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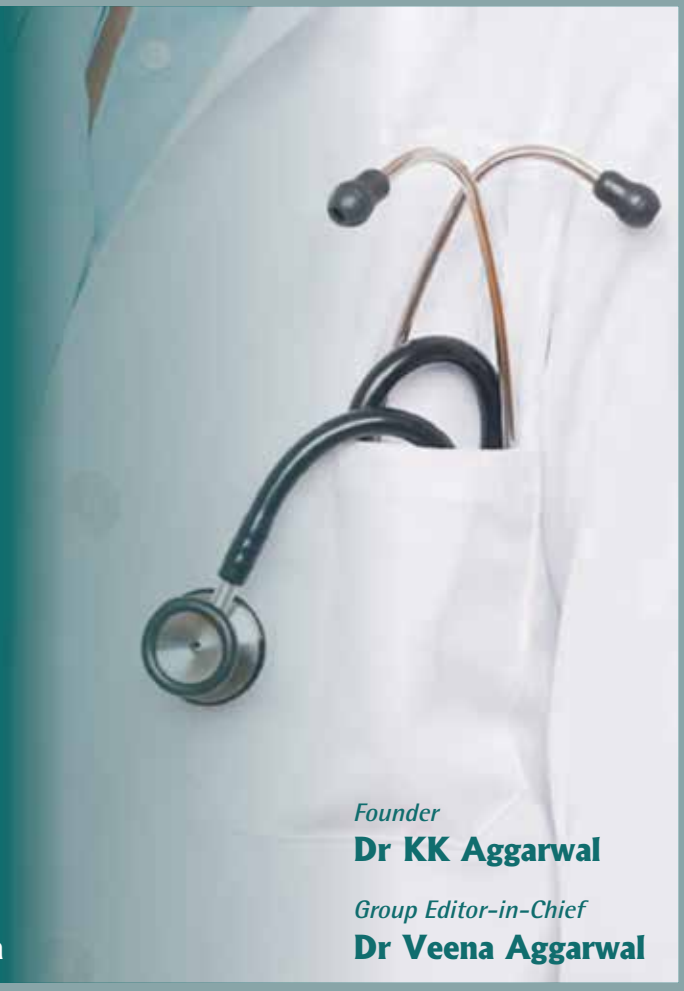

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Research Updates from Around the World

THE FIRST KNOWN DEATH FROM ALASKAPOX

The first known human death from Alaskapox of an elderly patient undergoing cancer therapy, has been reported from Alaska. The disease is caused by the Alaskapox virus, which is an orthopox virus similar to small pox, cowpox and monkeypox. It was first identified in 2015 in Alaska. Since then, 6 more cases have been reported. It is a zoonotic disease as the virus is transmitted from small mammals and symptoms include rash, arthralgia, myalgia and enlarged lymph nodes… (*Source: The Guardian. Feb. 14, 2024*).

EBOLA VACCINE SHOWS ENCOURAGING RESULTS

Administration of rVSVΔG-ZEBOV-GP Ebola vaccine led to nearly 50% reduction in mortality following confirmed Ebola virus infection besides decreasing the odds of acquiring the infection. It is a single dose intramuscular vaccine. The mortality rate was 56% in the unvaccinated patients, whereas among the vaccinated group, the mortality was 25%. The study involved over 2,000 patients in the Democratic Republic of Congo, reported to be the second-largest outbreak of Ebola… (*Source: Lancet Infectious Diseases, Feb. 7, 2024*).

A NOVEL CELL THERAPY FOR METASTATIC OR UNRESECTABLE MELANOMA

Lifileucel, a tumor-derived autologous T-cell immunotherapy, has been approved for the treatment of adult patients with unresectable or metastatic melanoma that has been earlier treated with other therapies such as a PD-1 blocking antibody, and a BRAF inhibitor with/without a MEK inhibitor if *BRAF* V600 mutation positive. It is the first cell therapy for solid tumors… (*Source: FDA. Feb. 16, 2024*).

FREQUENT CONSULTATIONS MAY BE A RED FLAG FOR SUICIDE RISK

Patients, aged ≥15 years, who consulted frequently (more than once in a month) for pain, depression, medication review, among other reasons, are at 5-times higher risk of suicide with odds ratio (OR) of 5.88 regardless of the presence/absence of a known psychiatric disorder. Girls and women were at highest risk (OR 9.50), patients aged 15 to 45 years (OR 8.08), patients who were socioeconomically better off (OR 6.56) and those with psychiatric conditions (OR 4.57)… (*Source: Br J Gen Pract. Feb. 8, 2024*).

OMALIZUMAB NOW ALSO APPROVED TO REDUCE RISK OF FOOD ALLERGY REACTION

Omalizumab, a monoclonal antibody, is now available for treating adults and children aged ≥1 year with immunoglobulin E-mediated food allergy. Available as an injectable formulation, the drug is intended to reduce the risk of type 1 hypersensitivity reactions after accidental exposure to foods and not for emergency treatment of allergic reactions, including anaphylaxis. It has been previously approved for treatment of moderate to severe persistent allergic asthma and chronic spontaneous urticaria and chronic rhinosinusitis with nasal polyps… (*Source: FDA. Feb. 16, 2024*).

STUDY LINKS ACHALASIA TO COVID-19

A new study has found that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can lead to the development of achalasia, a motility disorder of the esophagus. Compared with pre-COVID-19 (coronavirus disease 2019) long-term achalasia and non-COVID-19 long-term achalasia, patients with post-COVID-19 achalasia had significantly higher levels of SARS-CoV-2 nucleocapsid (N) protein mRNA, which correlates with a significant increase in the inflammatory markers NLRP3 and tumor necrosis factor… (*Source: Am J Gastroenterol. Jan. 24, 2024*).

