articles included randomized clinical trials, systematic reviews and meta-analyses, and narrative reviews. Concurrent with the initial literature search, a list of indications for denosumab was decided, these included osteoporosis, joint replacement therapy, and avascular necrosis. A 12-member expert panel was then formed, the selection criteria being their medical specialty, research, and clinical experience in the field of interest, and relevance to the agenda discussions. A 2-day meeting was conducted with the panelists to discuss the objectives of the consensus meeting. All the panelists were given pre-read materials, a list of selected indications, and a compilation of literature selected after the literature search. Following the meeting, the given themes were selected: osteoporosis and denosumab, joint replacement therapy and denosumab, avascular necrosis and osteoporosis, and combination therapy with denosumab. The manuscript was developed and shared with all the panel members for their review and feedback.

OSTEOPOROSIS AND DENOSUMAB

Denosumab is a human monoclonal IgG2 antibody with a high affinity and specificity for human receptor activators of nuclear factor kappa-β ligand (RANKL), the principal regulator of osteoclastic bone resorption. Denosumab binds to RANKL, preventing RANKL from activating its receptor, RANK, on formation, function, and survival, thereby reducing bone resorption[5].

Clinical Evidence

The results of FREEDOM (Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months) is a 3-year phase III trial that showed significant relative risk reduction for vertebral fractures (68%), hip fractures (40%), and nonvertebral fractures (20%) with the use of denosumab compared with placebo[6]. The results of the FREEDOM trial provided the base for the Food and Drug Administration (FDA) approval of denosumab for the treatment of postmenopausal women with osteoporosis at high risk for fracture[5].

The results of the FREEDOM Extension trial (up to 8 years of therapy) showed a mean increase in bone mineral density (BMD) from baseline in the denosumab group, an 18.5% increase in the lumbar spine (LS), and an 8.2% increase in the total hip in the long-term group. It was also seen that after a further 5 years from the FREEDOM trial duration, new vertebral and nonvertebral fracture rates remained low throughout the extension study period, with a hip fracture rate during year 8 of 0.2% in the long-term group and 0.1% in the crossover group[7].

The results of the DECIDE (Determining Efficacy; Comparison of Initiating Denosumab vs. Alendronate) trial showed a significantly higher BMD increase at the total hip compared to alendronate (3.5% denosumab, 2.6% alendronate, $p < 0.0001$) at the end of 12 months of treatment. A treatment difference of 0.65 was observed at the femoral neck and 1.1% at LS[8]. Similar results were seen in the STAND (Study of Transitioning from Alendronate to Denosumab) trial, which investigated denosumab versus alendronate in individuals already being treated with alendronate. At the end of 12 months of therapy, a statistically significant increase in BMD with denosumab (1.9% increase) was seen compared with continuing alendronate (1.05% increase), $p < 0.0001$[9].

Another comparative study of denosumab with risedronate in postmenopausal women who were treated with but suboptimally adherent to alendronate showed that after 12 months of therapy, denosumab led to a higher gain in BMD at total hip (2.0% denosumab, 0.5% risedronate), femoral neck (1.4% denosumab, 0% risedronate), and LS (3.4% denosumab, 1.1% risedronate), $p < 0.0001$ at all sites[10].

In another study, ADAMO (A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety of DenosumAb vs. placebo in Males with Osteoporosis), 12 months of therapy with denosumab resulted in a BMD increase of 5.7% at the LS, 2.4% at the total hip and 2.1% at the femoral neck. The results showed robust effects on further analyses controlling for baseline covariates, such as baseline testosterone levels, BMD T-scores and 10-year osteoporotic fracture risk. The results of this trial formed the basis of FDA approval for the use of denosumab in the treatment of men with osteoporosis at high risk of fracture[11].

The HALT (Hormone Ablation bone Loss Trial) provided results that led to the FDA approval of denosumab use in men undergoing androgen-deprivation therapy for nonmetastatic, hormone-sensitive prostate cancer. At 24 months of therapy, BMD of the LS had increased by 5.6% in the denosumab group as compared with a loss of 1.0% in the placebo group ($p < 0.001$); significant differences in the therapy were noted as early as 1 month and maintained through a period of 36 months. Individuals treated with denosumab had a reduced incidence of new vertebral fractures at 36 months[12].

Another randomized controlled trial of 2 years was conducted in women with hormone receptor-positive nonmetastatic breast cancer treated with adjuvant aromatase inhibitor therapy. This trial provided the ground for basing the FDA decision in approving denosumab use to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. In the study, LS BMD increased by 5.5% at 12 months and 7.6% at 24 months higher in the denosumab group versus the placebo group ($p < 0.0001$ at both time points)[13].

The Denosumab Adherence Preference Satisfaction (DAPS) study showed that less nonadherence to therapy was found in the denosumab group versus alendronate, and 92.4% of study participants showed a preference for denosumab over alendronate[14].

Many clinical trials have also shown the reversibility of denosumab-mediated effects on bone. A phase 3 study showed that when individuals treated with denosumab for 2 years were followed for 24 months after discontinuation[15].

JOINT REPLACEMENT THERAPY AND DENOSUMAB

Periprosthetic bone loss is a significant cause of aseptic loosening that leads to implant failure. It usually starts in the first postoperative year and gradually declines after 7 years[16]. Several medicines are suggested for the long-term survival of the implants, such as bisphosphonates[17].

Denosumab is known to be the most powerful inhibitor of osteoclastic activity, with significantly high reductions of bone resorption. The reduction in serum levels of C-telopeptide was close to maximal within 3 days after dosing[18]. Denosumab can prevent periprosthetic bone loss after total hip arthroplasty, especially in Gruen zone 7; the BMD can be increased by as much as 7%[19]. Another study showed that denosumab increases the BMD of the proximal femur, administered for 6 to 12 months after surgery. This helps the bone to respond locally to prevent stem migration[20]. In this study, the patients received denosumab subcutaneously, 60 mg once every 6 months for 12 months, starting a month before surgery. Denosumab significantly reduced bone loss in the medial femoral neck and increased periprosthetic BMD in the greater trochanteric and lesser trochanteric regions[20]. Nagoya et al also showed that the denosumab given post-total knee arthroplasty significantly prevented early prosthetic bone loss and decreased periprosthetic tibial bone atrophy for up to 12 months[19]. Another study reported that denosumab assisted in achieving better early stability and prognosis by significantly decreasing prosthetic bone loss in the early postoperative period[21]. Denosumab also reduces the early migration of the tibial part by reducing the total point motion. It leads to better early and long-term stability of the implant[22]. Denosumab persistently preserves the periprosthetic BMD after uncemented total hip arthroplasty[15]. In a 6-year-long study, where patients were scheduled for revision surgery for symptomatic osteolysis, it was seen that there were 83% fewer osteoclasts at the osteolysis membrane-bone interface in the denosumab group[23].

Achieving early stable fixation in total knee replacement is important to prevent late loosening. In a randomized controlled trial in patients undergoing total knee replacement, it was seen that denosumab reduces early migration by one-third and, hence, may be beneficial for long-term results. The study authors suggested that denosumab could also eliminate the need for most revisions due to aseptic loosening[22].

COMBINATION THERAPY WITH DENOSUMAB

Treatment approaches that adopt the use of anabolic agents followed by potent antiresorptive therapies are highly efficacious in reducing fracture risk rapidly and leading to large BMD gains. The results of the FRActure study in postmenopausal woMEn with osteoporosis (FRAME) study showed that individuals receiving bone-forming agent romosozumab for 12 months followed by 12 months of denosumab had a sustained reduction in fracture risk and a further increase in BMD in the 24 months treatment sequence[24] and an additional year of denosumab in the FRAME Extension study[25].

The Denosumab and Teriparatide Administration (DATA) study showed that at 12 months, LS BMD increased more in the denosumab and teriparatide combination group than in the teriparatide or denosumab groups. A similar result was seen in total-hip BMD (combination, 4.9% [2.9]; teriparatide, 0.7% [2.7], $p < 0.0001$; denosumab 2.5% [2.6], $p = 0.0011$)[26]. Denosumab leads to more effective de-linking of bone resorption and formation. Denosumab also suppresses teriparatide-induced bone resorption while only partially decreasing it-induced bone formation[5]. In the DATA-Switch study, individuals treated with bone-forming teriparatide for 24 months and then switched to denosumab for 24 months experienced a significant increase in BMD. However, individuals who were randomized to receive denosumab as initial therapy for 24 months and then switched to teriparatide for

24 months experienced progressive or transient bone loss at the hip during teriparatide therapy, even though spine BMD increased[27]. While there is no data as yet, it is suggested that patients who remain at high risk of fracture despite denosumab treatment should be given teriparatide additionally and continue denosumab[28].

Teriparatide and denosumab can be used sequentially in pulsating therapies. It has been seen that when used in sequential therapy of 6 months of teriparatide followed by 6 months of denosumab for 36 months, the hip radius and BMD benefits were better at 18 months follow-up, while nosignificant difference was observed at 36 months[29]. Another study has also shown that when patients transitioned from bisphosphonate to denosumab or teriparatide, hip BMD increased with denosumab over 2 years, but no change was seen with teriparatide[30]. In this study, the patients were treated with bisphosphonates for at least 12 months before they were switched to teriparatide or denosumab, and the follow-up was 6 to 27 months after the initiation of teriparatide or denosumab.

AVASCULAR OSTEONECROSIS AND DENOSUMAB

In a study on patients with steroid-induced osteonecrosis of the femoral head (ONFH), it was seen that denosumab had a positive effect on preventing femoral head collapse in patients with steroid ONFH. The effect is known to be associated with the inhibition of osteoclasts and their autophagy[31]. In a case report, it has been seen that denosumab can be used to normalize the bone-remodeling parameters in patients with bone alterations caused by radiotherapy[32].

Recommendations for Denosumab Use in Clinical Practice

- Osteoporosis is a condition that requires long-term monitoring and treatment. The current published maximum follow-up time is 10 years, but there is no absolute limit on the treatment duration. The decision to continue denosumab has to be customized based on the variable BMD treatment targets, patient age, bisphosphonate tolerance, underlying comorbidities, and fall risk.
- Denosumab should be given 6 to 12 months prior to surgery and continued for 12 months to preserve bone structure and improve bone stability.
- Denosumab could be given postoperatively in joint replacement to prevent early bone resorption around the implants. If given, the recommendation is to administer two doses of denosumab (immediately after surgery and in 6 months) in patients undergoing joint replacement surgery.

CONCLUSION

The article underscores the significant prevalence of osteoporosis and osteopenia in India, particularly among postmenopausal women and the elderly; given the escalating incidence of fractures and associated morbidity, there is a need for effective management strategies. Denosumab is a pivotal therapeutic intervention backed by substantial clinical evidence. Denosumab showcases superiority over other treatments like alendronate and risedronate, emphasizing its role in enhancing BMD. Notably, denosumab also proves beneficial in joint replacement therapy, preventing periprosthetic bone loss and enhancing implant stability.

Additionally, in conditions like avascular osteonecrosis, denosumab exhibits promise in mitigating femoral head collapse. Combination therapies incorporating denosumab, such as romosozumab or teriparatide, amplify BMD gains and reduce fracture risk. Denosumab's multifaceted benefits in managing osteoporosis, joint replacement, and avascular necrosis underscore its pivotal role as a cornerstone in modern therapeutic approaches. The recommendations in the present review are based on the available evidence and clinical practice of the experts.

However, many experts are of the view that there is a need for further clinical research on the use of denosumab joint replacement therapy, its interaction with drugs it is combined with or substituted in the treatment of osteoporosis, and long-term use.

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Hepatic Granulomas: A Clinician's Perspective

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ABSTRACT

Hepatic granulomas are focal aggregates of transformed epithelioid histiocytes with or without multinucleated giant cells that are cuffed by lymphocytes and plasma cells. They represent delayed-type specialized cell-mediated immunity to a wide-spectrum of antigenic stimuli. Hepatic granulomas are found in up to 10% of liver biopsies and the causes are usually multifactorial. Different antigens like infectious agent, medication, foreign body and malignancy can initiate granuloma formation. Hepatic granulomas *per se* seldom cause architectural changes and often provide a clue to a systemic disease. Most often, to a practicing clinician, it is a combination of clinical presentation, laboratory parameters with information on the typical localization and characterization of the granuloma within the liver by the pathologist that often provides a clue to a definitive diagnosis.

Keywords: Hepatic granulomas, transformed epithelioid histiocytes, multinucleated giant cells, cell-mediated immunity, antigenic stimuli

Granulomas are aggregates of modified macrophages (epithelioid cells) and other inflammatory cells that accumulate after chronic exposure to an antigen and are seen in several systemic diseases. The extent of inflammation associated with formation of granuloma is variable. Bland granulomas have little or no associated inflammation. The term granulomatous hepatitis is used when the inflammation is severe, within or around the granuloma and granulomatoid reaction refers to a poorly delineated granuloma[1]. The presence of a granuloma may be the first harbinger to an ongoing systemic disease.

PREVALENCE OF LIVER GRANULOMAS

The prevalence of granulomas in liver biopsy ranges from 2.4% to 15%[2-9]. Conn et al[10] reported that 66% of their cases of granulomatous reaction were secondary to a systemic disease, 28% to primary liver disorders and 6% were idiopathic. The frequency of granulomas is reportedly high and ranges from 16% to 75% in select groups like patients with fever of unknown origin or those with a human immunodeficiency virus (HIV) infection[11]. In India, granulomas are most often reported in tuberculosis (55%) followed by leprosy, sarcoidosis, histoplasmosis, brucellosis, amebic liver abscess, lymphoma, and malignant granuloma in that order[12].

ETIOLOGICAL CONSIDERATIONS

- Autoimmune: Sarcoidosis, primary biliary cirrhosis.
- Infections:
  - Bacterial- tuberculosis, leprosy, brucellosis, Q fever, rickettsia, listeriosis, Bartonella, *Tropheryma whipplei*
  - Parasites- schistosoma, leishmania
  - Viruses- hepatitis C
  - Fungal- Histoplasma.
- Drugs and chemicals.
- Malignancy.

HISTOPATHOLOGICAL CHARACTERISTICS OF GRANULOMA

A typical granuloma is an inflammatory reaction to a foreign body like microbial organism, drug, etc. It is essentially a compact spherical circumscribed lesion that consists of aggregated epithelioid histiocytes, measuring 50-300 μm. A typical granuloma consists of a central portion of macrophages and is surrounded by lymphocytes and fibroblasts. Differential diagnosis of a granuloma is largely based on its histological characteristics and the location within a hepatic lobule.

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The histological variants include[13-15]:

- **Necrotizing (caseating):** These are large and destroy the adjacent structures with no respect to the liver architecture. Common example is tuberculosis.
- **Noncaseating:** These are seen in sarcoidosis.
- **Granulomatous inflammation:** These are poorly formed granulomas with indistinct edges and consist of mixed inflammatory cells. Examples include drug-induced hepatocellular and/or ductular injury.
- **Lipogranuloma:** This is often seen in steatosis and comprises of aggregates of lipid-containing histiocytes, e.g., mineral oil.
- **Microgranulomas** contain 3-7 cells in cross-section, often admixed with other inflammatory cells and/or apoptotic hepatocytes. This pattern is nonspecific.
- **Foreign body granulomas** consist of inclusions of particulate material like mineral oil, starch and silicone within cytoplasmic vacuoles.
- **Lymphohistiocytic granulomas** are similar to epithelioid granulomas, but unlike the latter, these comprise of accumulations of macrophages and lymphocytes with distinct absence of epithelioid cells.
- **Fibrin ring or epithelioid granuloma:** The fibrin ring or an epithelioid granuloma consists of a central lipid vacuole surrounded by a fibrin ring. The activated macrophages differentiate and aggregate to form giant cells or Langhans cells. These granulomas are seen in infections like cytomegalovirus, hepatitis A, leishmaniasis, toxoplasmosis, Q fever, drugs such as allopurinol and in Hodgkin's disease.

Per se, granulomas can be located in almost all lobules. However, the distinct forms of necrosis as well as location of a granuloma can provide a clue to its origin and this helps in narrowing the differential diagnosis. For example, caseating necrosis is found in tuberculosis, while noncaseating necrosis is common in sarcoid granulomas[16]. The latter are located in the portal and periportal regions. In primary biliary cirrhosis, granulomas are seen near the porta. The drug-induced granulomas are poorly defined and are located anywhere within the hepatic lobules[16].

PATHOGENESIS

The failure of humoral or cellular immune response to eliminate the offending foreign material leads to granuloma formation[17]. Granulomatous reaction is essentially of 2 types, i.e., an immunological reaction to either an inert foreign body or to an active antigen[18]. The response to the agent depends on whether it is located within or outside the cell. For intracellular agents, there is a Th1 response while for extracellular, there is a Th2 immunological response. With the former, several cytokines such as interferon-γ, interleukin (IL)-2 and IL-12 are produced soon after phagocytosis of the agent by the macrophages, which reduce them to small peptides. With the Th2 response, there is secretion of IL-4, 5, 6 and 10. A vicious cycle ensues wherein by positive feedback mechanism the cytokines constantly stimulate the T cells. Thus, the formation and maintenance of liver granulomas is based on cytokine release[16].

With the release of cytokines, clusters of histiocytes and lymphocytes are seen. The histiocytes and macrophages are transformed into epithelioid histiocytes, which conglomerate to a granuloma. The latter have abundant pale cytoplasm. Apart from cytokines, epithelioid cells in particular, within a granuloma secrete proteins like collagenase, lysozyme, and angiotensin-converting enzyme (ACE) (e.g., sarcoidosis)[18]. Elevated ACE levels suggest an active sarcoid.