TESTING FOR DEMENTIA IN THE LAB

Persons with higher levels of glial fibrillary acidic protein (GFAP) are 2.32 times more likely to develop dementia; they were also 2.91 times more at risk of developing Alzheimer's disease and 2.45 times greater risk of vascular dementia. Risk of dementia was also associated with increased levels of other proteins such as neurofilament light chain (NfL) (hazard ratio [HR] 2.32) and growth/differentiation factor 15 (HR 1.70)... (*Source: Nature Aging. Feb. 12, 2024*).

FDA CAUTIONS AGAINST USE OF NONINVASIVE SMARTWATCHES TO MONITOR BLOOD GLUCOSE

The US Food and Drug Administration (FDA) has cautioned about the use of noninvasive smartwatches or smart rings that claim to measure blood glucose levels without finger pricks or skin piercing. It's always best to rely on FDA-authorized devices that pierce the skin, like continuous glucose monitoring devices (CGMs) for accurate and safe blood glucose monitoring… (*Source: US FDA. Feb. 21, 2024*).

POINT-OF-CARE PROCALCITONIN TEST TO DIAGNOSE PNEUMONIA IN CHILDREN WITH INFLUENZA-LIKE ILLNESS

Point-of-care testing for procalcitonin can help diagnose suspected pneumonia in children with influenza-like illness and fever (>4 days) and thus preclude the need for unnecessary chest X-ray. A cut-off point >0.5 ng/mL was used as an indication for performing a chest X-ray… (*Source: Indian Pediatr. Jan. 15, 2024*).

FDA NOW MANDATES BOXED WARNINGS FOR CAR-T CELL THERAPIES

All chimeric antigen receptor T-cell, or CAR-T cell therapies will now carry a boxed warning about the risk of secondary T-cell malignancies in blood cancer patients who have been treated with this form of immunotherapy… (*Source: JAMA. Feb. 21, 2024*).

CLOSING THE GENDER GAP: BENEFITS OF EXERCISE

Women experience greater benefits of regular exercise compared to men even with equivalent amounts of exercise. The all-cause mortality reduced by 24% in women (vs. 15% in men) and the cardiovascular mortality reduced by 36% (vs. 14% in men)… (*Source: J Am Coll Cardiol. Feb. 27, 2024*).

STUDY SHOWS HIGH EFFICACY OF NOVEL HEPATITIS E VACCINE

Ten-year results from a phase 3 trial of a novel hepatitis E vaccine demonstrate durable protection against hepatitis E. Vaccine-induced antibodies were still detectable for 8.5 years in over 85% persons after intramuscular administration of three doses of the vaccine… (*Source: Lancet. Feb. 19, 2024*).

A SIMPLE BLOOD TEST TO DIAGNOSE SARCOIDOSIS: NIH

A NIH study has successfully evaluated a blood test to quickly diagnose sarcoidosis. In the study, the researchers were able to differentiate between sarcoidosis and other respiratory disorders such as tuberculosis, lung cancer with the help of a novel peptide-based sarcoidosis immunoassay… (*Source: NIH. Feb. 22, 2024*).

THE FIRST FDA-APPROVED INTERCHANGEABLE, HIGH-CONCENTRATION HUMIRA BIOSIMILAR

Adalimumab-ryvk has been approved as the first interchangeable, high-concentration, citrate-free adalimumab biosimilar by the US FDA. It is the 10th adalimumab biosimilar to be approved by FDA. It has been approved for the treatment of rheumatoid arthritis, psoriatic arthritis, Crohn's disease, ulcerative colitis, juvenile idiopathic arthritis, ankylosing spondylitis, plaque psoriasis, hidradenitis suppurativa and uveitis… (*Source: Medscape. Feb. 26, 2024*).

USTEKINUMAB AND APREMILAST APPROVED FOR PSORIASIS IN EUROPE

The Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) has approved the use of ustekinumab for the treatment of plaque psoriasis, including pediatric plaque psoriasis, psoriatic arthritis, ulcerative colitis and Crohn's disease. Apremilast has also been approved for psoriasis, psoriatic arthritis and Behçet disease… (*Source: Medscape. Feb. 23, 2024*).

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Ayurvedic Aristology: Dining Etiquette in Ayurveda

"*Food is the vital breath of living beings*."

—*Charaka Samhita*, Sutra Sthanam XXVII:349.

While nutrition and diet are an integral part of both Ayurvedic and modern medicine, Ayurveda pays equal attention to culinary etiquette, or *ahara vidhi vidhana*. Food is considered the ultimate medicine, or *Mahabhaishajya*. Just as the route and method of administration of a drug is as important as determining the correct nature and dose of a drug, dining etiquette is an important as food itself. Table 1 summarizes the teachings of Ayurveda in this regard.[1,2]

Table 1. Ayurvedic Aristology

Meal preparation
• Consume warm food
• Consume unctuous food
Meal pattern and portion size
• Consume food in proper quantity
• Consume food only after previous meal has been digested
Medical aspects
• Consume food that is not contraindicated in medical illness
• Consume food in comfortable ambience and atmosphere, using preferred accessories
Manners and social grace
• Do not consume food too fast or too slowly
• Do not speak or laugh while eating
Mindful eating
• Consume food after due consideration of one's needs

In this editorial, we discuss aristology, or the art and science of dining, from an Ayurvedic perspective.

MEAL PREPARATION, PORTION SIZE AND PATTERN

Consuming warm food (*ushnam bhunjita*) is a cardinal rule of Ayurveda. People are cautioned against consuming very hot, cold as well as reheated food. At the same time, patients with severe *pittaja* diseases, exhaustion or internal hemorrhage should be administered medicated cold infusion (*shadanga paniya*) if they have fever.

Consuming food that is unctuous (*snigdham bhunjita*) is advised, as it is easily digested and contributes to growth, strength and complexion. This guidance is not meant for persons with *kaphaja* diseases such as obesity, dyslipidemia (*meda dhatu* related disorders), diabetes (*prameha*) and ascites (*udara*), as high fat meals may aggravate their condition.

Consuming food in proper quantity (*maatravat bhunjita*) is necessary to achieve health and longevity. As mentioned in Sutra Sthanam, *Charaka Samhita*, heavy foods should be consumed till half satiety, and intake of lighter foods should not exceed satiety levels. It is suggested that food intake should be according to the level of one's digestive fire, and should fill just half or one third of the stomach's capacity.

Consuming food after digestion of previously consumed food (*jirne bhunjita*) is another pillar of Ayurvedic culinary medicine. One should not take a meal until the previous meal has been digested. While healthy persons may manage with a 2-meal pattern (morning and

evening), other may need 3 hourly meals. Another person-centered way of understanding this advice is to take food only when one is hungry.

Consuming food that is not contraindicated (*viryavirudham bhunjita*) is a reminder that foods which are incompatible with, or contraindicated in, particular disease states, should not be taken. Similarly, some foods may become incompatible of combined, e.g., a substance with *sheet virya* (cold potency) cannot be clubbed with one that has *ushna virya* (hot potency).

DINING STYLE, SPEED AND SOCIAL GRACE

Dining etiquette or aristology, finds prominent mention in Ayurveda. Consuming foods in places that are pleasant to mind, and with required cookery (*ishte deshe ishta sarvopaka bhunjita*) is an Ayurvedic injunction. One should dine in a comfortable ambience, using preferred accessories (crockery and cutlery). One must not eat in unsheltered places, on one's bed, under hot sunlight or in a dark place, and should not use broken or soiled utensils.

Neither consuming food too fast (*naatidrutam bhunjita*) nor too slowly (*naativilambitam bhunjita*) is recommended in Ayurveda. Not speaking or laughing while eating (*ajalpan ahasan tanmana bhunjita*) is suggested as well. These timeless concepts have been given the modern label of mindful eating.

ALCOHOL USAGE

This etiquette extends to the use of alcohol or wine as well. Chapter XXIV of the Chikitsa Sthanam, *Charaka Samhita* describes drinking etiquette in depth and detail.[3] It suggests that one drinks only if one is "pure and perfumed, sitting or reclining comfortably, using clean vessels and attended by trained bartenders". Pre-drinking preparation is based upon the predominant dosha of the individual: massage, bath and unctuous hot food for *vaatik*, cooling regimens and sweet, unctuous cold food for *pittaja*; and hot regimens, barley, wheat and meat seasoned with black peeper for *kaphaja* individuals. "Suitable fruits, wholesome green vegetables, salted and seasoned seasonal food items; various roasted meat" preparations are recommended for consumption with wine.

Chikitsa Sthanam describes how to identify satvik, rajsik and tamsik drinking companions, and how to bond with suitable friends. Ayurveda reminds us that wine is like nectar if taken in moderation, with wholesome food, according to individual disposition, but can act like poison if taken in an unwholesome manner. It describes the stepwise progression of *mada* (intoxication), and explains how to manage it. With insight and intuition, it suggests that just like rain stimulates the growth of crops, so does wine stimulate men. And just as fire exposes the nature of gold, whether superior, average or inferior, so does alcohol expose the nature of men.

PERSON-CENTERED DIET

A phrase that is thought to have been created by modern medicine, person-centered care,[4] actually finds mention in ancient South Asian medicine.[5] *Charaka Samhita* describes the Quadruple of Atreya, and expounds upon individualized, person-centered dietary therapy. Here, it is prescribed that one must consume food after due consideration of self (*aatmanam abhisameekshija samyak bhunjita*). Ayurveda shares the basic rules of dining and dieting, and then clarifies that autognosis or self-diagnosis, and self-awareness and self-consideration are important contributors to choose of eating styles and patterns. Food should be consumed after an assessment of one's needs and requirements. One should not follow any rules blindly, without understanding their necessity and relevance in one's own context.

"*One taking wholesome food, with controlled self, lives healthy for 100 years, and is liked by the good men*."

—*Charaka Samhita*, Sutra Sthanam XXVII:348.

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REVIEW ARTICLE

Pattern of Glomerulonephritis in Nigeria and Challenges Faced in Treating It

SOTUBO SOTOMIWA*, SOURABH SHARMA†, AMISU MUMUNI*, ODEYEMI AYOOLA*

ABSTRACT

Glomerulonephritis is one of the leading causes of chronic kidney disease in Nigeria. The pattern of glomerulonephritis is said to be different from other parts of the world which can be attributed to the prevalence of *APOL1* gene in the black population and prevalence of tropical diseases. Treating glomerulonephritis in Nigeria can be challenging due to poor awareness and understanding of the disease, limited access to health care facility and lack of trained nephrologist. Possible solutions to this problems include creating awareness and education of the populace, partnering with NGOs to subsidize treatment and training of Nephrologist.

Keywords: Challenges, patterns, glomerulonephritis, Nigeria

Glomerulonephritis (GN) is a disease that affects the kidneys, specifically the glomeruli, which are the tiny blood vessels that filter waste and excess fluids from the blood.[1] The disease is common in Nigeria, where it is one of the leading causes of chronic kidney disease (CKD).[2,3] The pattern of GN in Nigeria is distinct from that in other parts of the world, and treating it presents several challenges. Here is what you need to know.