Typically surrounding the granulomatous reaction is a cuff of lymphocytes, a few plasma cells and eosinophils. Multinucleated giant cells are result of fusion of macrophages. Granulomas when infiltrated by eosinophils are suggestive of either a drug reaction or a parasitic infection. Thus macrophages play a key role in granuloma formation while tissue necrosis (necrotizing granulomas) is largely initiated by epithelioid histiocytes, characteristically seen in infections like tuberculosis.[19]

Accumulation of these effector cells in the portal tract leads to injury of the septal and interlobular bile ducts that can cause cholestasis[16].

CLINICAL PRESENTATION

Majority of the patients are asymptomatic at presentation or have clinical manifestations of underlying systemic disease. Nonspecific symptoms include fever (tuberculosis, sarcoidosis, infectious disease), weight loss, anorexia, and night sweats. Lymphadenopathy may be present in systemic diseases[19-23].

Two-thirds of patients have a hepatomegaly with an elevated alkaline phosphatase and gamma-glutamyl transferase.[21] Jaundice is rare unless there is bile duct injury. Portal hypertension is reported in schistosomiasis (noncirrhotic portal hypertension), sarcoidosis and primary biliary cirrhosis[16]. Final diagnosis is at histology.

DIAGNOSTIC EVALUATION

A comprehensive medical history and physical examination should be pursued along with an extensive medication and travel history. Symptoms and signs are helpful in developing a differential diagnosis. Blood investigations, serological tests and biopsy lead to a definitive diagnosis. Ultrasound can detect a hepatomegaly. Granulomas of 0.5 cm in diameter or greater can be identified on magnetic resonance imaging (MRI) as multiple nodular lesions or, less commonly, isolated hepatic granulomas. Caseating granulomas as in tuberculosis have a high or low signal in T1-weighted MRI, and no enhancement or sometimes peripheral enhancement after gadolinium injection in comparison to noncaseating granulomas in sarcoidosis, which have intermediate signals on T1-weighted images with gadolinium enhancement that may or may not persist on late images[24-26]. However, these findings are operator dependent and difficult to interpret.

In a study[27] on 251 explant livers, we found the prevalence of liver granulomas to be 7.2%. Five patients who had undergone transarterial chemoembolization prior to transplantation, had foreign body granuloma. Five patients were diagnosed to have caseating

Table 1. Salient Features of Important Causes of Hepatic Granulomas

Categories	Causes	Clinical picture	Biochemistry	Granulomas
Autoimmune	Sarcoidosis	Hepatic involvement: 5-15% Asymptomatic, cholestatic liver disease, cirrhosis, PHT, hepatic vein thrombosis	Raised SAP, GGT	Noncaseating epithelioid granuloma Location: Portal tract
	PBC	Cholestatic liver disease	AMA +	Simulates sarcoidosis
Infections: Bacterial, viral, fungal, parasitic, rickettsial, spirochaetal	Tuberculosis	Systemic symptoms: Fever, night sweats, fatigue, anorexia, and weight loss Jaundice rare	Abnormal LFT; raised GGT and SAP	Around portal tract, caseating or noncaseating, AFB ± 90%: military TB 70%: extrapulmonary TB, 25%: isolated liver
	HIV-related: Associated infections e.g., *M. tuberculosis*, *M. avium* intracellulare, *C. neoformans*, CMV, histoplasmosis, toxoplasmosis	Symptoms of primary infection	Abnormal LFT: Raised SAP, GGT, hepatomegaly	Usually similar to infective granulomas
Cirrhosis	HCV, alcohol, HCC, NASH	Features of cirrhosis	Raised SAP, GGT	Often epithelioid granulomas: treatment related (e.g., Interferon or primary disease)
Malignancy	Hodgkin's, non-Hodgkin's lymphoma, renal cell carcinoma	Primary disease	Raised SAP, GGT	Granulomas not considered for staging in lymphomas
	HCC			May be related to primary etiology, e.g., HCV or may be intratumoral
Drugs	Allopurinol, sulfa, chlopropamaide, quinidine	History of drugs		Diffuse, ill-defined
Foreign body	Post-TACE	History	>HCC	Microgranulomas with suppuration
Idiopathic	10-36%	Granulomatous hepatitis: Fever, myalgia, arthralgia, hepatoslenomegaly	Raised ESR	

PHT = Portal hypertension; SAP = Serum alkaline phosphatase; GGT = Gamma-glutamyl transferase; PBC = Primary biliary cirrhosis; AMA = Antimitochondrial antibodies; LFT = Liver function tests; AFB = Acid-fast bacilli; TB = Tuberculosis; HIV = Human immunodeficiency virus; CMV = Cytomegalovirus; HCV = Hepatitis C virus; HCC = Hepatocellular carcinoma; NASH = Nonalcoholic steatohepatitis; TACE = Transarterial chemoembolization; ESR = Erythrocyte sedimentation rate.

granulomas and were started on four drug regimen for tuberculosis - isoniazid, rifabutin, pyrazinamide, and ethambutol. All responded well to treatment. Three patients with hepatitis C virus infection showed portal microgranulomas/granulomas. These were compact, non-necrotizing, epithelioid granulomas of varying sizes observed within portal tracts and lobules. Five cases, where the diagnosis of granulomas remained elusive, isoniazid prophylaxis was given for 9 months to reduce the risk of reactivation of tuberculosis.

The presence of granulomas suggestive of tuberculosis in the explant liver is associated with the development of tuberculosis in the recipients[28]. Granulomas in hepatitis C virus patients could be due to an interferon-mediated stimulation of Th1 immune response or intravenous drug use[29].

The differential diagnosis (Table 1) for hepatic granulomas can be broadly classified as those associated with:

- Infections
- Drugs
- Autoimmune disorders
- Malignancy
- Idiopathic.

CONCLUSIONS

Hepatic granulomas are of multifactorial origin. A definite diagnosis regarding the granulomas can only be made using clinical data and histopathology. In a quarter, the cause for a granuloma remains unknown. In Indian setting, treatment for tuberculosis should be initiated in presence of caseating granulomas and a high index of disease suspicion.

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Temporal Association Between COPD Exacerbations and Cardiovascular Events

Chronic obstructive pulmonary disease (COPD) patients with severe exacerbations are at a high immediate risk of experiencing cardiovascular events, within 1 to 14 days post-exacerbation. Conversely, patients with moderate exacerbations were at highest risk 14 to 30 days following the acute exacerbation event. The risk remained elevated 1 year later irrespective of the severity of exacerbation. These findings from a population-based study from the UK were published April 15, 2024 in the *American Journal of Respiratory and Critical Care Medicine*[1].

This study investigated the temporal relationship between exacerbations of COPD and new-onset nonfatal cardiovascular events. Data for COPD patients in England was sourced from the Clinical Practice Research Datalink Aurum primary care database from 2014 to 2020. Information about various individual and composite cardiovascular events such as acute coronary syndrome, arrhythmia, heart failure, ischemic stroke, and pulmonary hypertension was determined from the linked hospital data. The index date was defined as the occurrence of the first COPD exacerbation; for those without exacerbations, it was defined as the date of eligibility for the trial.

Out of the 2,13,466 patients assessed; 1,46,448 (68.6%) reported at least one exacerbation. Over half (~56%) of these had moderate exacerbations, while ~13% had severe exacerbations. A total of 40,773 cardiovascular events occurred during the course of the study.

Analysis revealed an immediate period of heightened cardiovascular risk within 1 to 14 days after any exacerbation as indicated by the adjusted hazard ratio (aHR) of 3.19. The elevated cardiovascular risk declined progressively but persisted beyond the immediate post-exacerbation period, with an aHR of 1.84 after 1 year.

The risk was highest within 14 days after a severe exacerbation with aHR of 14.5. In patients with moderate exacerbations, the risk was highest after 14 to 30 days with aHR of 1.94.

Patients were nearly 13 times more likely to develop arrhythmia within 2 weeks of a severe exacerbation with aHR of 12.7. The likelihood of HF was also elevated almost ninefold with aHR of 8.31.

To conclude, cardiovascular events after moderate exacerbations occur a little later than after severe exacerbations. By demonstrating the differences in the timing of cardiovascular events following moderate and severe COPD exacerbations, this study highlights significant increases in cardiovascular risk following exacerbations. The extended duration of heightened cardiovascular risk beyond 1 year, regardless of exacerbation severity, underscores the chronic impact of COPD exacerbations on cardiovascular health. This emphasizes the ongoing need for being vigilant and proactively monitor and proactive manage cardiovascular risk in COPD patients, even in the absence of acute exacerbations. The authors also note "*postexacerbation intervention approaches should include the management of cardiopulmonary risk to reduce the risk of COPD and cardiovascular events in the short and long terms*".

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CLINICAL STUDY

Birth Defects with the Use of Valproate: An Impact on the Prescribing Pattern amongst the Health Care Professionals in India

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ABSTRACT

Objective: The present study was carried out to evaluate the impact of Pharmacovigilance Programme of India (PvPI) initiative to reduce the use of sodium valproate/valproic acid (SV/VA) in the women of childbearing age group. **Methods:** In our questionnaire-based study, 251 health care professionals (HCPs) participated from 41 medical colleges across India, which are also working as Adverse drug reaction Monitoring Centres (AMCs) under PvPI. **Results:** The data collected at the National Coordination Centre (NCC) shows the significant decrease in the use of SV/VA in the women of childbearing age group after the PvPI initiative on Information, Education, and Communication (IEC) materials for HCPs. However, it was found that 40% of HCPs of Gynecology and Neurology Department were still not aware of the initiative taken by the Government of India to reduce the use of SV/VA in the women of childbearing age group. **Conclusion:** PvPI, therefore, needs to take more measures to increase the reach of their resource materials to all HCPs.

Keywords: Sodium valproate, valproic acid, pharmacovigilance, AMCs, health care professionals

Sodium valproate (SV) is chemically sodium 2-propylpentanoate. It is also known as sodium dipropylacetic acid, sodium 2-propylvalerate, sodium dipropylacetate, sodium di-n-propylacetate, etc. SV is a white crystalline powder with a characteristic odor of valproic acid (VA). The chemical name of VA is 2-propylpentanoic acid. It is also known as n-dipropylacetic acid, 2-propylvaleric acid, dipropylacetic acid. Valproic acid is a colorless viscous liquid[1].

GLOBAL STATUS OF SV

In 1981, the Central Drugs Standard Control Organisation (CDSCO) approved an application of SV/VA for the treatment of all forms of epilepsy in India by the manufacturer. SV freeze dried powder 400 mg/mL injection was approved in year 1999 for the treatment of generalized epilepsy as well as for partial epilepsy in patients for whom oral therapy is temporarily not possible. SV tablet/syrup was approved in year 2000 for additional indications of manic episodes associated with bipolar disorders[2].

Currently, it is available in different strength. Divalproex tablets 125 mg, 250 mg, 500 mg, 750 mg, and 1 g; syrup - 250 mg/5 mL. Valproic acid tablet - 200 mg, 300 mg, 500 mg; injection (sodium valproate) 100 mg/mL and 250 mg/mL; valproic acid oral solution 200 mg/5 mL; SV tablets 100 mg, 200 mg[3].

SV/VA has been associated with multiple adverse effects such as hepatotoxicity, neurotoxicity including psychotic features and hallucinations, headache, abdominal pain, dizziness, hyponatremia, pancreatitis, thrombocytopenia, etc[4]. The drug has been included under the Schedule H of Drugs and Cosmetics Act, 1940, wherein the drug needs to be prescribed by a Register Medical Practitioner and cannot be sold without a prescription. Over the years, SV/VA related safety concerns in women of childbearing age, particularly birth defects, have been observed and reported[5]. Within several years after receiving United States Food and Drug

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Administration (US FDA) approval in the late 1970s, valproate was shown to increase the risk for major congenital malformations and learning disabilities in the offspring of women who used the drug during pregnancy[6]. The European Medicines Agency (EMA) has taken several initiatives to reduce the risk associated with SV/VA. Countries such as Netherlands, Germany, Finland, Denmark, Australia, Sweden, United States of America (USA), United Kingdom (UK) have reported congenital anomalies due to the maternal use of SV/VA[7]. France has banned the use of SV during pregnancy, claiming to be the first country in Europe to take such a step[8].

The published literature recommends training of both pregnant women taking valproate and the clinicians prescribing them[9]. The Netherlands and the UK have introduced a special training program for pharmacists for prescription of SV/VA in the childbearing age group women, and consideration of other alternative antiepileptics has been suggested because of the safety issues. The US FDA has also issued a drug safety communication with reference to use of SV/VA and other valproate-related products regarding teratogenic effects like neural tube defects, low IQ and cognitive impairment in children born to SV/VA exposed women[10]. Women of childbearing age taking valproate should be warned of its teratogenicity and advised to plan pregnancies, take a higher dose of folate, discuss reducing the dose of valproate or changing the medication with their physician, and have antenatal screening. After birth, the infant should be examined for a wide range of reported abnormalities. Neurodevelopmental assessment should continue throughout childhood. The World Health Organization (WHO) through its program for International Drug Monitoring has been continuously involved in education and advocacy for the member states to reduce the risk of SA/VA in women of childbearing age[11].

A survey-based questionnaire was developed and circulated to all regional Adverse drug reaction Monitoring Centres (AMCs) across India. The present survey-based study demonstrated the prescribing pattern of SV/VA among the health care professionals (HCPs) for the treatment of epilepsy in women of childbearing age group in India.

MECHANISMS OF TERATOGENICITY WITH SV/VA

Even though a range of potential mechanisms have been reported for SV/VA-induced teratogenicity, including histone deacetylase (HDAC) inhibition and folate antagonism, the exact mechanism is not yet fully understood and several hypotheses have been proposed (Fig. 1). It has been demonstrated experimentally, using enzyme-linked immunosorbent assays (ELISAs) and cell culture modeling that VA serves as a noncompetitive inhibitor of the high affinity folate receptors. Assays in HEK293T cells have shown that the membrane-bound folate receptors of VA treated cells bind significantly lower amounts of folic acid than do untreated cells[12]. Another proposed theory is the possible influx of proteins monocarboxylate transporter 1 (MCT1) and MCT2, if concentrations are increased or if polymorphisms alter the expression of MCT proteins, the corresponding influx of VA increases maternally and therefore, within the fetus. VA causes chronic impairments in developing human neurons; its exposure alters neuronal properties by inhibiting HDAC and glycogen synthase kinase (GSK)-3 pathways[13].

The cytoskeletal protein myristoylated alanine-rich C-kinase substrate like protein 1 (MARCKSL1) has been proposed to mediate VA-induced morphological defects. A review of studies has shown that intrauterine exposure to VA in rats is associated with changes in hippocampal cell numbers as well as folate metabolism. The mechanism of action is believed to be "neuroprotective" in various disease models such as stroke, neurodegenerative disease or traumatic injury to the central nervous

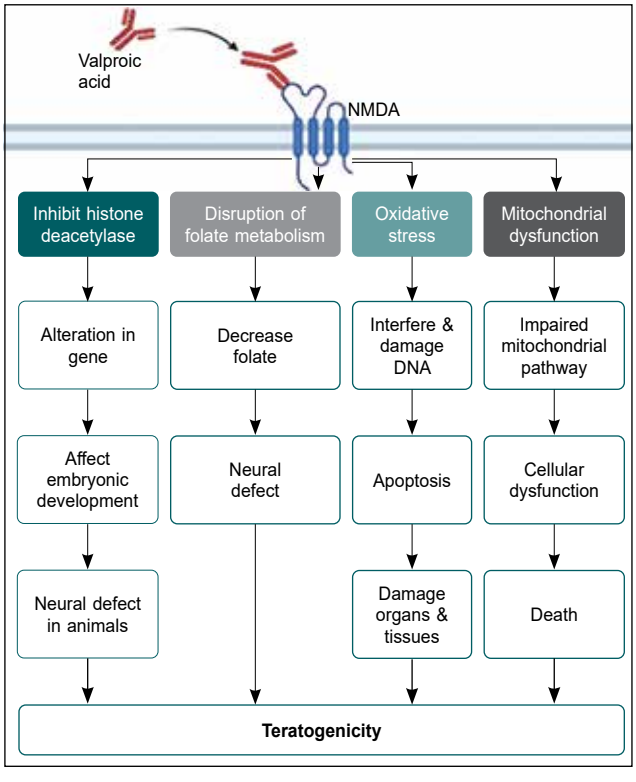

Figure 1. Proposed schematic mechanism of SV/VA-induced teratogenicity.

system. However, this effect may not be beneficial during intrauterine development. Because programmed cell death is an important component of normal brain development, VA exposure may interfere with normal embryonically regulated apoptotic programs, resulting in cell type-selective overgrowth that could contribute to the defects observed in VA-exposed off springs[14].

The mechanism of SV/VA-induced teratogenicity are as follows:

- **Inhibition of HDACs**: SV/VA is known to inhibit HDACs, which can lead to alterations in gene expression and affect embryonic development. HDAC inhibition has been shown to cause neural tube defects in animal studies[15].
- **Disruption of folate metabolism**: SV/VA has been shown to decrease folate levels in the body, which is essential for neural tube formation during embryonic development. Low folate levels have been associated with an increased risk of neural tube defects[16].
- **Oxidative stress**: SV/VA has been shown to increase oxidative stress in cells, which can damage DNA and interfere with embryonic development. This oxidative stress can also lead to apoptosis, which can disrupt the normal development of organs and tissues[17].
- **Mitochondrial dysfunction**: SV/VA has been shown to impair mitochondrial function, which can lead to cellular dysfunction and death. Mitochondrial dysfunction has been linked to a range of developmental disorders and may contribute to the teratogenic effects of SV/VA[18].