PATTERN OF GLOMERULONEPHRITIS IN NIGERIA

Glomerulonephritis in Nigeria has a unique pattern compared to other parts of the world. According to studies, the most common type of GN in Nigeria is focal segmental glomerulosclerosis (FSGS).[3,4] In contrast, IgA nephropathy is the most common type of GN in many other parts of the world.[5,6]

There are several factors that contribute to the unique pattern of GN in Nigeria. These include genetic factors, infectious diseases and environmental factors such as exposure to toxins and pollutants.[4]

More than 600 genes have been implicated in kidney diseases such as FSGS, IgA nephropathy and membranous nephropathy just to mention a few.[7]

Of note is the *APOL1* gene, which is associated with increased risk of CKD and is predominantly higher in Blacks.[7,8]

In a study done by Kopp et al, it was seen that *APOL1* gene increased the risk of FSGS by 17 folds, risk of human immunodeficiency virus-associated nephropathy (HIVAN) by 29-fold along with rapid progression to end-stage kidney disease (ESKD).[9]

Infections like HIV, tuberculosis, hepatitis B and C are said to be endemic in Africa, especially in Nigeria,[10-12] which can lead to HIVAN, renal amyloidosis, membranous and membranoproliferative GN, respectively.[13-16] Tropical diseases like schistosomiasis, onchocerciasis and lymphatic filariasis have also been associated with membranoproliferative GN.[17,18]

In some areas of Nigeria like Yobe, exposure to toxins and heavy metals has been shown to correlate with the incidence of CKD in the region.[19] Ojo et al[20] found the same trend among CKD patients attending outpatient clinic at Owo; hence, advocating that the sources of this exposure be identified and eliminated.

CHALLENGES FACED IN TREATING GLOMERULONEPHRITIS IN NIGERIA

Treating GN in Nigeria presents several challenges. The following are some of the most significant challenges (Table 1).

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Table 1. Challenges Faced in Treating GN in Nigeria

Challenges
Limited access to health care
Lack of trained nephrologists
Limited availability of medications
Poor awareness and understanding of the disease
Poor infrastructure

- **Limited access to health care**: Access to health care is limited in many parts of Nigeria, particularly in rural areas.[21,22] This makes it difficult for patients with GN to receive timely and appropriate care, which can lead to complications and worsen the prognosis.[23]
- **Lack of trained nephrologists**: There is a severe shortage of trained nephrologists in Nigeria, which makes it challenging to provide specialized care for patients with GN.[24] Many patients are treated by general practitioners who may not have the expertise or experience to manage the disease effectively.[25]
- **Limited availability of medications**: The cost of medications is a significant barrier to treatment in Nigeria. Many patients cannot afford to buy the drugs they need, and even when the medications are available, they may be of poor quality or counterfeit.[26] Drugs like tacrolimus, mycophenolate mofetil (MMF), cyclosporine and rituximab used in some cases of GN, are expensive for the average Nigerian patients, who need it for treatment.
- **Poor awareness and understanding of the disease**: There is limited awareness and understanding of GN among the general population and even some health care professionals in Nigeria. This can lead to delayed diagnosis and inappropriate treatment, which can worsen the prognosis.[25,27]
- **Poor infrastructure:** The health care infrastructure in Nigeria is inadequate, with many hospitals lacking the necessary equipment, facilities and personnel to provide quality care.[28]

Kidney biopsy is critical in the diagnosis of GN; unfortunately the cost of procedure and standard histologic analysis makes it impossible for many patients to be able to afford it.[29] This can hinder the delivery of appropriate treatment for patients with GN.

Genetic testing should be considered in patients with a positive family history, early age of onset of renal impairment and presence of extrarenal symptoms as they have a high likelihood of having a monogenic kidney disease.[7]

However, genetic testing facilities are not readily available and expensive in our environment.[30] Early diagnosis with genetic testing has been shown to be helpful in showing down progression of CKD and also donor workup in high-risk families; however, our patients are not able to benefit from its advantages.[7]

WHAT IS THE WAY FORWARD?

Kidney Biopsy

With political will and relationship with sister organizations, standard local laboratories that can analyze kidney biopsy samples using at least 2 out of the 3 recommended methods (light microscope, immunofluorescence, electron microscope), will go a long way in reducing cost. This will put a stop to sending samples out of Nigeria for analysis, which comes with a huge cost.

Government should encourage local industries to make the biopsy needles locally to also reduce cost. Increasing the number of biopsies done yearly will go a long way in improving the skills of the nephrologists and also presents an opportunity to train nephrology trainees.

Immunosuppressive Medications

Till date, drugs like tacrolimus, MMF, rituximab and many more, are shipped into Nigeria as it is not yet locally manufactured by pharmaceutical companies in Nigeria. Because of the increasing use of these medications and the increasing number of kidney transplants,[31] government should support local pharmaceutical companies in partnering with international organizations to set up companies that can manufacture these drugs locally.[28]

Inaxaplin, a novel small molecule inhibitor of *APOL1* channel has been demonstrated to reduce proteinuria in patients with *APOL1*-associated FSGS.[32]

This is likely to have impact on the incidence of GN; however, cost will remain a major barrier in getting it across to patients in Nigeria that will benefit from it.

AWARENESS AND TARGETED EDUCATION

Awareness and education by the nephrology community is key so as to improving health seeking behavior of the population and raise the index of suspicion of non-nephrologist for prompt referral of GN patients to the nephrologist.

CONCLUSION

In conclusion, the pattern of GN in Nigeria is distinct from that in other parts of the world, and treating it presents several challenges. Limited access to health care, a shortage of trained nephrologists, limited availability of medications, poor awareness and understanding of the disease and poor infrastructure are some of the challenges that need to be addressed to improve the management of GN in Nigeria. Addressing these challenges will require a concerted effort from policymakers, health care professionals and the general public.

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■■■■

Recurrence Risk of Adverse Pregnancy Outcomes

Around 40% of women who have had an adverse pregnancy outcome (APO) in their first pregnancy also experienced an APO during their second pregnancy, suggests a study presented February 13, 2024 at The Pregnancy Meeting, the 44th Annual Meeting of the SMFM.[1]

This study sought to determine factors that are present early in the first pregnancy and are potentially associated with the occurrence of APOs in a second pregnancy.

Researchers examined data of 2,830 women from the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be Heart Health Study (nuMoM2b HHS). Women who had experienced two pregnancies lasting at least 20 weeks each were included in the present analysis. The nuMoM2b HHS investigated the link between pregnancy problems and heart disease and includes nulliparous pregnant women from the early stages of their first pregnancy through delivery followed by an in-person visit 2 to 7 years after delivery.

Various demographic, clinical and laboratory variables from the first trimester of the first pregnancy were evaluated as potential risk markers for APOs, which referred to a range of complications that can occur during pregnancy, including hypertensive disorders (such as pre-eclampsia), preterm birth (delivery before 37 weeks), delivering a baby who is small for their gestational age (less than fifth percentile), fetal demise (stillbirth) or gestational diabetes. Logistic regression was used as the statistical method to assess the association between these risk markers and adverse outcomes in the second pregnancy while controlling for the APOs in the first pregnancy.

The mean time between pregnancies for the included participants was 2.9 years. Overall, 32% participants had experienced an APO in their first pregnancy; of these, 40% also experienced an APO in their second pregnancy. Among those without an APO in their first pregnancy, 15% had an APO in their second pregnancy.

Several markers from the first trimester of the first pregnancy were associated with the occurrence of APOs in the second pregnancy. These markers include BMI, blood pressure and cardiometabolic serum analytes. Race/ethnicity was also found to influence the recurrence risk of APOs with the highest risk observed in non-Hispanic Blacks.

This study has identified various factors in the first pregnancy, which are associated with APOs in a second pregnancy. Since some of these markers are modifiable, it suggests that interventions targeting these factors could potentially reduce the risk of APOs in subsequent pregnancies. Since the impact of prior APOs on the risk of recurrence of APOs in subsequent pregnancies varied among different racial and ethnic groups, it is important to consider such factors in prenatal care and risk assessment.

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CLINICAL STUDY

Retinal Vascular Changes in Pregnant Women with Gestational Diabetes Mellitus A2: A Cross-sectional Study

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ABSTRACT

Diabetes complicates a significant proportion of pregnancies, with gestational diabetes mellitus (GDM) posing a considerable health concern. While the incidence of GDM is rising, its implications extend beyond pregnancy, affecting both maternal and fetal health. Notably, diabetic retinopathy (DR) presents a substantial risk, particularly in women with pre-existing diabetes. However, there remains a dearth of data on retinal vascular changes in pregnant women with GDM managed with medication, particularly in the South Indian population. This study aims to address this gap by evaluating retinal vascular changes in pregnant women with GDM managed with medication, focusing specifically on GDM type A2. We conducted a comprehensive assessment of retinopathy prevalence and associated factors in this population, employing various imaging modalities including fundus photography, optical coherence tomography angiography and Doppler sonography.

Keywords: Diabetes, gestational diabetes mellitus, diabetic retinopathy, retinal vascular

Diabetes in pregnancy, gestational diabetes or pre-existing diabetes, complicates up to 5% of all pregnancies.[1] Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance developing or first detected during pregnancy.[2] GDM can be classified as GDMA1 and GDMA2 by White's classification system. Gestational diabetes managed without medication and that is responsive to medical nutritional therapy is diet-controlled gestational diabetes or GDMA1. On the other hand, gestational diabetes managed with medication is GDMA2.

Out of all pregnant women with diabetes, 87.5% have GDM, 7.5% have type 1 diabetes mellitus (T1DM) and 5% have type 2 diabetes mellitus (T2DM).[1] The incidence of GDM is on the rise because of higher rates of obesity in the population and more pregnancies occurring in older women.[3]

Metabolic and cardiovascular complications of hyperglycemia during pregnancy for mother and child are now generally recognized with major implications for public health. Women with GDM are not only at risk of short-term pregnancy adverse effects such as pre-eclampsia, but they also have increased long-term risk of obesity, dyslipidemia and T2DM. Women with history of GDM are at 10 times higher risk of developing T2DM in the 1 year after delivery.[4] Defects in insulin secretory response and decreased insulin sensitivity, have been observed in GDM mothers similar to that of T2DM which is a major risk factor for cardiovascular disease (CVD), perhaps through endothelial and small vessel dysfunction.[5]

Diabetic retinopathy (DR) is a microvascular complication and is the leading cause of blindness in women during childbearing years.[6] The prevalence of DR in early pregnancy in T2DM is approximately 14% and for T1DM, the estimates range from 43% to 56%.[7,8]

Chronic hyperglycemia in overt diabetes leads to vasoconstriction, which reduces the blood flow and increases tissue hypoxia. In pregnancy, the pregnant state itself is a risk factor for progression in addition to duration of

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diabetes, severity of retinopathy at conception, glycemic control, anemia and coexisting hypertension.[6]

As the glucose intolerance in GDM in most cases is transient, these women are not generally at risk of developing DR in pregnancy. However, some women with GDM have undiagnosed T2DM; this subgroup may develop DR during or following pregnancy. Retinal vascular imaging is a noninvasive tool to study the small vessel dysfunction in overt diabetes.

Due to lack of data on fundus changes in women with GDM, a few studies[9-15] over the last decade have attempted to assess the fundus in women with GDM during pregnancy as well as postpartum using different modalities.