It is important to note that the exact mechanism of SV/VA-induced teratogenicity may be multifactorial and may involve a combination of these mechanisms. Additionally, the risk of teratogenicity may be influenced by factors such as the dose, the timing of exposure and genetic susceptibility. Women of childbearing age who are prescribed VA should be counseled on the potential risks of the medication during pregnancy and advised to use effective contraception[19].

The Pharmacovigilance Programme of India at Indian Pharmacopoeia Commission (PvPI-IPC) as the National Coordination Centre (NCC) is also working to reduce the risk of SV/VA. Several educational materials have been developed for this purpose and circulated to all the AMCs across the country for sensitization of the HCPs.

METHODOLOGY

Methods

A questionnaire-based cross-sectional study was conducted to evaluate the outcome of the post-sensitization activities since 2017 regarding the safety of SV/VA use in the women of childbearing age group. A questionnaire was prepared by the NCC-PvPI and circulated via e-mail to all the AMCs across the country. Figure 2 shows the flow of information during the study.

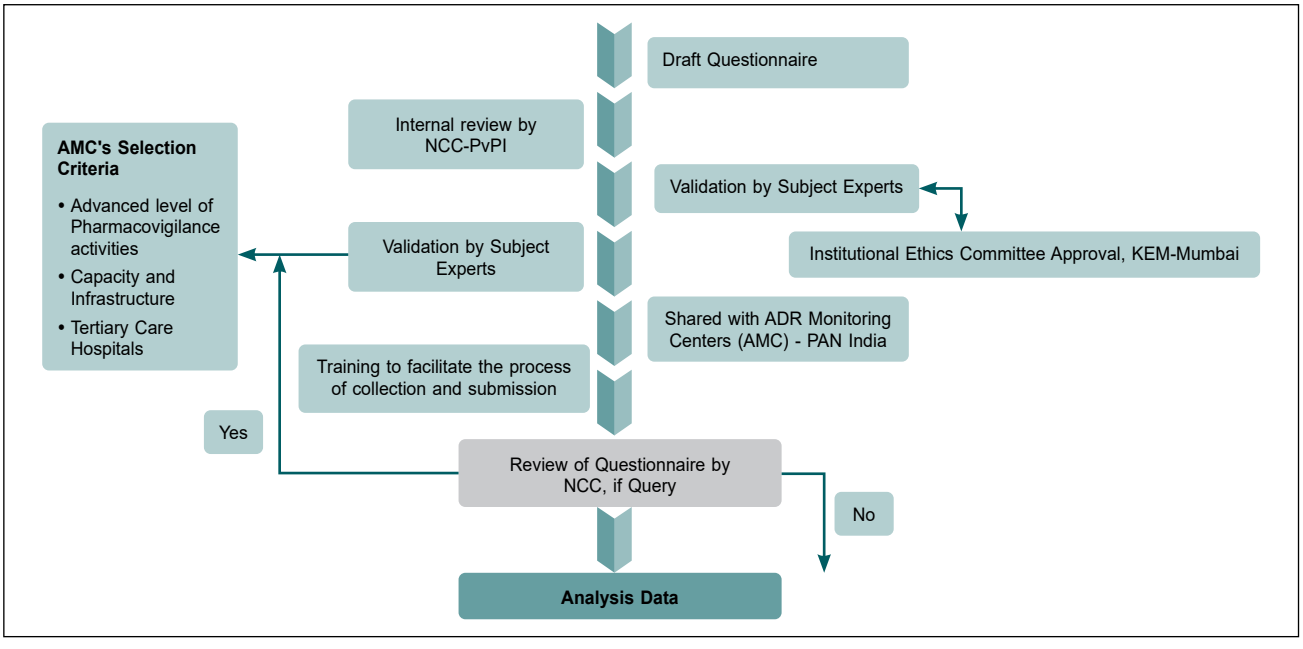

Figure 2. Flow diagram depicting data collection.

Brief About the Questions

The questions were designed on the basis of general information regarding the use of SV/VA in women of childbearing age group, its dose, and any adverse events, which the HCPs had faced during the therapy, etc. Gynecologists/obstetricians and neurologists were selected as participants for this survey study as this was the health care worker population most likely to use SV/VA in pregnant and childbearing age group women.

The details of the participants were kept confidential and their identities were not obtained in their responses (only their qualification as obstetrician/gynecologist or neurologist was obtained). The questions pertaining to the identity of the patient were not added to maintain the confidentiality of the patients.

Questionnaire Validation by Circulation

At the time of the questionnaire circulation, NCC-PvPI had a strong network of 534 AMCs for reporting of adverse drug reactions/adverse events. Of these, 134 AMCs were selected by applying the criteria such as, quality of the specialized care services, quantity and frequency of ADR Reporting and Pharmacovigilance Capacity at the Centre (Fig. 2).

The questionnaire was validated by trained and skilled Pharmacovigilance teams at the AMCs and 10 questions were finalized focusing the prescribing pattern, adverse event reporting and preventive measures for SV/VA use in childbearing age group women. The NCC-PvPI provided study assistance to the PvPI team at the AMCs so that they could complete the questionnaire as planned.

Period of study

The study was conducted from 2017 to 2022 and the survey was open for the 6 months from December 2021 to June 2022.

Ethics Committee approval

The approval for the study was obtained from Institutional Ethics Committee (IEC)-I relating to Biomedical and Health Research (BHR), Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India, with the registration Number EC/OA-51/2022.

VigiLyze

During the same study period, we also attempted to analyze the trend or pattern of SV/VA adverse event reporting from these centers. The VA/SV safety data was extracted from VigiLyze. These data showed that there was a significant decreasing trend in the pattern of SV/VA individual case safety reports (ICSRs) in women of childbearing age (Fig. 3).

RESULTS

Out of 134 AMCs, 41 AMCs responded to the questionnaire, which included a total of 251 responses from HCPs. Out of these, 50 responses were obtained from gynecologists/obstetricians, 22 from neurologists, and 179 from the interns/resident doctors in the AMCs. There were 93 responses in which it was mentioned that SV is not being used by that HCP.

- Have you ever noticed any adverse event(s) associated with the use of SV/VA in the women of childbearing age (18-40 years)?

  Yes ☐ No ☐

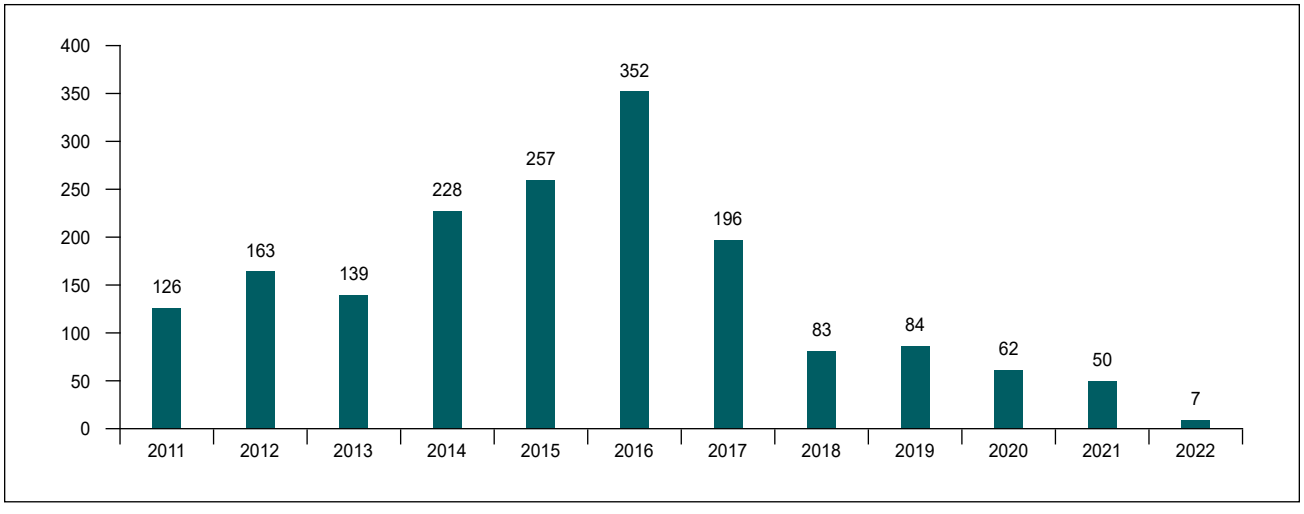

Figure 3. VigiLyze displayed significant decreasing trend in the pattern of SV/VA ICSRs.

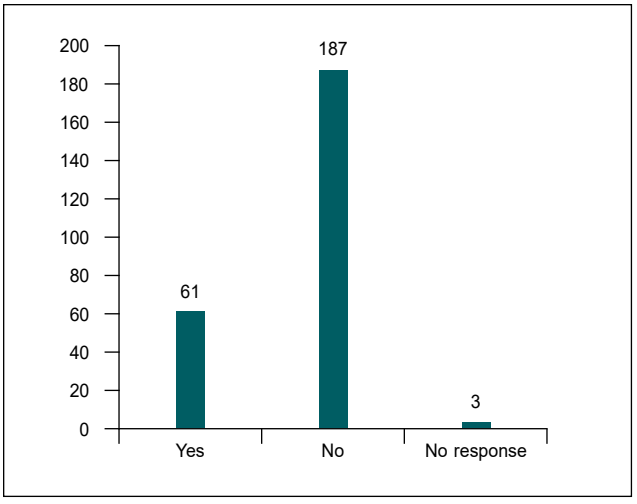

Figure 4. Significant numbers of HCPs had never noticed any adverse events with SV/VA in women of childbearing age group.

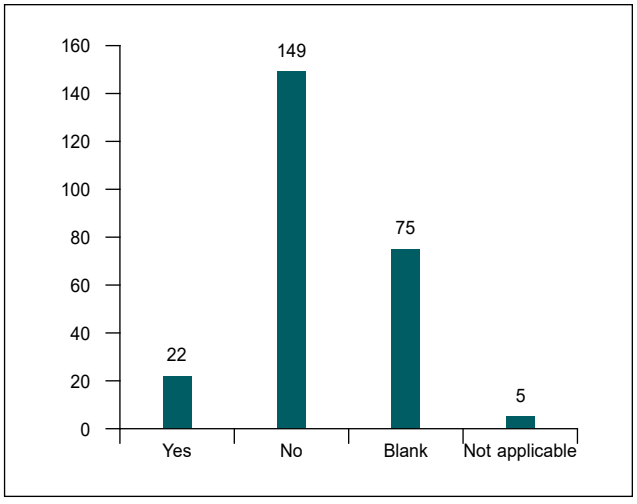

Figure 5. Reporting of adverse events with the use of SV/ VA to AMCs.

Reply: One hundred eighty-seven HCPs mentioned that they had not noticed any adverse event(s), while 61 HCPs had noticed. Three HCPs did not provide any response (Fig. 4).

- If yes, have you reported this to AMC/Regional Centre/National Pharmacovigilance Centre?

  Yes ☐ No ☐

  Reply: Only 22 HCPs had mentioned that they reported such events to Regional AMCs. However, 149 respondents mentioned that they had not reported and 75 left the question blank (Fig. 5).

- If yes, what common adverse effects have you come across related to SV/VA among the women of child bearing age?

  Birth Defects ☐ Others_____

  (Please specify the adverse events if any in maternal or neonatal)

  Reply: There were 20 reports of birth defects and related events, 6 fetal bradycardia, 6 polycystic ovary syndrome, 10 events of weight gain and 4 events of alopecia. Abdominal discomfort, gingival hyperplasia, increase in liver enzyme, gastritis, menstrual irregularities, acneiform eruptions, neuro-developmental disorder, gingival enlargement, spina bifida, headache, drowsiness, tremors, dizziness, vomiting, weakness were the other infrequent events reported due to use of SV/VA in women of childbearing age.

- What about the dose, duration, and frequency of administration of SV/VA to cause the adverse event(s) mentioned in question number 3?

  Dose of SV/VA_____

  Frequency of administration_____

  (Please specify the dose administered for total number of days/ months/years/duration of treatment)

  Reply: The SA/VA was taken by the patients as per the standard dosage regimens for respective indications.

- The adverse events with the use of SV/VA have been noticed in childbearing age group of women but could not be reported because of

  Time constraint ☐ Legal issues ☐

  Unwillingness ☐

  Not aware of where to report ☐

  Others _____

  Reply: Thirty-three ADRs were not reported by the HCPs because of time constraints, 4 HCPs were avoiding reporting due to the fear of legal issues, 13 HCPs were not willing to report, 35 HCPs were not aware of where to report, and 128 HCPs had other reasons (Fig. 6).

- Due to the adverse events associated with the SV/ VA among this special age group, did you prescribe any alternate drug?

  Yes ☐ No ☐

  Reply: One hundred (100) HCPs responded that they had started prescribing an alternative medicine to SV/VA due to the ADR, while 86 HCPs still continued with SV/VA. The remaining did not respond.

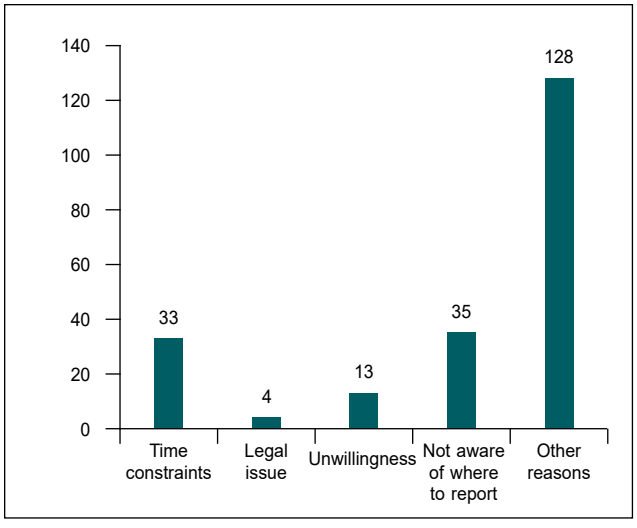

Figure 6. Significant numbers of HCPs were not reported.

- If yes, name those drugs below:

  Alternate drugs _____

  Reply: As an alternative medicine to sodium valproate, medicines prescribed by HCPs were as enumerated in Box 1.

Box 1. Alternative Drugs Prescribed by the HCPs

Olanzapine	Carbamazepine
Risperidone	Phenytoin
Lamotrigine	Flunarizine
Oxcarbazepine	Propranolol
Levetiracetam	

- When did you start prescribing alternative drugs?
  a. After alert/educational materials received from National Pharmacovigilance Centre or WHO
  b. Based on my own clinical judgment
  c. Others (please specify)

  Reply: Twelve HCPs started prescribing alternative drugs after awareness received from National Pharmacovigilance Centre or WHO, while 110 HCPs prescribed them based on their own clinical judgment.
- How did you share the experiences related to SV/VA safety in childbearing age group women to the HCPs and others?
  a. Seminar/trainings/meetings/social media campaigns
  b. Not shared because_____
  (you may specify the reason)

  Reply: One hundred two HCPs had shared the WHO and IPC newsletters and bulletins among their colleagues via seminar/meetings, etc. to disseminate the information, whereas 149 number HCPs applied their own clinical experiences for not using the SV.

DISCUSSION

Up to April 2022, 93 of the 134 centers contacted did not complete the questionnaire because they said the drug was not in use in the centers since the guidance was issued in 2016.

The responses showed that only 20 of the 58 HCPs (34.5%), who observed an ADR in women aged 18 to 40, reported the event. The reasons for not reporting included: did not know where to report (16.6%), time constraints (13.3%), unwillingness (6.2%), and legal issues (2.1%). The most frequent ADRs concerned birth defects. The dose and frequency of administration reported varied widely: 200 mg/day to 2,000 mg, QD or BID or TID with duration from 7 days to 3 years.

A total of 100 HCPs reported they had prescribed an alternative treatment because of the adverse events associated with SV/VA. These treatments included carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, olanzapine, propranolol, and second-generation antipsychiatric drugs.

Out of 116 respondents, 71 started prescribing alternative medication based on their clinical judgment, 24 followed the alert of educational materials received from their National Pharmacovigilance Centre or WHO, and 21 during the study. Out of 142 respondents, 94 shared their experience with safety of valproate containing treatments in women of childbearing age through seminars, training, meetings, and social media, 7 shared during ward rounds and clinical teaching and the remaining 41 did not share for a variety of reasons including no permission from department head, or legal reasons.

The WHO has advised about the safety and use of SV/VA in childbearing age group, particularly events related to birth defects[20]. The IPC, NCC-PvPI has published several IEC materials for stakeholders about the risk associated with SV/VA use in women of childbearing age group. Subsequent to this advisory from NCC-PvPI, we found that there was a decrease in the ICSRs reporting among the childbearing age group

women in the Indian database. This can be attributed to compliance with NCC-PvPI Advisory.

However, a decreased overall reporting by chance or other reasons could also have occurred. The responses reveal that 40% were aware and 60% were unaware of SV/VA teratogenic effects. Around 37% of HCPs involved in the study stated that they were not using the drug. The IEC material for Pharmacovigilance played an important role in creating awareness amongst HCPs and other stakeholders.

LIMITATION OF STUDY

The study is limited to two departments, i.e., Gynecology and Neurology. The reason of including these two departments was that the exposure of SV/VA is generally expected to be maximum in these two departments.

Another limitation that the response to the questionnaire was poor among the AMCs despite multiple reminders (only 41 out of 134 AMCs responded). The use of option 'others' in the questionnaire was not properly answered by the responders.

CONCLUSION

The data shows that the efforts of IPC, NCC-PvPI through Resource Material (i.e., Newsletter, Posters, Advisory, etc.), training, seminars, etc. might have resulted in a decrease in the trend of ICSRs with use of SV/VA in women of childbearing age group.