A wide range of retinal vascular changes have been described in GDM women in these studies.[9-15] Arterial changes such as narrower arteriolar caliber, reduced fractal dimension and larger arteriolar branching angle have been observed. Changes in veins seen were decreased venular caliber and fractal dimension.[9] In contrast, another study showed retinal venular widening in GDM mothers to be associated with 5-year metabolic syndrome.[12] Hence, there is no clarity about which venular changes are actually associated with GDM on digital retinal photograph images.

Advanced imaging techniques like optical coherence tomography angiography (OCT-A) have shown reduction in vascular density in superficial capillary layer and increase in density in deep capillary layer in pregnant women including mothers with GDM.[10] Doppler sonography has also been used, which found a decreased velocity in central retinal artery and ciliary artery in GDM women.[11]

On the other hand, a cross-sectional study conducted in UK, studied retina using fundus photographs in GDM women, who were on both diet and insulin and found only 2 patients (1.3%) with a single microaneurysm, thereby questioning the utility of routine retinal screening.[15] There is a paucity of data regarding changes in the maternal retinal vasculature during pregnancy specifically in women with GDMA2. This is the first study in South Indian population to evaluate retinal vascular changes and contributing factors in pregnant women with diabetes mellitus with specific focus on GDMA2.

The primary objective of the study was to estimate the proportion of retinopathy in pregnant women with GDMA2. The secondary objective was to assess the factors contributing to retinopathy in pregnant women with GDMA2.

MATERIALS AND METHODS

Sampling Population

Pregnant women with GDMA2 were recruited from the antenatal OPD or antenatal ward of Women and Children Hospital, JIPMER, Pondicherry, India

Sample Size Calculation

Sample size was calculated using OpenEpi software version 3.1. The expected proportion of pregnant women with DR in T2DM is 14% and GDM is 1.3%.[15] Assuming the proportion of DR in GDMA2 to be 10%, with absolute precision of 3.5% and confidence level of 90%, the minimum required sample size was 196.

Parameters Assessed

Primary outcome

- Proportion having retinopathy
- Grade of retinopathy

Secondary outcome

- Factors contributing to retinopathy

Statistical Analysis

Continuous variables (age, body mass index [BMI], glucose tolerance test [GTT] values, fasting blood glucose [FBG]/postprandial blood glucose [PPBG]) were analyzed by mean (± SD) or median (IQR) depending on the normality of data. Categorical values (parity, education, socioeconomic status, gestational age at diagnosis of GDM, coexisting medical disorders, antidiabetic drugs) were calculated as proportion.

The primary outcome variables (proportion of retinopathy and grade of retinopathy) were calculated as proportion along with 95% confidence interval. Contributing factors for retinopathy were assessed using Chi-square test (for categorical variables) and Students *t*-test (for continuous variables). P value <0.05 was taken as statistically significant.

RESULTS

Baseline Characteristics

Age

The age distribution of the study population is shown in Table 1 and Figure 1.

The mean age of the study population was 27 ± 3.97 years.

Table 1. Age Distribution

Age (years)	n = 196	Percentage (%)
19-34	190	96.94
≥35	6	3.06

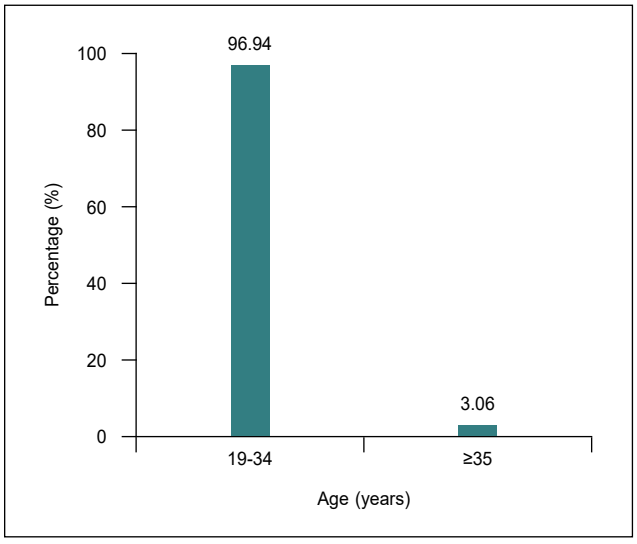

Figure 1. Age distribution.

Educational status

The educational status of the study participants is given below in Table 2 and Figure 2.

Majority of the study population had completed graduation (48.48%) followed by higher secondary schooling (33.16%).

Socioeconomic status

The socioeconomic status of the participants in the study is described in Table 3 and Figure 3.

Most of the women belonged to low socioeconomic status, mainly lower middle class (66.33%).

BMI

BMI status of the study participants is shown in Table 4 and Figure 4.

Among the study participants, 60.2% of the women were overweight and 36.23% had obesity.

Obstetric Characteristics

Parity

The parity of the participants in the study is depicted in Table 5 and Figure 5.

There was equal distribution of primiparous and multiparous women amongst the study population.

Table 2. Educational Status

Educational status	n = 196	Percentage (%)
Primary	2	1.02
High school	19	9.69
Higher secondary	65	33.16
Graduate	95	48.48
Professional	15	7.65

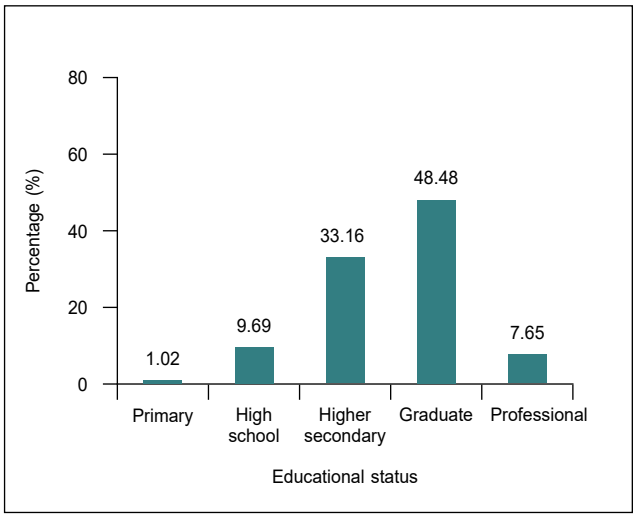

Figure 2. Educational status.

Table 3. Socioeconomic Status

Socioeconomic status	n = 196	Percentage (%)
Upper	0	0
Upper middle	39	19.97
Lower middle	130	66.33
Upper lower	27	13.70
Lower	0	0

Coexisting medical disorders

Coexisting medical disorders in pregnancy among the study participants are depicted in Table 6.

About 20.41% of women had other medical disorders, mainly hypertension and CVD.

GDM Characteristics

Gestational age at diagnosis of GDM

The distribution of study participants based on gestational age at the time of testing 75 g GTT is given in Table 7 and Figure 6.

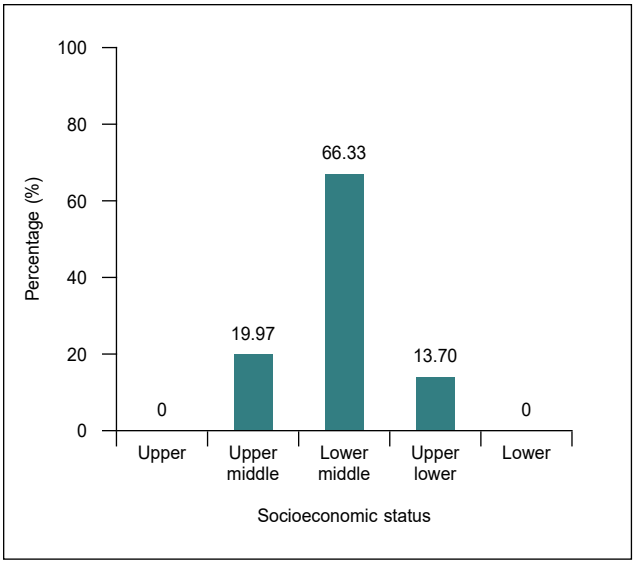

Figure 3. Socioeconomic status.

Table 4. BMI Distribution

BMI category	n = 196	Percentage (%)
Normal (18.5- 24.9 kg/m^2)	7	3.57
Overweight (25-29.9 kg/m^2)	118	60.20
Obese (≥30 kg/m^2)	71	36.23

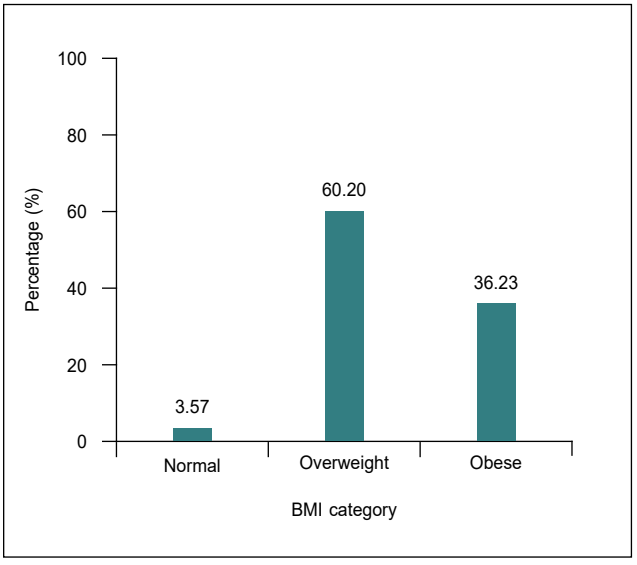

Figure 4. BMI distribution.

Table 5. Distribution of Parity

Parity	n = 196	Percentage (%)
Primiparous	91	46.43
Multiparous	105	53.57

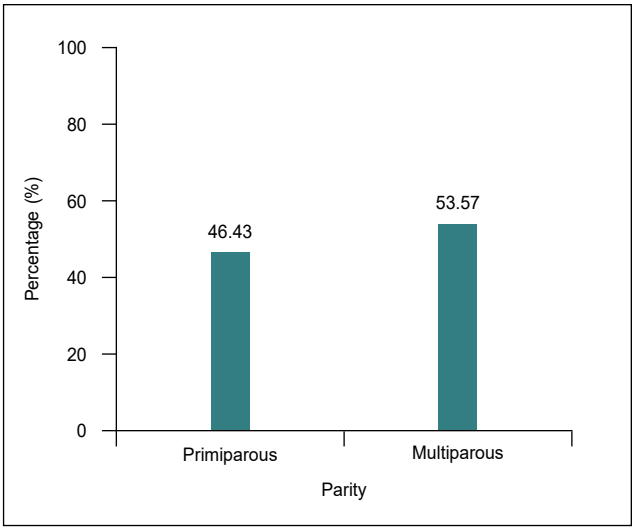

Figure 5. Distribution of parity.