Nevertheless, on account of the low awareness levels regarding reporting of ADRs and the availability of IEC materials, further strategies need to be developed to improve the penetration of NCC-PvPI activities at the level of the AMCs. This data can help in promoting the safe use of SV/VA and taking appropriate steps for protecting the safety of vulnerable population at the global level. IPC as a WHO Collaborating Centre will support WHO to expand/initiate this survey-based questionnaire study to its member states.

Competing Interests

Nil conflict of interest.

Funding

Not applicable.

Availability of Data and Materials

The data is available in the form of soft copy received from various health care professionals.

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Clinical Outcomes in Asymptomatic *Mycobacterium avium* Complex Pulmonary Infections

Even in the absence of symptoms, a notable proportion of asymptomatic patients with *Mycobacterium avium* complex pulmonary infection (MAC-PI) had cavitary lesions, which are typically associated with more severe disease. Younger patients and those with specific risk factors like cavitary lesions, positive acid-fast bacilli (AFB) smear were more likely to need treatment. These findings from a retrospective analysis were published in the May 2024 issue of the journal *Respiratory Medicine*[1].

A team from Japan conducted this retrospective analysis of patients newly diagnosed with MAC-PI, as per the established microbiological and radiological criteria, at Fukujuji Hospital between January 2018 and June 2020. Out of the 200 patients included in the study, 111 patients were symptomatic and 89 were asymptomatic at the time of their diagnosis. The aim of this study was to compare the clinical characteristics and course of asymptomatic and symptomatic patients, and to identify factors influencing the commencement of treatment.

Data analysis showed that cavitary lesions were present in nearly 16% of asymptomatic patients, whereas 28.8% of the symptomatic group had cavitary lesions at the time of presentation. "Despite milder radiologic findings", note the authors, 38 asymptomatic patients (42.7%) started treatment. Risk factors that influenced the decision to initiate treatment in this group were younger age, positive AFB smear and presence of cavitary lesions.

Twenty-two patients (57.9%) experienced progression of disease that required treatment during follow-up. Of these, 13 patients (34.2%) showed radiological progression without worsening of symptoms. Treatment regimens were consistent across both groups. The two groups were comparable in terms of rates of culture conversion, microbiological recurrence, or spontaneous culture conversion between asymptomatic and symptomatic patients.

This study shows that symptomatic patients with MAC-PI are more likely to have cavitary disease. It further demonstrates that some asymptomatic MAC-PI patients with certain risk factors are more likely to progress and require therapy. Since the clinical course in asymptomatic patients can be similar to that in patients with symptoms, it is essential to diagnose and treat asymptomatic disease.

Hence, these patients should regularly undergo careful evaluation, especially radiological monitoring, which is critical in diagnosing and assessing the severity of the condition. The findings highlight the necessity for individualized treatment plans based on comprehensive risk assessments rather than depending only on the presence of symptoms to start treatment. This approach ensures timely intervention and optimizes outcomes for both asymptomatic as well as symptomatic patients.

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CLINICAL STUDY

Role of Beta-Blockers in Prevention of Hepatopulmonary Syndrome in Chronic Liver Disease: An Observation

ASHISH GAUTAM*, PRABHAT AGRAWAL*, ASHWINI NIGAM*

ABSTRACT

Aim: Study was initiated to study the presence of hepatopulmonary syndrome (HPS) in chronic liver disease patients, and role of beta-blockers in its occurrence. **Methods:** Patients admitted in Dept. of Medicine and patients attending the Medicine OPD were examined and investigated for presence of HPS irrespective of its typical clinical features as explained in the literature. Patients having ascites or pleural effusion were managed by means of paracentesis and pleural tap first and then included in the study. Patients having any other primary pulmonary disease like bronchial asthma or chronic obstructive pulmonary disease were excluded from the study. Arterial blood gas analysis and contrast-enhanced echocardiography was done to confirm presence of arterial hypoxemia and pulmonary shunt, the diagnostic criteria. **Results:** During 1 year study, total 125 patients were enrolled in the study after appropriate selection criteria. Twenty-eight out of 125 patients were not taking propranolol. Propranolol is contraindicated in these patients for one or two reasons. Four out of these 28 patients developed HPS. One out of 97 patients who were on propranolol developed HPS. Total 5 patients were confirmed having HPS. The Fisher's exact test statistic value is 0.008887. The result is significant at $p < 0.01$. **Conclusion:** Patients of cirrhosis with portal hypertension on treatment with propranolol were having significantly lower chances of development of HPS then those without propranolol. Propranolol may have preventive role for development of HPS.

Keywords: Hepatopulmonary syndrome, beta-blockers, chronic liver disease

Hepatopulmonary syndrome (HPS) and porto-pulmonary syndrome are two rare, but fatal extrahepatic complications of chronic liver disease and portal hypertension. Till date, no definitive treatment options are available for managing these complications. Few studies claim liver transplantation as the definitive treatment. Flückiger in 1884 for the first time recognized this clinical entity as complication of liver cirrhosis. Liver disease, with presence of arterial hypoxemia evident on arterial blood gas (ABG) analysis, and intrapulmonary vascular shunt as evident on contrast-enhanced echocardiography or use of technetium-99m–labeled macroaggregated albumin for lung scanning with quantitative brain uptake makes the triad of HPS. Clinical presentations are nonspecific and may include dyspnea on exertion or rest, presence of spider angiomas, clubbing, cyanosis and severe arterial hypoxemia. This study was conducted with the aim to evaluate patients of chronic liver disease for presence of HPS. Diagnostic criteria for HPS are given in Table 1[1]. Retrospective data regarding diagnosis and treatment were collected and evaluated for treatment given so far for management of cirrhosis.

METHODS

One hundred twenty-five patients with liver disease of varied etiologies were enrolled in the study after

Table 1. Diagnostic Criteria for the Hepatopulmonary Syndrome[1]

Oxygenation defect	Partial pressure of oxygen <80 mmHg or alveolar-arterial oxygen gradient ≥15 mmHg, while breathing ambient air
Pulmonary vascular dilatation	Positive findings on contrast-enhanced echocardiography or abnormal uptake in the brain (>6%) with radioactive lung-perfusion scanning
Liver disease	Portal hypertension (most common) with or without cirrhosis

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appropriate selection criteria. Patients with any evidence of primary respiratory or cardiac disease were excluded. Cirrhosis and portal hypertension was confirmed by history, clinical examination, pathological investigations and radiology.

Patients were further evaluated for presence of platypnea, cyanosis, clubbing, and angiomas; the typical associations of HPS. Irrespective of the grade of cirrhosis and presence of signs and symptoms all selected patients were evaluated for pulmonary shunt. For this a transthoracic contrast echocardiography was done using agitated saline. Visibility of micro-bubbles in the left atrium between 3 to 6 cardiac cycles after they were seen in right-atrium indicated micro-bubble passage through an abnormally dilated vascular bed. A due consent was taken from patients for this examination.

An ABG analysis was done in these patients. ABG was done in both resting supine position and in sitting upright position after 5 minutes. As per the diagnostic criteria in Table 1, cut-off value for considering HPS were resting PO_2 <80 mmHg and/or ΔPO_2, i.e., PO_2 (A-a) ≥15 mmHg. We used resting PO_2 in our study. Using these criteria 5 patients were diagnosed to have HPS. Out of 125 patients, 97 were using propranolol, whereas 28 were not using propranolol as it was contraindicated in them due to one or more side effects in them. Propranolol is a drug used in portal hypertension as prophylaxis for secondary variceal bleeding. Four out of 28 developed HPS, whereas only one out of 97 developed HPS. The Fisher's exact test statistic value is 0.008887. The result is significant at $p < 0.01$.

RESULTS

Out of 125 patients, 5 patients fulfilled the diagnostic criteria for presence of HPS. The mean age of patients was 52.6 years with standard deviation (SD) = 10.6. Eighty-four were male and 41 were females. Cause of chronic liver disease were alcoholic liver disease 56 (44.8%), chronic hepatitis B 38 (30.4%), chronic hepatitis C 14 (11.2%), noncirrhotic portal fibrosis 5 (4.0%); others and undetermined causes 12 (9.6%) (Table 2). Others included one case of autoimmune hepatitis. On the basis of examination and investigation, patients were categorized into Child's grade: A = 12, B = 20, and C = 93. On retrospective evaluation of medical records, it was found that 28 out of 125 patients were not taking propranolol or any other beta-blocker. They all had one or two contraindications for using beta-blocker. Beta-blockers are among preferred drugs used to reduce portal hypertension. Patients were categorized further in Group A (beta-blocker using group) n = 97, and Group B (beta-blocker contraindicated group) n = 28. In Group A, one out of 97 was diagnosed to have HPS. In Group B, 4 out of 28 patients were diagnosed to have HPS (Table 3).

The Fisher's exact test statistic value is 0.008887. The result is significant at $p < 0.01$. Causes of contraindications for beta-blocker use were sinus bradycardia, clinical postural hypotension, diabetes, prolonged PR interval.

Table 2. Clinical Characteristics of 125 Study Patients

Parameters	No. of patients
Sex	
Male	84
Female	41
Clinical features	
Platypnea	5
Cyanosis	12
Clubbing	42
Angiomas	3
Causes of CLD	
Alcohol	56
Hepatitis B	38
Hepatitis C	14
NCPF	5
Others	12
Reason for beta-blocker contraindications	21
Sinus bradycardia	18
Postural hypotension	2
Diabetes	3
Prolonged PR interval	

CLD = Chronic liver disease; NCPF = Noncirrhotic portal fibrosis.

Table 3. Characteristics of 5 Patients with HPS

	No. of patients
Sex	
Male	4
Female	1
Clinical features	
Platypnea	3
Cyanosis	5
Clubbing	5
Angiomas	0
Mean PaO_2	**78%**

DISCUSSION

Cirrhosis leads to a hyperdynamic state of circulation especially in presence of acute or chronic hepatocellular failure[2]. Peripheral vasodilatation and reduced peripheral vascular resistance manifests with peripheral flushing, erythema, decreased blood pressure, and bounding pulse. Cardiac output is increased to compensate for above. The numerous functionally inactive arteriovenous fistulas open up due to this profound vasodilatation. HPS is manifestation of similar mechanism in liver cirrhosis, which develops when the pulmonary venous shunt is at its extreme[3]. Cyanosis and reduced oxygen saturation is a frequent finding in decompensated cirrhosis[4]. Various medications are tried in HPS with variable effectiveness but most do not seems to be effective in its reversal. Pentoxyphyllin[5] and methylene blue[6] till date are found effective up to a certain extent in HPS reversal.

Beta-blockers are among the preferred drugs for patients with portal hypertension. They are given in titrated doses to prevent primary and secondary bleeding from esophageal varices. Beta-blockers were clearly declared ineffective in management of HPS[7]. Still, there are few hopes in theory favoring them to use in HPS. A case report published in 1994 by Saunders et al, in which a patient improved from HPS proved by serial exercise testing[8]. This patient was on beta-blocker for some time after which he showed signs of improvement. Although author itself was not able to describe the role of beta-blocker in improvement from HPS still comparing the data from our study with this case may open the new ways of thoughts in using beta-blockers as prophylaxis or may be for treatment of HPS.

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CASE REPORT

A Rare Convergence: A Case Report on Bilateral Hypoglossal Schwannoma in a Patient with Charcot-Marie-Tooth Disease 2

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ABSTRACT

This case presents a rare co-occurrence of Charcot-Marie-Tooth disease type 2 (CMT2) and schwannoma, shedding light on the intricate relationship between two neurogenic disorders. CMT is a hereditary sensorimotor peripheral neuropathy while schwannoma is a benign encapsulated tumor involving Schwann cells. The co-occurrence has been previously described in 2 patients in a family with CMT type 1A. Our case reports the first documented instance of the co-occurrence of bilateral hypoglossal schwannoma in CMT2.

Keywords: Hereditary motor and sensory neuropathy, axonal neuropathy, CMT2, schwannoma, bilateral hypoglossal schwannoma

Charcot-Marie-Tooth disease (CMT) is the most common inherited neurological disorder that affects sensory and motor peripheral nerves leading to sensory loss and progressive muscle weakness. Inheritance pattern can be autosomal dominant/autosomal recessive/X-linked recessive (AD/AR/XLR) depending on the specific gene involved. These disorders cause demyelination, axonal loss, and abnormal interactions between Schwann cells and the axons they ensheath. The rare combination of CMT1A and median nerve and spinal cord schwannomas have been previously reported[1]. Our case is the first documented case of bilateral hypoglossal schwannoma in CMT2.

CASE HISTORY

A 41-year-old female developmentally normal till 15 years of age presented with insidious onset gradually progressive symmetric, distal more than proximal, weakness of all four limbs, lower limbs followed by upper limb involvement, with wasting (Fig. 1) and foot deformities. Sensory examination revealed graded sensory loss of all modalities (both small fiber and large fiber) with impaired joint position and vibration sense with no peripheral nerve thickening and spinal deformities with no significant family history with normal higher mental function, cranial nerves including hypoglossal (Fig. 2) (with no atrophy, weakness, or fibrillations), cerebellum, and autonomic functions. In view of the chronic long-standing slowly progressive distal prominence neuropathy with pes cavus (Fig. 3) and hammer toes (Fig. 4), the possibility of hereditary sensory and motor neuropathy was considered. On investigating complete blood count (CBC), random blood sugar (RBS), renal function test (RFT), liver function test (LFT), serum electrolytes, serum B12, thyroid profile, autoimmune panel, voluntary counseling and testing center (VCTC), split skin smear for leprosy were negative. Serum electrophoresis and urine Bence-Jones protein, paraneoplastic workup and other relevant investigations to exclude acquired pathology were negative.

Nerve conduction study revealed bilateral lower limb sensory-motor axonal and bilateral upper limb sensory axonal polyneuropathy[2]. As a part of routine investigation and to exclude structural pathology, magnetic resonance imaging (MRI) brain with spine contrast was done, which revealed two well-defined T1 hypointense and T2 hyperintense mildly enhancing

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Figure 1. Illustrates small muscle wasting of hand.

Figure 2. No atrophy of tongue.

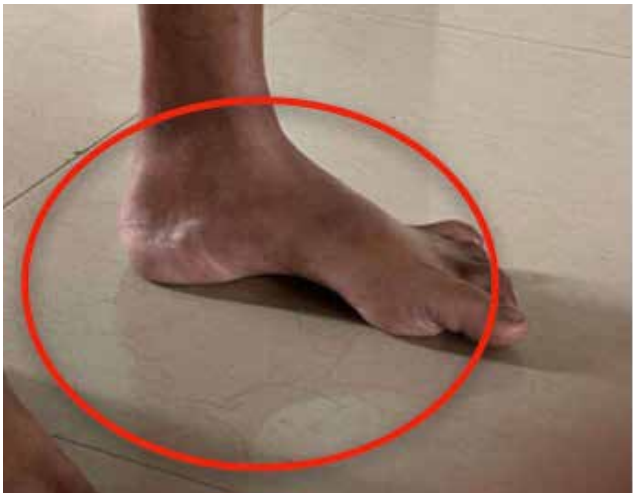


Figure 3. Illustrates pes cavus.

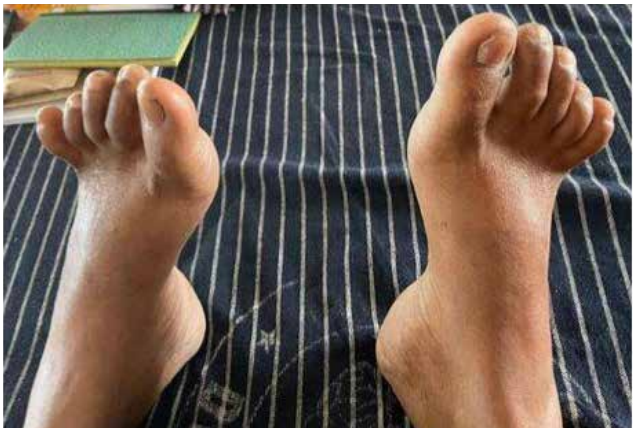
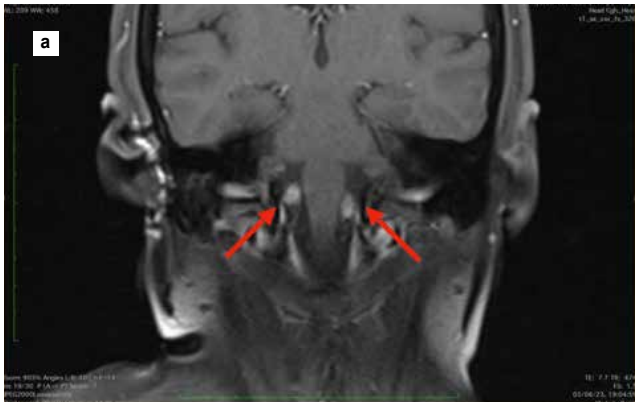


Figure 4. Illustrates hammer toes.

lesions of size 7 × 4 mm on right and 8 × 4 mm in left lateral cerebellomedullary cisterns with no diffusion restriction or mass effect over adjacent structures suggestive of bilateral hypoglossal schwannoma (Fig. 5 a and b)[3]. Sural nerve biopsy showed severe axonal neuropathy with no granulomas, inflammation, storage material, or amyloidosis (Fig. 6). Fite-Faraco stain for *Mycobacterium leprae* was negative. CMT diagnosis is a



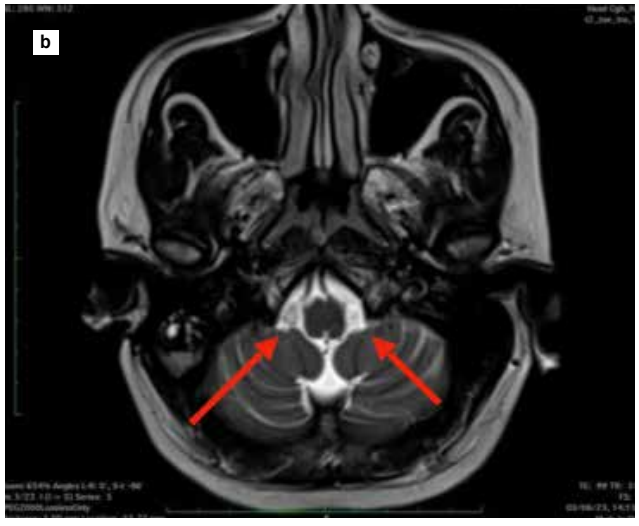


Figure 5 a and b. MRI T1 coronal contrast (**a**) and T2 axial (**b**) showing two well-defined enhancing lesions in lateral cerebellomedullary cisterns suggestive of hypoglossal schwannoma.

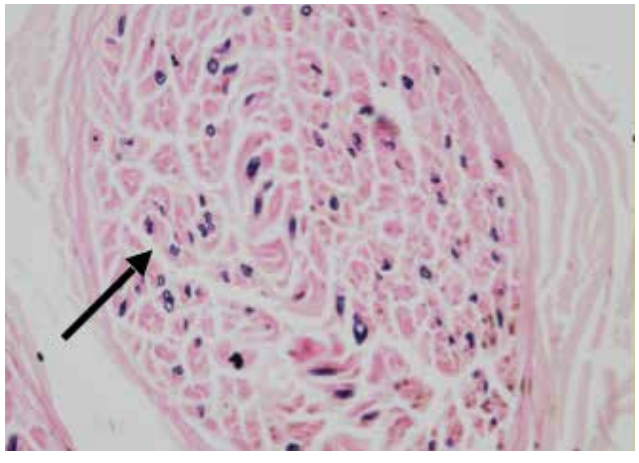


Figure 6. Histopathological examination of right sural nerve showing severe axonal loss with Kulchitsky stain.

comprehensive approach that involves clinical findings, electrodiagnostic findings and genetic analysis for specific gene mutations.

With this clinical background of slowly progressive course that did not lead to severe disability, electrodiagnostics (upper limb motor nerve conduction velocities >45 m/s) and nerve biopsy showed predominant axonal involvement; hence, the probability of CMT2 was considered in our case[4]. Due to logistic reasons, genetic analysis was planned during follow-up.

DISCUSSION

Charcot-Marie-Tooth disease and schwannomas are distinct neurological conditions with limited reported associations. Heckmann et al reported a case of hereditary neuropathy with liability to pressure palsy (HNPP) in which *PMP22* gene deletion is demonstrated[5]. A case report on schwannomas of spinal cord and median nerve have been reported in 2 patients in a family with CMT1A with *PMP22* gene duplication[1]. These case reports suggested that the dysfunction of *PMP22* gene may not only result in peripheral neuropathy but also schwannomas providing a common pathogenic basis for Schwann cell abnormality. However, to the best of our knowledge, after reviewing the available literature no case has been reported in CMT2. This is the first documented case in CMT2. Several genes involved in CMT2 includes *MFN2* (Mitofusin 2), *GARS* (Glycyl-tRNA synthetase), *NEFL* (Neurofilament light chain), *HSPB1* (Heat shock protein beta 1), *MPZ* (Myelin protein zero), and several other genes. Further studies are needed to shed light on the exact pathophysiology behind shared pathogenesis of schwannoma and CMT2.

CONCLUSION

This is the first case report on bilateral hypoglossal schwannoma in a patient with CMT2 despite lacking genetic analysis due to the rarity of this co-occurrence.

Further genetic research is needed to study the occurrence of schwannomas in CMT2 and that would guide us to establish optimal management settings for affected patients.

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■■■■

BRIEF COMMUNICATION

Unveiling the Nexus of Cognitive Impairment in Diabetes: Exploring the Enigmatic "Diabetic Melancholy"

RITWIK GHOSH*, SUBHANKAR CHATTERJEE†, RANA BHATTACHARJEE‡, SOUVIK DUBEY#

ABSTRACT

Patients living with diabetes suffer from a spectrum of cognitive and mood disorders. To encompass the diverse neuropsychological aspects of diabetes, the authors herein propose the new construct of "diabetic melancholy", which stands for memory impairments, executive dysfunctions, language impairments, psychomotor retardation, low mood, and apathy. Authors have also described the underlying neural basis of cognitive dysfunction in diabetes.

Keywords: Diabetes, cognition, dementia, mood disorders

Diabetes mellitus, a chronic metabolic disorder characterized by hyperglycemia, has emerged as a global health concern, affecting over 400 million individuals worldwide[1]. Beyond its well-documented effects on systemic health, diabetes exerts a profound impact on cognitive function, presenting a complex interplay between metabolic dysregulation and neural vulnerability[2]. In recent years, the convergence of Alzheimer's disease (AD), vascular dementia (VaD), and cognitive impairment in diabetes has sparked intense scientific interest, prompting a re-evaluation of the neuropathological underpinnings and clinical manifestations of cognitive decline in this population[3].

PATHOPHYSIOLOGY OF COGNITIVE IMPAIRMENTS IN DIABETES

The pathophysiology of cognitive impairments in diabetes is multifaceted, involving a constellation of interconnected mechanisms that span molecular, cellular, and system levels[4]. At the molecular level, insulin resistance, a hallmark feature of type 2 diabetes mellitus (T2DM), disrupts insulin signaling pathways within the brain, impairing glucose uptake and metabolism, and precipitating neuronal dysfunction[5]. Insulin, traditionally known for its role in glucose homeostasis, also serves as a neurotrophic factor, promoting neuronal survival, synaptic plasticity, and cognitive function[6]. Dysregulation of insulin signaling pathways, as observed in insulin resistance, compromises these neurotrophic effects, leading to synaptic loss, impaired neurotransmitter release, and cognitive decline[7].

Concurrently, chronic low-grade inflammation, fuelled by adipose tissue-derived cytokines and activated microglia, instigates neuroinflammatory cascades that exacerbate neuronal injury and synaptic loss[8]. Proinflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) disrupt synaptic plasticity, impair neurotransmitter metabolism, and promote oxidative stress, further exacerbating neuronal dysfunction in diabetes[9,10].

Furthermore, the formation of advanced glycation end products (AGEs) and oxidative stress engender oxidative damage to cellular macromolecules, including proteins, lipids, and nucleic acids, precipitating neurodegenerative processes and compromising neuronal viability[11]. AGEs, formed through nonenzymatic glycation of proteins and lipids, accumulate in the brain parenchyma and cerebral vasculature, promoting neuronal apoptosis, blood-brain

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barrier dysfunction, and neurovascular uncoupling[10,11]. Oxidative stress, arising from an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, further exacerbates neuronal injury, leading to mitochondrial dysfunction, DNA damage, and impaired synaptic transmission[12].

Moreover, dysregulation of sirtuins, a family of NAD^+-dependent deacetylases implicated in cellular homeostasis and longevity, and tau protein phosphorylation precipitates tau pathology, contributing to synaptic dysfunction and cognitive decline[13]. Sirtuins, particularly SIRT1 (silent information regulator sirtuin 1), regulate multiple cellular processes, including energy metabolism, DNA repair, and stress response, through deacetylation of target proteins such as histones, transcription factors, and metabolic enzymes[14]. Dysregulation of sirtuin activity, as observed in diabetes, disrupts mitochondrial function, promotes oxidative stress, and impairs synaptic plasticity, contributing to cognitive dysfunction[13]. Tau protein, a microtubule-associated protein implicated in microtubule stabilization and axonal transport, undergoes hyperphosphorylation in diabetes, leading to the formation of neurofibrillary tangles and synaptic loss[15]. Tau pathology, akin to that observed in AD, disrupts neuronal function, impairs synaptic transmission, and precipitates cognitive decline in diabetes[16].

PATTERN OF COGNITIVE IMPAIRMENTS IN DIABETES

A nuanced understanding of the cognitive phenotype in diabetes necessitates a comprehensive evaluation of diverse cognitive domains, encompassing memory, executive function, attention, language, and visuospatial skills[17]. Memory impairments, ranging from deficits in working and immediate memory to impaired incidental memory, are pervasive in diabetes, reflecting disruptions in hippocampal and prefrontal cortical circuits. Executive dysfunctions, encompassing deficits in cognitive flexibility, inhibitory control, and task switching, further underscore the cognitive burden of diabetes[17-19]. Disruptions in attentional control, reflected in impaired sustained and divided attention, compromise cognitive performance and functional independence in diabetes. Moreover, language deficits, encompassing impaired verbal fluency, comprehension, and expressive language, impede communication and social interaction in diabetes. Visuospatial impairments, characterized by deficits in visuoconstruction, visual memory, and spatial orientation, further contribute to cognitive dysfunction and functional decline in diabetes. The heterogeneity of cognitive impairments in diabetes underscores the complex interplay between metabolic dysregulation, neural vulnerability, and individual differences in cognitive reserve and resilience[2,17].

NEUROANATOMICAL SUBSTRATES INVOLVED IN DIABETES

The neuroanatomical correlates of cognitive impairments in diabetes are intricately woven into the fabric of neural circuits governing mood, memory, and executive function. Neuroimaging studies have revealed structural and functional alterations in regions such as the ventromedial prefrontal cortex (VMPFC), anterior cingulate cortex (ACC), and hippocampus, implicated in mood regulation, attentional control, and episodic memory encoding[20]. Moreover, disruptions in neurotransmitter systems, particularly serotonin, have been implicated in the pathogenesis of mood disorders and cognitive impairments in diabetes[21]. Aberrant serotonergic signaling within the prefrontal-limbic circuitry may contribute to the development of depression and apathy, prevalent features among patients with diabetes.

EXPLORING COGNITIVE FUNCTIONS

The intricate interplay between cognitive functions and neural substrates in diabetes unveils a complex tapestry of neurocognitive dysfunction, spanning diverse domains such as memory, attention, language, and executive function[22]. Memory circuits, encompassing the hippocampal formation and associated limbic structures, are vulnerable to the deleterious effects of hyperglycemia and insulin resistance, precipitating deficits in episodic memory and semantic memory retrieval[23]. Disruptions in attentional control, mediated by dysregulation of prefrontal cortical and thalamic circuits, compromise cognitive performance and functional independence in diabetes[24-26]. Moreover, language processing, a quintessential human faculty, is subserved by distributed neural networks encompassing the auditory cortex, Broca's area, and the anterior temporal lobe[27]. In diabetes, disruptions in syntactic processing and semantic retrieval may manifest as decreased verbal fluency and comprehension, reflecting underlying alterations in frontal-temporal connectivity. Executive dysfunctions, encompassing deficits in cognitive flexibility, planning, and problem-solving, underscore the cognitive burden of diabetes. Disruptions in dorsolateral prefrontal cortical (DLPFC) circuits, coupled with aberrant dopaminergic signaling within the mesocorticolimbic pathway may contribute to a deficit in reward processing and motivation observed in diabetes[28].

Information processing speed, a cardinal feature of cognitive efficiency, emerges as a sensitive marker of cognitive impairment in diabetes. Disruptions in frontal-subcortical networks, mediated by insulin resistance and neuroinflammation, contribute to slow cognitive processing and impaired attentional control, precipitating deficits in task-switching and inhibitory control[7]. Dysfunction within the prefrontal-striatal circuits impairs the ability to initiate and sustain goal-directed behavior, leading to deficits in cognitive flexibility and planning[29].

Moreover, alterations in the connectivity and function of the default mode network (DMN), a set of brain regions implicated in introspection and self-referential thought, may contribute to cognitive dysfunction in diabetes[30]. Dysfunctional DMN connectivity has been associated with rumination, excessive worry, and depressive symptoms, highlighting the potential role of maladaptive cognitive processes in the development and progression of "diabetic melancholy"[24,25,30].

THE ENIGMA OF "DIABETIC MELANCHOLY"

Against the backdrop of cognitive impairments and mood alterations in diabetes[31], the concept of "diabetic melancholy" emerges as a unifying framework to elucidate the complex interplay between cognitive dysfunction and affective symptoms[32]. **M**emory impairment, **E**xecutive dysfunction, **LAN**guage deficit, psy**CHO**motor retardation, **L**ow mood, and Apath**Y** converge to define the heterogeneous phenotype of "diabetic melancholy" (Fig. 1).

This wide spectrum of cognitive dysfunctions and mood alterations in diabetes reflects the profound impact of metabolic dysregulation on neural circuits governing emotion regulation, reward processing, and stress response.

Moreover, the bidirectional relationship between cognitive impairment and mood disorders in diabetes underscores the need for integrated treatment approaches that target both cognitive and affective symptoms[33]. Pharmacological interventions, such as insulin sensitizers, anti-inflammatory agents, and neurotrophic factors, hold promise for mitigating neuronal injury and preserving cognitive function in diabetes. Psychosocial interventions, including cognitive-behavioral therapy, mindfulness-based interventions, and lifestyle modifications, may complement pharmacotherapy by addressing maladaptive cognitive and emotional patterns and promoting adaptive coping strategies[34,35].

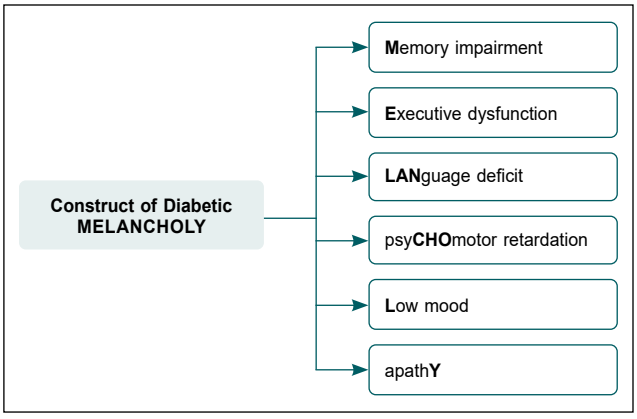

Figure 1. Components of "diabetic melancholy".

CONCLUSION

The elucidation of "diabetic melancholy" heralds a paradigm shift in our understanding of the intricate interplay between metabolic dysregulation, neural vulnerability, and cognitive dysfunction in diabetes. By unraveling the neuropathological underpinnings and clinical manifestations of cognitive impairments in diabetes, we pave the way for targeted interventions and therapeutic breakthroughs aimed at mitigating the cognitive burden of this pervasive metabolic disorder. From molecular mechanisms to clinical phenotypes, the journey to unravel the enigmatic "diabetic melancholy" promises to yield insights that transcend disciplinary boundaries and transform the landscape of diabetes care. Integrating scientific knowledge with clinical expertise and patient-centered care will be essential for addressing the complex interplay between cognitive impairment, mood disorders, and metabolic dysregulation in diabetes.

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Patient Care and Medical Decision-Making

STANDARDS OF CARE AND TREATMENT GUIDELINES

In 2011, the Institute of Medicine (IOM) defined clinical practice guidelines as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options". Clinical guidelines enable practice of evidence-based medicine (EBM)[1].

Adherence to the recommendations in clinical practice guidelines enhance quality of care by reducing likelihood of adverse events. By standardizing care, they also reduce variations in clinical practice. A survey of 3,098 general practitioners (GPs) was conducted in Germany between April and August 2020. A little over half (52%) of those surveyed held a positive attitude towards guidelines. The outcomes of compliance to guidelines were an increase in evidence-based approach (69%), standardization of diagnosis and treatment (62%) and decrease in overprovision or underprovision of care (57%). Sixty-seven percent of the GPs opined that abiding by the guidelines sharpened their clinical skills, while 62% felt that guidelines positively impacted quality of care[2].

Guidelines should be[1]:

- Developed using the best available scientific evidence,
- Developed by a multidisciplinary panel using consensus methods,
- Well disseminated, and
- Updated from time to time incorporating latest evidence.

Clinical guidelines developed by renowned professional bodies can be relied upon and may be used in medical negligence cases[3]. However, physicians are not legally obligated to follow guidelines. If they are not applicable to some patients, then doctors may choose not to follow the recommendations provided therein. However, they must justify any deviation from the guidelines[4]. The reasons for not following the recommendations must be duly recorded in the patient's medical record[5].

"The standard of care is the benchmark that determines whether professional obligations to patients have been met"[6]. Failure to provide treatment that is consistent with the standard of care is liable for negligence. The standard of care and degree of care are not synonymous. The standard of care is similar in all patients, the degree of care differs. This means that a GP and a specialist have to meet the same standard of care, but the degree of care provided by them is not the same. "The specialist is expected to exercise the ordinary skill of his speciality and not that of the GP"[7].

The Supreme Court has defined medical negligence in the case of Jacob Mathew vs. state of Punjab and Anr on 5 August, 2005 as follows:

"*The essential components of negligence, as recognised, are three: 'duty', 'breach' and 'resulting damage', that is to say:*

- *The existence of a duty to take care, which is owed by the defendant to the complainant;*
- *The failure to attain that standard of care, prescribed by the law, thereby committing a breach of such duty; and*
- *Damage, which is both causally connected with such breach and recognised by the law, has been suffered by the complainant (Para 1.23). If the claimant satisfies the Court on the evidence that these three ingredients are made out, the defendant should be held liable in negligence (Para 1.24).*"

Liability in negligence is unassailable if all the three can be established on the preponderance of probabilities (civil lawsuit) or beyond reasonable doubt (criminal prosecution). The onus of proving negligence lies on the complainant. It is just not enough to allege a breach of duty; it has to be conclusively proven that the injury occurred "directly" on account of the action of the doctor.

The Bolam test has been traditionally used to assess two main issues of medical negligence – the standard of care as required by the law and whether the doctor accused of medical negligence has complied with that standard of care.

In Jacob Mathew v. State of Punjab, the Supreme Court of India has observed: *"A simple lack of care, and error of judgment or an accident, is not proof of negligence on the part of a medical professional. So long as a doctor follows a practice acceptable to the medical profession of that day, he cannot be held liable for negligence merely because a better alternative course or method of treatment was also available or simply because a more skilled doctor would not*

have chosen to follow or resort to that practice or procedure which the accused followed. When it comes to the failure to taking precautions what has to be seen is whether those precautions were taken which the ordinary experience of men has found to be sufficient; a failure to use special or extraordinary precautions which might have prevented the particular happening cannot be the standard for judging the alleged negligence. So also, the standard of care, while assessing the practice as adopted, is judged in the light of knowledge available at the time of the incident, and not at the date of trial. Similarly, when the charge of negligence arises out of failure to use some particular equipment, the charge would fail if the equipment was not generally available at that particular time (that is, the time of the incident) at which it is suggested it should have been used."

Errors can be made in an Emergency even by Experts and may not Amount to Negligence

In Martin F. D'Souza vs. Mohd. Ishfaq on 17 February, 2009, the cases Supreme Court of India has observed: *"The higher the acuteness in an emergency and the higher the complication, the more are the chances of error of judgment …."*

Medical Accident is not Negligence

In Jacob Mathew v. State of Punjab, the Supreme Court of India has observed: *"Mere accident is not evidence of negligence."* The order also clarifies that the difference of opinion or error of judgment cannot be termed negligence, also adverse reactions or medical accidents cannot be classified under medical negligence.

"Not Getting Cured" is not Negligence

In Jacob Mathew v. State of Punjab, the Supreme Court of India has observed: "*Simply because a patient has not favourably responded to a treatment given by a physician or a surgery has failed, the doctor cannot be held liable per se by applying the doctrine of res ipsa loquitur.*"

Error of Judgment is not Negligence

In Jacob Mathew v. State of Punjab, the Supreme Court of India has observed: "*An error of judgment on the part of a professional is not negligence per se.*"

Wrong Diagnosis does not Amount to Medical Negligence

In the matter of Vinod Jain vs. Santokba Durlabhji Memorial Hospital & Anr (Civil Appeal No. 2024 of 2019 Arising out of SLP(C) No. 32721/2017, dated February 25, 2019), the Supreme Court upheld the order of the National Consumer Disputes Redressal Commission (NCDRC), which had held that the case "would at best be a case of wrong diagnosis, but not medical negligence".

"Deviation from normal practice is not necessarily evidence of negligence. To establish liability on that basis, it must be shown:

1. *That there is a usual and normal practice;*
2. *That the defendant has not adopted it; and*
3. *That the course adopted is no professional man of ordinary knowledge skill would have taken had he been acting with ordinary care."*

In the judgment in Kusum Sharma & Ors vs. Batra Hospital and Medical Research Centre & Ors on 10 February, 2010, the Supreme Court observed that *"while deciding whether the medical professional is guilty of medical negligence following well known principles must be kept in view.*

I. *Negligence is the breach of a duty exercised by omission to do something which a reasonable man, guided by those considerations which ordinarily regulate the conduct of human affairs, would do, or doing something which a prudent and reasonable man would not do.*

II. *Negligence is an essential ingredient of the offence. The negligence to be established by the prosecution must be culpable or gross and not the negligence merely based upon an error of judgment.*

III. *The medical professional is expected to bring a reasonable degree of skill and knowledge and must exercise 4 (1968) 118 New LJ 469 5 (supra) a reasonable degree of care. Neither the very highest nor a very low degree of care and competence judged in the light of the particular circumstances of each case is what the law requires.*

IV. *A medical practitioner would be liable only where his conduct fell below that of the standard so far reasonably competent practitioner in his field.*

V. *In the realm of diagnosis and treatment there is scope for genuine difference of opinion and one professional doctor is clearly not negligent merely because his conclusion differs from that of other professional doctor.*

VI. *The medical professional is often called upon to adopt a procedure which involves higher element of risk, but which he honestly believes as providing greater chances of success for the patient rather than a procedure involving lesser risk but higher chances of failure. Just because a professional looking to the gravity of illness has taken higher element of risk to redeem the patient out of his/her suffering which did not yield the desired result may not amount to negligence.*

VII. Negligence cannot be attributed to a doctor so long as he performs his duties with reasonable skill and competence. Merely because the doctor chooses one course of action in preference to the other one available, he would not be liable if the course of action chosen by him was acceptable to the medical profession.

VIII. It would not be conducive to the efficiency of the medical profession if no doctor could administer medicine without a halter round his neck.

IX. It is our bounden duty and obligation of the civil society to ensure that the medical professionals are not unnecessarily harassed or humiliated so that they can perform their professional duties without fear and apprehension.

X. The medical practitioners at times also have to be saved from such a class of complainants who use criminal process as a tool for pressurizing the medical professionals/hospitals particularly private hospitals or clinics for extracting uncalled for compensation. Such malicious proceedings deserve to be discarded against the medical practitioners.

XI. The medical professionals are entitled to get protection so long as they perform their duties with reasonable skill and competence and in the interest of the patients. The interest and welfare of the patients have to be paramount for the medical professionals."

CLINICAL DECISION-MAKING AND EVIDENCE-BASED MEDICINE

Evidence-based medicine has been the cornerstone of clinical decision-making for several years now. It is defined as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients." EBM is an amalgamation of up-to-date research and clinical decision-making leading to better patient outcomes. It also takes into consideration patient's values such as autonomy and what is available and affordable for a particular patient.

While knowledge undoubtedly aids in accurate clinical decision-making, experience makes the process more efficient. "EBM should be used to guide, and not replace, clinical decision-making"[8].

There are two stages in clinical reasoning[9].

- **Early stage:** Developing one or more diagnostic hypotheses.
- **Verification stage:** Testing the hypotheses generated and confirming the final diagnosis.

The dual process theory of cognition is an interplay of two systems of thinking. One which is intuitive, fast and almost unconscious thinking, called "system 1 thinking", while the other is slower, analytical and effortful thinking called "system 2 thinking". Both systems of thinking are implicated in both stages of clinical reasoning[9]. This dual system also applies to decision-making in clinical medicine[10].

Clinical Decision-making Checklist[9]

Taking the history	Ordering investigations
Performing the physical examination	Formulating a diagnosis
Generating a differential diagnosis	Documenting decisions

The process of confirming a diagnosis entails the following steps[10]:

- **Information gathering:** "It is a capital mistake to theorize before one has data", said Sherlock Holmes. Appropriate information must be gathered from the history, physical examination, including laboratory/imaging investigations before reaching to a conclusion. One should stay alert so as to not miss findings on history and physical examination that may turn out to be significant.
- **Hypothesis generation:** A list of differential diagnoses corresponding to the patient's illness is worked out.
- **Hypothesis testing and reflection:** The hypothesis that is generated must be examined and discarded, if appropriate.

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Treatment of Post-Kidney Transplant Osteoporosis

Denosumab is effective in increasing bone mineral density (BMD) and reducing fracture risk in kidney transplant recipients with osteoporosis, according to a retrospective study from Italy published May 10, 2024 in the journal *Calcified Tissue International*[1]. It was also safe with no significant adverse effects attributable to it on kidney function or graft survival.

The study objective was to evaluate the long-term effectiveness of denosumab in improving BMD in kidney transplant recipients with osteoporosis and compare these outcomes with those not receiving any treatment for osteoporosis. BMD was measured at the femoral neck, lumbar spine and hip using dual-energy X-ray absorptiometry scans at baseline and at regular intervals during follow-up.

The study included 46 patients who had received a kidney transplant and had osteoporosis. Denosumab was administered subcutaneously in the dose of 60 mg/6 months to this study group of 23 patients. They were matched 1:1 with a group of 23 age- and sex-matched untreated kidney transplant recipients, which acted as the control group. All patients were given oral cholecalciferol and calcium supplementation. Data on serum creatinine, alkaline phosphatase (ALP), 25-hydroxyvitamin D and parathyroid hormone (PTH) were also collected. The primary outcome was changes in the BMD at 4 years.

In the denosumab-treated group, there was a significant increase in BMD from baseline, with an average increase of 9.0% at the lumbar spine. The total hip BMD increased by an average of 3.8%. On the other hand, there was a significant decrease in BMD at all sites in the untreated group. The lumbar spine and total hip BMD decreased by an average of −3.0% and −6.3%, respectively. The differences in percent BMD changes between the denosumab-treated and untreated groups were statistically significant at all measured sites. “Similar results were found for the respective Z-scores”, state the authors.

In the denosumab-treated group, ALP serum levels significantly decreased from baseline. The between-group difference in ALP changes was statistically significant. Both groups maintained normal levels of PTH and 25-hydroxyvitamin D. No significant differences in serum creatinine levels, incidence of hypocalcemic events and acute graft rejection rates were observed between the denosumab-treated and untreated groups.

These findings suggest that denosumab is a beneficial treatment for osteoporosis in kidney transplant recipients, contributing to improved bone health and potentially reducing the risk of fractures. It was also safe in terms of kidney function and graft survival. This supports the consideration of denosumab as a standard viable treatment option in managing osteoporosis in this group of patients, alongside calcium and vitamin D supplementation.

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64th Annual Conference of the Indian Society of Gastroenterology (ISGCON 2023)

ORGANIC DYSPEPSIA – INTESTINAL METAPLASIA CANCER

Dr Prateek Sharma, USA

- Organic dyspepsia is characterized by the presence of an established organic, systemic or metabolic cause with symptoms, and resolution or improvement occurs after addressing the underlying condition. Examples include gastroesophageal reflux disease (GERD), drug-induced mucosal injury, peptic ulcer disease, malignancy (gastric, pancreatic, colorectal), intestinal ischemia, and abdominal aortic aneurysm.
- Gastric intestinal metaplasia (GIM) and gastric cancer are the main concerns of untreated/under-treated dyspepsia.
- GIM is a premalignant condition of the human stomach with a 10-fold increased risk of gastric cancer.
- GIM serves as a histological step before gastric dysplasia.
- A high-quality esophagogastroduodenoscopy with retroflexion and careful inspection of the cardia and fundus is recommended to identify patients who benefit from surveillance.
- Around 4-8 biopsies of two topographic sites (at the lesser and greater curvature, from both the antrum and the corpus) should be taken.
- The management of GIM involves detailed and careful endoscopy with sampling, stratifying for the severity and extent of chronic atrophic gastritis and GIM, and testing and eradicating *Helicobacter pylori*. Risk assessment should be individualized through shared decision-making, and endoscopic surveillance every 3 to 5 years is recommended for those at higher risk, focusing on early detection and prevention.

CHOOSING BIOLOGICS AND SMALL MOLECULES IN 2024

Dr Ashwin Ananthakrishnan, USA

- The process of picking the right treatment begins with the initial evaluation of the patient, which includes defining the severity of the disease and prognostic factors.
- For Crohn's disease, predictors of an unfavorable course include age 40, the need for steroids in the first flare, perianal disease, upper GI lesions, ileocolonic lesions and stricturing and penetrating behavior.
- Similarly, for ulcerative colitis, predictors of an unfavorable course encompass younger age, female gender, extensive colitis, nonsmoking status and low serum albumin.
- When deciding on the right treatment in a clinical setting, there are preferences, good options, last choices (not necessarily wrong) and treatments with sparse data.
- For moderate to severe luminal Crohn's disease, the preference is given to infliximab, adalimumab, risankizumab and ustekinumab. Upadacitinib is considered a good option, while azathioprine (?) and vedolizumab are the last choices.
- In the case of perianal Crohn's disease, infliximab is preferred, and good options include adalimumab, vedolizumab, and ustekinumab. Risankizumab and upadacitinib have sparse data on their efficacy and safety.
- For individuals with both inflammatory arthritis and inflammatory bowel disease (IBD), the preference is for anti-TNF (tumor necrosis factor) medications. Janus kinase (JAK) inhibitors and ustekinumab are considered good options, while vedolizumab is the last choice. Ozanimods have sparse data on their efficacy and safety.
- Similarly, for those with both psoriasis and IBD, preferences include anti-TNF and ustekinumab. Vedolizumab is a last choice, and ozanimod and JAK inhibitors (excluding arthritis) have sparse data on their efficacy and safety.

FUNCTIONAL DYSPEPSIA DEMYSTIFYING FOR CLINICIANS

Dr Shobna Bhatia, Jaipur

- Rome IV diagnostic criteria for functional dyspepsia necessitate the presence of one or more bothersome

symptoms such as postprandial fullness, early satiation, epigastric pain, or epigastric burning. Additionally, there should be no evidence of a disease, as determined by negative findings in upper endoscopy, likely to explain the symptoms.

- Immune function, inflammation, and epithelial permeability play a role in functional dyspepsia, with low-grade mucosal inflammation, increased eosinophils and mast cells in the stomach and duodenum, and elevated duodenal eosinophil levels in both epigastric pain syndrome and postprandial distress syndrome cases. A higher incidence of atopy and food allergy is also noted.
- Psychology is intertwined with functional dyspepsia, as anxiety and depression are commonly associated. Stress, whether from pain or psychological comorbidities, can upregulate the hypothalamic-pituitary-adrenal axis, increasing corticotropin-releasing hormone levels and activating local inflammatory processes, potentially affecting gut function, including epithelial permeability, immune function and the microbiome.
- Overlap is a well-established phenomenon in functional GI disorders. Patients with overlap syndromes tend to experience more severe symptoms, with motor dysfunction in one GI tract segment impacting motility in another. Sensorimotor disorders are often generalized, and common mechanisms partially explain the observed overlap.

BENIGN ESOPHAGEAL STRICTURE

Dr Kulwinder S Dua, USA

- Refractory benign esophageal strictures are characterized by fibrotic restriction. Electrocautery shows a 100% response in 1 session for short strictures (<1 cm), while long strictures (1.5-5 cm) require a mean of 3 sessions with no complications.
- Regenerative medicine options include autologous pluripotent cell therapy, fabricated autologous epidermal cell sheets and tissue engineering.
- Esophageal stents demonstrate an overall success rate of 46% to 80%, with lower success rates for upper esophageal strictures ranging from 10% to 30%.

EUS-GUIDED VASCULAR THERAPY

Dr Praveer Rai, Lucknow

- Visceral artery aneurysms are often asymptomatic and are incidental findings on CT and MRI. Mortality from their rupture ranges from 25% to 100%.
- Indications of treatment of true aneurysms include size >2 cm irrespective of anatomical site, symptomatic patients and increasing size of the aneurysm, size <2 cm in women who wish to become pregnant and patients who require liver transplant.
- All false aneurysms should be treated, irrespective of their size or location.
- Complications of endovascular treatment are technical failure to catheterize the artery, arterial thrombosis/embolism, coil migration, aneurysm recurrence, hematoma or pseudoaneurysm at the puncture site and abdominal pain, fever (post-embolization syndrome).
- The role of endoscopic ultrasound (EUS) in vascular therapy is still evolving.
- EUS-guided therapy has high technical and clinical success rates with no significant adverse events. It is effective and less invasive than surgery/percutaneous options.
- It is a day care procedure and does not require general anesthesia and can be done in conscious sedation. It permits precise targeting of aneurysm and precise injection. Less expensive than radiological treatment and can be repeated safely. A multicenter study is needed to further establish its role.
- Despite technical success, there are limitations of a small number of enrolled subjects and poor methodology, varied procedural techniques and lack of large randomized controlled trials.
- Indications should be clearly stated and patients carefully selected. Radiological and surgical back up is a must.

AVOIDING MISTAKES IN AUTOIMMUNE PANCREATITIS

Dr Shounak Majumder, USA

- Autoimmune pancreatitis (AIP) is classified into two types: Type 1 AIP, known as lymphoplasmacytic sclerosing pancreatitis, is considered the pancreatic manifestation of IgG4-related disease. Type 2 AIP is characterized as idiopathic duct-centric pancreatitis.
- The imaging appearance of AIP is highly suggestive/typical when there is a diffusely enlarged gland with featureless borders, delayed enhancement with or without a capsule-like rim and long or multiple main pancreatic duct strictures without upstream dilation. Supportive/indeterminate features include

a focally enlarged gland without features highly suggestive of cancer.

- Recognition of relapse in AIP is defined by the development of radiologic findings or biochemical abnormalities consistent with a new or worsening inflammatory process, requiring re-treatment, or an increase in the dose of steroids that was previously being tapered.
- Establishing the diagnosis of AIP can be challenging, and it is crucial to recognize clinical and radiologic features that differentiate AIP from pancreatic cancer.

Key Points

- Serum IgG4 elevation is not pathognomonic of AIP and can be elevated in pancreatic cancer.
- Serum CA 19-9 can be falsely elevated in benign cholestasis.
- The presence of main pancreatic duct dilation and vascular invasion favors a diagnosis of pancreatic cancer. Lack of steroid response indicates an alternative diagnosis.
- About a third of patients with AIP have refractory disease and benefit from maintenance therapy.
- Pancreatic atrophy is common and can result in endocrine and exocrine dysfunction.

GURU GYAAN: CHAT WITH DR PATRICK KAMATH

Dr Patrick Kamath, USA

How will you Find Happiness in Your Career?

- Finding happiness in your career involves recognizing the distinction between a job, which is short-term, and a career, which is long-term. While a job may lead to leaving work feeling angry, a career aims to leave work with satisfaction. In the context of financial gain, a job helps collect money, whereas a career focuses on accumulating valuable experiences.
- Requirements for a successful career include expertise, a bit of luck, the ability to be a clutch performer, mentorship and maintaining a healthy work-life balance. Being a clutch performer entails traits such as focus, discipline and adaptability, requiring individuals to give their best effort, or 110%, every day despite stress.
- Engaging in meaningful activities to prevent burnout is crucial, dedicating at least 2 hours a day to something that holds personal significance.
- Pro tips for a successful career emphasize the importance of maintaining good health, as a healthy individual can better contribute to the well-being of others, Dream big, continuously learn and prioritize service to patients before self.

BLOATERS AND BELCHERS

Dr Uday C Ghoshal, Kolkata

- Excessive belching, as per Rome IV, is when it is bothersome enough to disrupt usual activities and occurs more than 3 days per week. It may occur either as an isolated symptom or may be associated with GERD, functional dyspepsia, gastroparesis, anxiety, and pregnancy.
- Functional bloating and distension is diagnosed when recurrent symptoms of abdominal illness or pressure or a visible increase in abdominal girth with symptoms at least 1 day per week and active for 3 months, with onset of 6 months and without a predominance of pain and alteration in bowel habits. Bloating too may occur as an isolated symptom, but may also be associated with irritable bowel syndrome (IBS), functional constipation/diarrhea/dyspepsia.
- Abdominal bloating and distension has multiple pathophysiological basis of which gut microbiota, foods and visceral hypersensitivity are most important. Multiple disorders of gut-brain interaction are associated with bloating.
- Belching may be supragastric or gastric in origin. The two conditions differ somewhat in pathophysiological basis and can be differentiated by impedance manometry. A comprehensive history and clinical observation may help to differentiate the two.
- Supragastric belching is a voluntary behavior disorder (aerophagia), while gastric belching is an involuntary disorder (physiologic). Supragastric belch is characterized by too frequent belching (up to 20 per minute); it does not occur during sleep, talking and distraction and increases with stress. Patients with severe and frequent belching often describe that their belching initially started with bloating or a bothersome sensation in the stomach. It is mostly unrelated to meals. The associated comorbid conditions include anxiety and neurosis.
- Gastric belch, on the other hand, is less frequent (few per hour) and occurs with greater force. It occurs after ingestion of meals and CO_2-containing beverages. GERD and functional dyspepsia are the usual comorbidities. The principles of treatment are to

empty the colon, improve motility, restriction of foods that generate gas, and manipulation of gut microbiota.

- Pharmacological treatment includes baclofen (both in supra and gastric belching) and proton pump inhibitors in GERD-associated belching.

REFEEDING SYNDROME

Dr Amit Yelsangikar, Bengaluru

- Refeeding syndrome is a common but under recognized condition.
- Many at-risk patients such as chronic alcoholism, liver disease, chronic pancreatitis, perioperative patients (bowel strictures, IBD, Koch's), GI cancer (chemoradiotherapy), patients referred for feeding access, will come to GI service.
- The key problems of refeeding are hypophosphatemia, thiamine deficiency, salt and water retention (edema/left ventricular failure). Hypophosphatemia is a life-threatening problem.
- Neuropsychiatric manifestations may occur due to thiamine deficiency (Wernicke's encephalopathy).
- NG feeding – higher risk than those given IV fluids or parenteral nutrition.
- Baseline evaluation includes labs (blood counts, electrolytes, phosphates, calcium, magnesium), liver biochemistry, KFT, sepsis screen, ECG, Echo, NT-proBNP, chest X-ray, and ultrasound.
- Do not rush to give carbohydrates, exercise caution regarding fluids. Document feeding protocol, adhere to it and audit periodically.

MONITORING IN IBD

Prof Simon Travis, UK

- Inflammatory bowel disease fluctuates between relapse and remission, semi-relapse and semi-remission. Monitoring is covalently linked to outcomes.
- The goal of monitoring is to change the course of the disease, to improve the quality of life (QoL) of the patients and prevent complications.
- Zealots advocate monthly FCal/FBC/CRP, colonoscopy and biopsy 12 weeks after change in therapy, bowel ultrasound in every visit, annual colonoscopy, annual B12/vit D/ferritin, annual MRE for CD and triennial DEXA.
- Pragmatists prefer continuity of care (look after your patients and patients will look after you), clinical assessment, FCal if it is unclear whether the symptoms are due to active disease or other cause, Flexi (rather than colonoscopy) if symptoms change and careful discussion on review to check adherence and achieve tailored care for individual patients.
- Monitoring means to observe and check the progress or quality of the disease over a period of time.
- When there are no symptoms, but there is endoscopic (or FCal/CRP activity), talk with the patient, explain that no one yet knows whether treatment escalation is best.

  Check compliance with current therapy. Be guided by the previous pattern of disease, drug safety and patient preference. Make a decision and check disease progression after an interval.
- Remember the patient; our role as HCPs is to care, not just to prescribe therapy. The goals of medicine are to improve the QoL and limit the consequences of the disease. IBD and its consequences are complex, so care becomes complex.

EUS-GUIDED PANCREATIC DUCT DRAINAGE

Dr Vinay Dhir, Mumbai

- Stent selection: Plastic stent (straight/pigtail), fully covered metal stent.
- To position the scope, identify proper dilated main pancreatic duct with good position. Scope direction to pancreatic head in stable position (transgastric or transduodenal). Short distance as much as possible with negative Doppler signal.
- Puncture with 19G FNA needle filled with saline or contrast. Check vessel, intervene with Doppler. 22G needle may be required for thin ducts.
- Select good wire: floppy angled tip with stiff sharp. Slowly manipulate the wire towards pancreatic head direction. Use torque and avoid shearing.

■■■■

News and Views

Routine PCR Testing in Patients with Suspected Community-Acquired Pneumonia

The use of polymerase chain reaction (PCR) testing on lower respiratory tract samples led to a significant reduction in the time to provision of pathogen-directed treatment in patients with suspected community-acquired pneumonia (CAP) in the emergency room (ER). Those who underwent PCR testing also received more targeted microbial treatment based on the specific pathogens identified. These findings from a single center trial were published in the journal *JAMA Network Open*[1].

Through this single-center study, the researchers aimed to assess the impact of syndromic PCR-based panel testing on the management of CAP. The study with a parallel-arm, single-blinded design was conducted between September 2020 and June 2022 in the emergency department (ED) of a tertiary hospital in Norway. The 374 patients, with median age 72 years, with suspected CAP were randomized 1:1 to either the intervention arm (rapid syndromic PCR testing + standard care) or the control arm (standard microbiological testing + standard care). Men comprised ~70% of the study population.

The primary outcome was pathogen-directed treatment tailored according to the specific pathogens identified in the PCR-based panel testing. The second primary outcome was time to provision of pathogen-directed treatment, i.e., efficiency of the intervention in facilitating timely initiation of appropriate treatment within 48 hours of randomization.

In the intervention arm, 66 out of 187 patients (35.3%) received pathogen-directed treatment based on the microbiological test results. In contrast, only 25 out of 187 patients (13.4%) in the control arm received pathogen-directed treatment. This corresponds to a reduction in the absolute risk of 21.9% points in the intervention arm compared to the standard-of-care arm. Participants in the intervention arm were at least thrice more likely to receive pathogen-directed treatment compared to those in the standard-of-care arm with odds ratio (OR) of 3.53.

In the intervention arm (PCR-based panel testing), the median time to provision of pathogen-directed treatment within 48 hours was 34.5 hours versus 43.8 hours in the control arm. The mean difference in time to provision of treatment between the two arms was −9.4 hours. The hazard ratio (HR) for intervention compared with standard of care was 3.08. These findings remained statistically significant even after adjustment for season.

These findings underscore the clinical utility of molecular testing in expediting the diagnosis thereby optimizing the management of CAP leading to improved clinical management and potentially better outcomes. The rapid turnaround time and ability to identify multiple pathogens simultaneously make PCR testing a valuable complementary or even a potential alternate test for selected standard, time-consuming laboratory-based diagnostics. By reducing unnecessary empirical antibiotic use it has the potential of mitigating the risk of antibiotic resistance.

Reference

1. Markussen DL, et al. Diagnostic stewardship in community-acquired pneumonia with syndromic molecular testing: a randomized clinical trial. JAMA Netw Open. 2024;7(3):e240830.

Impact of 24-hour Physical Behaviors on Type 2 Diabetes

Patients with obesity-related subtype of type 2 diabetes tend to have poorer sleep quality, lower overall physical activity levels, higher sedentary time, and lower intensity of movement compared to those with age-related diabetes subtype, suggests a study published in the April 2024 issue of the journal *Diabetes, Obesity and Metabolism*[1].

The objective of this 7-day study was to explore how physical behaviors differed across four different subtypes of type 2 diabetes namely insulin-deficient diabetes (INS-D), insulin-resistant diabetes (INS-R), obesity-related diabetes (OB), and age-related diabetes (AGE). The participants were part of the ongoing Chronotype of Patients with Type 2 Diabetes and Effect on Glycaemic Control (CODEC) observational study. Participants wore accelerometers for 7 days to track their physical behaviors throughout the day.

The 564 study participants, with mean age 63.6 years and ~40% females, were categorized into four subtypes based on clinical data such as age at onset of diabetes, glycated hemoglobin (HbA1c) level, homeostatic model assessment index of beta-cell function, homeostatic

model assessment index of insulin resistance and body mass index (BMI). The AGE cluster served as the reference group. There were 35 subjects (6.2%) in the INS-D, 88 (15.6%) in the INS-R group, 166 (29.4%) had OB, while 275 (48.8%) had AGE.

Examination of sleep characteristics across different type 2 diabetes subtypes revealed that participants with the OB subtype had a shorter sleep duration with a difference of −0.3 hours compared to the AGE subtype. They also exhibited lower sleep efficiency (difference of −2%) and greater variability in sleep duration, with an increase of 17.9 minutes.

When physical activity profiles across different type 2 diabetes subtypes were compared, it was found that participants with OB engaged in less total physical activity, with a difference of −2.9 mg and also spent less time doing moderate to vigorous physical activity (MVPA). The average MVPA was >30% lower in the OB subtype compared to the AGE subtype, with a difference of −6.6 minutes.

Participants in the OB group spent longer time being sedentary (749.2 min) compared to those in the AGE group (717.4 min), with an increase of 31.9 minutes. Movement intensity during the most active continuous 10 and 30 minutes of the day was lower in the OB group compared to the AGE cluster. The intensity of the most active continuous periods of the day for the OB cluster was up to 15.8% lower than for the AGE cluster.

These findings show that sleep characteristics and physical behaviors differ across type 2 diabetes subtypes. Patients with obesity-related diabetes exhibited the least favorable sleep quality and lowest overall physical activity levels compared to those with age-related diabetes. Targeting these specific behaviors with personalized 24-hour lifestyle interventions and incorporating them into treatment plans could be particularly beneficial in improving health outcomes in type 2 diabetes patients, particularly those with obesity-related type 2 diabetes.

Reference

1. Henson J, et al. Twenty-four-hour physical behaviour profiles across type 2 diabetes mellitus subtypes. Diabetes Obes Metab. 2024;26(4):1355-65.

Predictors of Heart Failure in Type 2 Diabetes

N-terminal pro B-type natriuretic peptide (NT-proBNP) and troponin T (TnT) levels, and BMI are independent predictors of incident heart failure (HF) in patients with type 2 diabetes, including those on sodium-glucose co-transporter 2 (SGLT2) inhibitors, says a study published in the journal *Diabetes, Obesity and Metabolism*[1]. Use of calcium channel blockers, urine albumin-creatinine ratio, HbA1c, age, and hematocrit were also found to be significant predictors.

In this study, the researchers developed a prediction model that would effectively identify type 2 diabetes patients at high risk of incident HF, including those taking SGLT2 inhibitors. Data was obtained from the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) trial, focusing on type 2 diabetes patients with specific conditions like albuminuria or cardiovascular disease.

To validate the model, it was tested externally in two separate cohorts: the placebo arm of the Canagliflozin Cardiovascular Assessment Study (CANVAS) trial, which included 996 participants with type 2 diabetes and high cardiovascular risk or established cardiovascular disease or, and another group comprising patients treated with canagliflozin. The study included 5,081 patients without HF and who had baseline measurements of NT-proBNP.

In the ALTITUDE trial, participants had a mean age of 64 years with a median serum NT-proBNP level of 157 pg/mL (with a range of 70-359 pg/mL). The study identified several significant and independent predictors of new-onset HF, including higher levels of NT-proBNP, TnT and BMI. Additionally, the model also incorporated urinary albumin-to-creatinine ratio, HbA1c, age, hematocrit, and the use of calcium channel blockers. The predictive model constructed from these variables demonstrated strong performance, with a C-statistic of 0.828 in the ALTITUDE. The validity of the model was further confirmed when applied to the CANVAS cohort, where it achieved a C-statistic of 0.800. When the model was applied to patients who received canagliflozin treatment for 1 year, its predictive performance improved, with a C-statistic of 0.847.

The development of a robust prediction model, as validated in this study, offers a promising clinical tool for early recognition of patients who are at a higher risk of new-onset HF. By leveraging these predictors, the treating clinicians can potentially stratify their type 2 diabetes according to their risk of developing HF. Early identification of the at-risk individuals enables timely personalized interventions including prevention strategies, ultimately improving clinical outcomes and reducing the burden of HF in patients with type 2 diabetes.

Reference

1. Said F, et al. Prediction of new-onset heart failure in patients with type 2 diabetes derived from ALTITUDE and CANVAS. Diabetes Obes Metab. 2024;26(7):2741-51.

Factors Influencing Time to Clinical Stability in Pediatric Pneumonia

Children with suspected CAP who were older or were dehydrated took longer to recover and reach clinical stability within 24 hours, according to new study published online on April 15, 2024 in the journal *Pediatrics*[1]. Younger age, absence of vomiting, decreased breath sounds and normal capillary refilling were the factors indicative of clinical stability.

The prospective cohort study included 571 children, aged 3 months to 18 years, from the CARPE DIEM (Catalyzing Ambulatory Research in Pneumonia Etiology and Diagnostic Innovations in Emergency Medicine) study, who had been hospitalized with suspected CAP from July 2013 to December 2017. The time from hospitalization to normalization of temperature, heart rate, respiratory rate, and oxygen saturation were the four parameters used to assess clinical stability. Through this study, the researchers aimed to understand the association between time to clinical stability (TCS) and disease severity, as well as to identify the factors that contribute to attaining early stability in children with suspected CAP.

Nearly one-third of the children (32.7%) had at least one abnormal parameter at discharge. Approximately 67% of children met all four criteria for clinical stability at discharge, while 7% had two abnormalities and 25% had one abnormality. None of the participants had ≥3 abnormal discharge parameters. The average hospitalization duration for patients with mild disease was 18.2 hours, while those with moderate disease including those receiving intravenous (IV) hydration or oxygen support had hospital stay of 40.8 hours. The length of stay was 70 hours for patients with serious disease.

Infants exhibited a higher proportion of having all four parameters stable at discharge compared to older children aged 12 to 18 years; 93% versus 49%, respectively. The median TCS for each parameter was <24 hours, indicating that most children achieved clinical stability relatively quickly after admission. "The median TCS for each parameter was <24 hours; respiratory rate was the least likely factor to reach stability at hospital release (65%), followed by heart rate (84%), temperature (95%), and oxygenation (97%)".

Clinical factors associated with earlier TCS during the course of the study were also identified. These were younger age, no vomiting, normal capillary refill and diffusely decreased breath sounds. Failure to attain stability did not necessarily correlate with the risk of post-discharge complications or disease recurrence.

Older children were less likely to reach clinical stability within 24 hours with adjusted odds ratio (aOR) of 0.96. Other factors associated with lower likelihood of reaching clinical stability within 24 hours were vomiting (aOR 0.77) and prolonged capillary refill (aOR 0.77).

This study found that several patient characteristics were associated with prolonged TCS. Older children were more likely to have 1 to 2 parameters that were unstable at discharge, as opposed to infants who were more typically discharged with all parameters stable. "*Older children and those admitted for IV fluids and potential dehydration may improve slower than other patients. Patients without these factors might be candidates for management on an observation or short-stay unit*," write the authors.

Hence, all 4 parameters should be considered together for children hospitalized with CAP. This offers several benefits including improved assessment of disease recovery, optimized discharge planning, and potentially reduced health care resource utilization leading to more efficient health care delivery. By ensuring that all physiological parameters have normalized, TCS helps minimize the risk of premature discharge and reduces the likelihood of post-discharge complications or relapse.

Reference

1. Field MR, et al. Time to clinical stability in children with community-acquired pneumonia. Pediatrics. 2024;153(5):e2023063480.

Pediatric Hypertension and Long-Term Cardiovascular Outcomes

Is childhood hypertension associated with greater risk of adverse cardiovascular outcomes in the long-term? To answer this question, a team of researchers from Canada, South Africa, and the United States conducted a population-based, retrospective, matched cohort study of all Canadian children, aged 3 to 18 years, from 1996 to 2022[1]. Children undergoing dialysis or with kidney transplant were not included in the study group. Data for the study was obtained from provincial administrative health databases.

The study population comprised 25,605 children with hypertension and 1,28,025 controls without hypertension. The median age in the hypertensive group was 15 years and nearly 60% were boys. Each case was matched by age, sex, birth weight, maternal gestational hypertension, and prior comorbidities such as diabetes, chronic kidney disease (CKD), cardiovascular surgery with 5 nonhypertensive controls to control for potential confounding variables, and a propensity score for hypertension. Occurrence of major adverse cardiac events (MACE), a composite of cardiovascular death,

stroke, hospitalization for myocardial infarction or unstable angina, or coronary intervention was the primary study outcome. The baseline characteristics were well-balanced between the two groups after propensity score matching and prior comorbidities were uncommon (hypertension vs. control cohort: malignancy, 5.7% vs. 6.2%; congenital heart disease, 4.3% vs. 4.2%; diabetes, 1.9% vs. 1.9%).

Results published in *JAMA Pediatrics* show that over a follow-up period of ~14 years, the incidence of MACE, including stroke, myocardial infarction, unstable angina, coronary intervention and congestive HF was significantly higher in children with hypertension when compared with controls; 4.6 per 1,000 person-years in children with hypertension versus 2.2 per 1,000 person-years in controls with HR of 2.1. The probability of experiencing MACE was higher in children younger than 13 years of age and those with CKD.

Children with hypertension were at elevated risk for stroke (HR 2.7), hospitalization for myocardial infarction or unstable angina (HR 1.8), coronary intervention (HR 4.1), and congestive HF (HR 2.6) compared to nonhypertensive controls. They also had a higher likelihood of other cardiovascular diagnoses (HR 1.7) and undergoing cardiovascular procedures (HR 2.6) versus controls. Interestingly, there was no significant difference in the risk of cardiovascular death between children with hypertension and nonhypertensive controls.

According to this study, children with hypertension were found to be at double the risk of developing MACE than the control group without hypertension.

These findings point out the profound impact of elevated blood pressure (BP) in childhood on long-term cardiovascular health and emphasize the importance of proactive management early in life to prevent or delay future cardiovascular events in this population group. The median age of the study subjects at last follow-up was 27 in both groups. This is relatively younger than the age at which cardiovascular events are expected to occur. Early detection, follow-up, and management of hypertension in pediatric patients is therefore critical. Regular BP monitoring, lifestyle modification, and appropriate pharmacological interventions should be initiated and maintained throughout childhood and into adulthood to ensure optimal management of BP to optimize cardiovascular health outcomes.

Reference

1. Robinson CH, et al. Long-term cardiovascular outcomes in children and adolescents with hypertension. JAMA Pediatr. 2024 May 6.

Antibiotic Exposure and Risk of Atopic Dermatitis in Infants

Use of systemic antibiotics during the first year of life is associated with an increased risk of atopic dermatitis (AD). This heightened risk is likely mediated by disruption in the gut microbiome due to exposure to antibiotics. These findings were published online April 24, 2024 in the *Journal of Allergy and Clinical Immunology*[1].

Courtney Hoskinson, from the University of British Columbia in Vancouver, Canada, and colleagues conducted this study to understand the timing of antibiotic exposure, oral or IV, its impact on the early-life gut microbiome and their relationship with AD development. For this, they used participants from the CHILD study, a nationwide birth cohort study involving 3,621 pregnant women and 3,455 Canadian infants who were born at 34 weeks of gestation (minimum) and did not have any congenital malformation. It explores how genetics and environmental exposures in early childhood influence the development of asthma, allergies, and other chronic childhood diseases. Stool samples from a subgroup of infants with a complete antibiotic history were collected at 1 year and species abundance were compared.

It was observed that compared to antibiotic usage later in life, antibiotic exposure during infancy was linked with an increased risk of AD, with an aOR of 1.81. A dose-response relationship between the number of antibiotic courses and AD risk was noted. Infants who received one course of antibiotics had an aOR of 1.67 for developing AD, while those who received two or more courses had a higher aOR of 2.16.

Eighteen out of the 72 species tested were significantly altered in participants with AD and 15 were altered by antibiotic exposure. Certain alterations in the 1-year infant gut microbiome were identified to be associated with later development of AD. These included increase in *Tyzzerella nexilis*, increased monosaccharide utilization along with decrease in *Bifidobacterium* and *Eubacterium* spp. as well as decreased fermentative pathways.

Atopic dermatitis is the most prevalent chronic inflammatory skin condition. Its multifactorial etiology involves a complex interplay of genetic predisposition and environmental factors. Pediatric AD is also the first step in the allergic march followed by other allergic conditions such as food allergy, allergic rhinitis and allergic asthma.

This study demonstrates a significant association between systemic antibiotics administered during the first year of life and an increased risk of AD. It elucidates

that early antibiotic use alters the microbial taxa, which subsequently contribute to the pathogenesis of AD. "*Microbiome alterations associated with both AD and systemic antibiotic usage fully mediate the effect of antibiotic usage on the development of AD*", write the authors.

These findings highlight the importance of the gut microbiome in modulating immune function and increasing susceptibility to inflammatory skin diseases like AD. It underscores the need for minimizing unnecessary antibiotic usage during infancy and the potential for microbiome-targeted preventative strategies to mitigate the adverse effects of antibiotic exposure on immune health and reduce the risk of developing AD in infancy.

Reference

1. Hoskinson C, et al. Antibiotics within first year are linked to infant gut microbiome disruption and elevated atopic dermatitis risk. J Allergy Clin Immunol. 2024 Apr 24:S0091-6749(24)00409-3.

Dry Eye Disease and Type 2 Diabetic Nephropathy

More than half of patients with type 2 diabetic nephropathy have dry eye disease, suggests a study from Vietnam published May 6, 2024 in the journal *Clinical Ophthalmology*[1]. Advanced age, high HbA1c levels and decreased estimated glomerular filtration rate (eGFR) were identified as factors that were independently associated with dry eye disease.

A total of 338 individuals, consisting of 169 patients with type 2 diabetic nephropathy and 169 patients with type 2 diabetes but without renal complications as a control group, were included in this cross-sectional study. All subjects were evaluated for Ocular Surface Disease Index (OSDI) via a questionnaire and test fluorescein tear-film break-up time (TBUT). Patients with OSDI scores <13 and TBUT values ≤10 seconds were diagnosed with dry eye. The aim of this cross-sectional study was to determine the prevalence of dry eye among patients with type 2 diabetic nephropathy and also identify factors potentially associated with dry eye in these patients.

The prevalence of dry eye among type 2 diabetic nephropathy patients was found to be significantly higher than the control group, with rates of 55.6% versus 37.3%, respectively. They had higher OSDI scores but lower TBUT than the type 2 diabetes alone group.

The type 2 diabetic nephropathy patients with dry eye were older and had a longer duration of diabetes. They also had a higher percentage of participants with hypertension, peripheral nerve complications, anemia including insulin users compared with those without dry eye in the group. This subgroup also had higher levels of plasma glucose, HbA1c, urea, creatinine and high-sensitivity C-reactive protein.

Advanced age, high HbA1c level and decreased eGFR were identified as independent factors associated with dry eye in type 2 diabetic nephropathy patients.

This study highlights dry eye as a common condition in patients with type 2 diabetic nephropathy compared to those with type 2 diabetes mellitus without renal complications. The authors note, "*kidney complications and eye complications often go together, and 'renal-retinal syndrome' originates from this coincidence*". It further elucidates on potential risk factors contributing to a better understanding of ocular complications in this population.

Reference

1. Tran Tat T, et al. Dry eye and some related factors in patients with type 2 diabetic nephropathy: a cross-sectional study in Vietnam. Clin Ophthalmol. 2024:18:1217-24.

■■■■

The Lips of Truth shall be Recognized Forever, a Lying Tongue is but for a Moment

This sutra from Bible has a very deep significance in day-to-day life. The truth is ever lasting and always ends up in internal happiness and self-realization. And, in the long run, it always gives you happiness and an all-win situation. A lying tongue, on the contrary, will only give you a momentary pleasure but will lead to or create some difficulty later in life.

Spoken words cannot come back just as in the case of a released arrow from the bow. Once lost, one cannot get back his youth, virginity, or respect. Similarly, spoken bad words cannot be taken back and once spoken will create negative waves in the other persons (on whom they were spoken) mind, which will persist as repressed thoughts or memory in the people's mind for ever. Such bad memories will keep on coming back in the person's mind causing damage to the personal relationships.

A spoken word is a karmic expression. For every karmic action there is an opposite and equal reaction. For every negative karmic action, one has to pay the debt either now or in future. The law of karma says that every debt has to be paid.

It is always better to avoid negative language both in spoken words as well as in the mind. The yoga sutras of Patanjali describe thinking, speaking or doing anything wrong as having the same karmic significance. We should not only purify ourselves in actions and spoken words but also in the mind. If a person keeps negative thoughts in the mind, sooner or later the same will be reflected to the outside world.

The momentary pleasure which one gets by "lying" has no spiritual significance as it only satisfies your ego sense or makes you attached to any of the five senses. The transient pleasure experienced by the body stimulates a chain of reactions, consisting of action, memory and desire leading to action again, which will only intensify the greed and attachments.

In the Mahabharata, Lord Krishna has given only two examples, which work as an exception to such a situation. Any truth, which harms others, may not be spoken and any lie which does not harm anyone but benefits a few may be spoken.

Truth is the opposite of doubt and it is always better to clear all the doubts from the mind as any repressed doubts can end up into causation of heart attack, paralysis, and cancer.

Truth also means taking conscious-based decisions as the consciousness will never lie. While taking any decision one should always ask oneself—Is it the truth? Is it necessary? And will it bring happiness to me and the people around?

Lord Krishna is also described as "SATCHITANAND", which only indicates qualities like truthfulness, conscious-based decisions, and internal happiness. Truthfulness has to be practiced for over a period of time and made a part and parcel of your daily life. To start with a person may have bad experiences but in the long run truthfulness will always win.

■■■■

INSPIRATIONAL STORY

How do we Affect Others

My second year attending college....

I moved 300 miles away from my home of 6 years and entered a private Christian college. I was thrilled that I was going to attend my first pick school. My favorite class was English I with Professor Wilcox. He encouraged creativity and open thought which was right up my alley.

Throughout high school I had been pretty much told what to write and what to think. I enjoyed the challenge of his vague writing assignments; it made me have to really think about what I put down on paper.

As the school year progressed I became very ill and missed several of my classes. I apologized over and over to my professors for missing their classes, and I did the assignments out of hospital rooms or between trips to specialists and weekly doctors' visits. At the end of the term, my medical condition had improved some and I was able to start doing some of the extra credit to make up for my daily grades. I worked double time to bring my grades up.

The day of my English final, Professor Wilcox approached me and handed me a single sheet of rose pink paper. He told me to read on my way home to Texas. I decided that I couldn't wait and the second I stepped into my dorm room I opened the paper and read aloud. He had wanted to thank me for encouraging him throughout the school year.

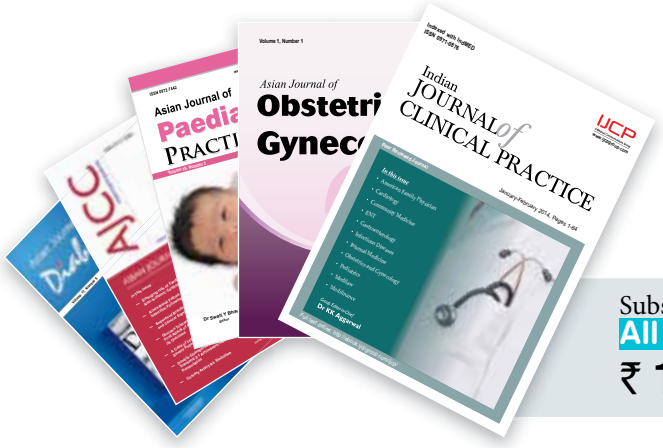
In his letter he described the plight of a young woman, the youngest in her class, struggling with sickness and a full class schedule that somehow managed to pull herself up by her bootstraps and muttle through the year.

The last line of his letter read as follows: "I have watched you thoroughly enjoy yourself in my class, and I have read of your struggle against all odds to stay in school. You truly personify my favorite verse in the book of Psalms. Thank you for showing the world how to be brave and how to rely completely on God." He then went on to quote the following verse: "I have set the Lord always before me; because He is at my right hand; I will NOT be shaken." —*Psalm 16:8*

I hadn't realized it at the time but everything we do and say affects other people.

My being sick had helped a professor I barely knew to get through a very trying time in his life. I just want everyone to know that even though things may seem rough, there will always be better days ahead.

■■■■



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Lighter Side of Medicine

HUMOR

A HOROSCOPE FOR THE WORKPLACE

Senior Management: Catty, cut-throat, yet completely spineless, you are destined to remain at your current job for the rest of your life. Unable to make a single decision you tend to measure your worth by the number of meetings you can schedule for yourself. Best suited to marry other "Senior Managers," as everyone in your social circle is a "Senior Manager."

CARPENTER'S DISTANCE

A carpenter was giving evidence about an accident he had witnessed. The lawyer for the defendant was trying to discredit him and asked him how far away he was from the accident.

The carpenter replied, "Twenty-seven feet, six and one-half inches."

"What? How come you are so sure of that distance?" asked the lawyer.

"Well, I knew sooner or later some idiot would ask me. So, I measured it!" replied the carpenter.

ANNIVERSARY GIFT

After she woke up, a woman told her husband, "I just dreamed that you gave me a pearl necklace for our anniversary. What do you think it means?"

"You'll know tonight," he said.

That evening, the man came home with a small package and gave it to his wife. Delighted, she opened it – to find a book entitled

"The Meaning of Dreams."

NEVER BE RUDE TO ANYONE

An American tourist asked a boat guy in Zanzibar, "Do you know Biology, Psychology, Geography, Geology, or Criminology?"

The boat guy said, "No. I don't know any of these."

The tourist then said, "What the hell do you know on the face of this Earth? You will die of illiteracy!"

The boat guy said nothing. After a while the boat developed a fault and started sinking. The boatman then asked the tourist, "Do you know Swimology and Escapology from Crocodiology?"

The tourist said, "No!"

The boat guy replied, "Well, today you will Drownology and Crocodiology will eat you. I will not Helpology and you will Dieology because of your Badmouthology."

FIVE MINUTES LATER

Man calls up the doc at 2 AM. "Doc, my wife is having severe abdomen pain. I think it's her appendix."

"What nonsense!" says the doc sleepily.

"I took out your wife's appendix 2 years ago. Go back to sleep."

Five minutes later, the phone rings and it's Santa again.

"Doc, I'm sure it's her appendix."

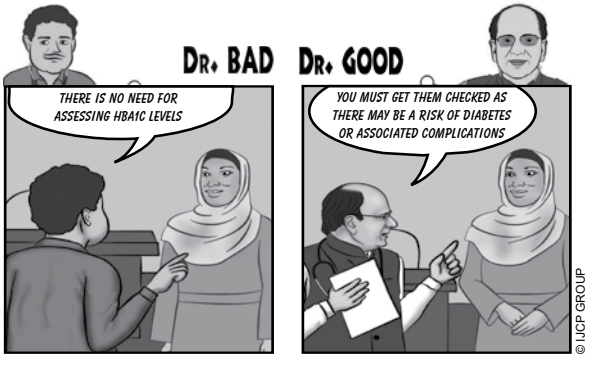
"Oh God!" the doctor groaned.

"Did you ever hear of anyone having a second appendix?"

"No. But I'm sure you must have heard of someone having a second wife!!!!"

Dr. Good and Dr. Bad

SITUATION: An individual with high oxidized LDL levels was asked to get his HbA1c levels checked.



LESSON: A significant link between oxidized LDL levels and HbA1c has been established in nondiabetic individuals, indicating higher risk of diabetes mellitus or CV events. Thus, HbA1c can be considered a biomarker for determining people at risk of developing complications even with nondiabetic glycemic levels.

Clin Chim Acta. 2017;471:171-6.

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Books

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

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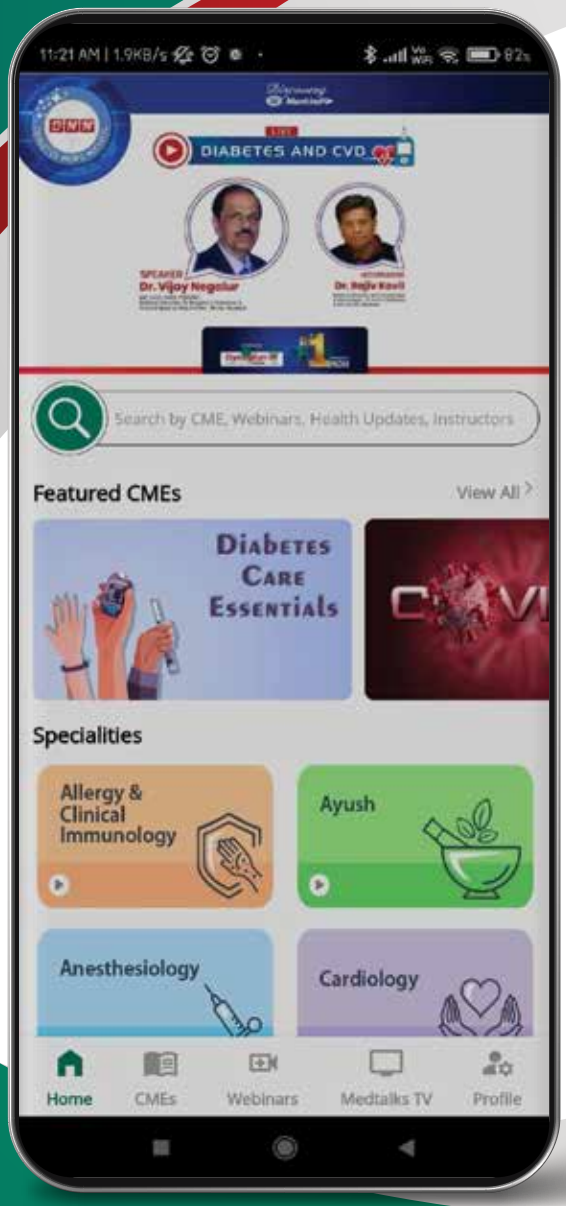

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