Table 6. Coexisting Medical Disorders in Pregnancy

Medical disorder	n = 196	Percentage (%)
Hypertensive disorder of pregnancy (HDP)	26	13.27
Cardiovascular disease (CVD)	14	7.14
Eye disease	0	0
Renal disorders	0	0

Table 7. Gestational Age at Diagnosis of GDM

Gestational age (weeks)	n = 196	Percentage (%)
20-23^{+6}	107	54.49
24-28	80	40.82
>28 weeks	9	4.69

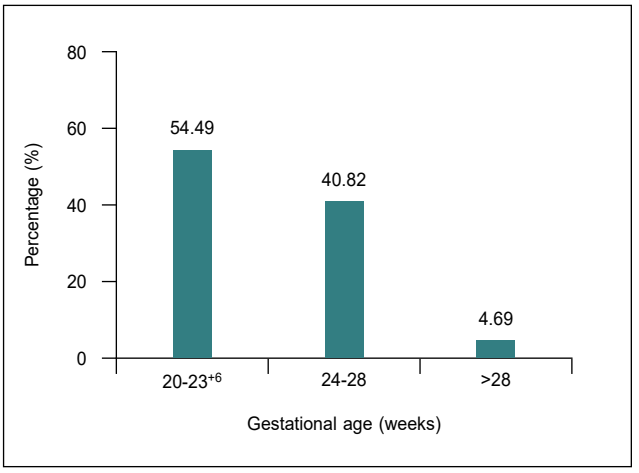

Figure 6. Gestational age at diagnosis of GDM.

Half of the participants, 54.49% had their 75-g GTT performed at 20-23^{+6} weeks of gestation, followed by 40.82% who had GTT between 24-28 weeks and another 9 women had GTT after 28 weeks.

GTT values

Distribution of study participants based on the number of abnormal 75 g GTT values is showed in Table 8.

About 2.55% of the patients had one abnormal value, 27.03% had two abnormal values and 70.40% had all three values abnormal on 75 g GTT.

Antidiabetic drugs

The distribution of different antidiabetic drugs use among study participants is given in Table 9 and Figure 7.

Approximately two-thirds of the women were on metformin therapy in addition to diet and exercise; one-third were on insulin and only 2 patients required combination of insulin and metformin.

Blood sugar profile

Fasting and postprandial blood glucose values are summarized in Tables 10 and 11, respectively.

Around 61% to 63% of study participants had their blood sugar levels within normal range with medication, diet and exercise at the time of fundus examination.

Table 8. Distribution of Abnormal GTT Values

Blood glucose	n = 196	Percentage (%)
One abnormal value		
Fasting	2	1.02
1 hour	1	0.51
2 hour	2	1.02
Two abnormal values		
Fasting & 1st hour	8	4.08
Fasting & 2nd hour	9	4.59
1st & 2nd hour	36	18.36
Three abnormal values	138	70.40

Table 9. Distribution of Antidiabetic Drugs

Antidiabetic drugs	n = 196	Percentage (%)
Insulin	56	28.70
Metformin	138	70.00
Insulin and metformin	2	1.30

Retinal Vascular Changes in Pregnant Women with GDMA2

The proportion and grade of DR are shown in Figure 8 and Table 12, respectively.

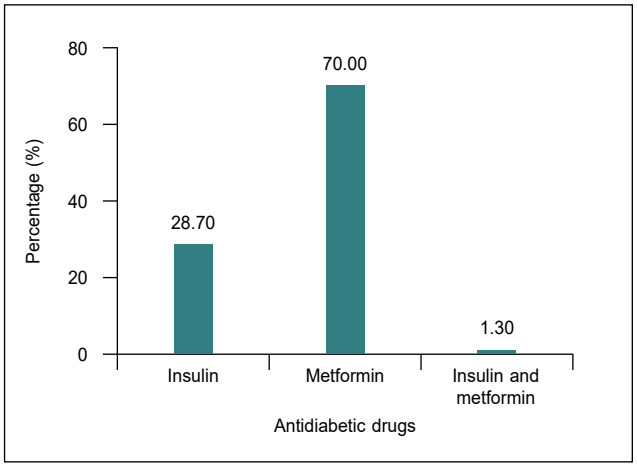

Figure 7. Distribution of antidiabetic drugs.

Table 10. Fasting Blood Glucose

Fasting blood glucose (mg/dL)	n = 196	Percentage (%)
<95	124	63.27
≥95	72	36.73

Table 11. Postprandial (2-hour) Blood Glucose

Postprandial blood glucose (2-hour) (mg/dL)	n = 196	Percentage (%)
<120	120	61.22
≥120	76	38.78

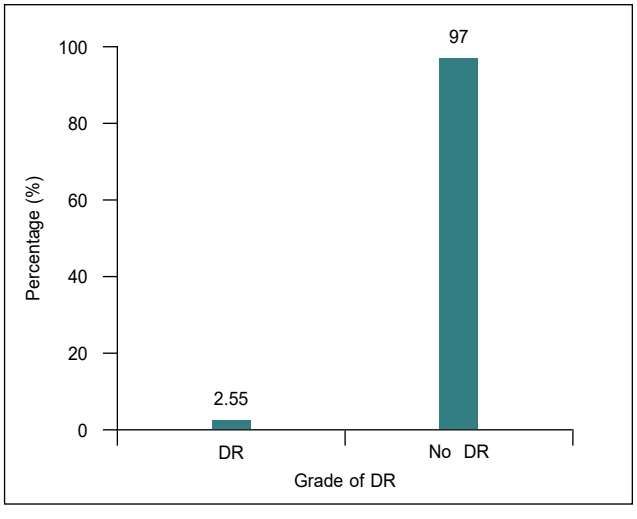

Figure 8. Proportion of diabetic retinopathy.

Proportion of retinopathy

Five women (2.5%) with GDMA2 had DR.

Grade of retinopathy

All the 5 women with DR had mild nonproliferative diabetic retinopathy (NPDR) changes and the fundoscopy images in these women are shown in Figures 9-13.

Table 12. Grade of Diabetic Retinopathy

Grade of DR	n	Percentage (%)
Stage 2 DR	5	2.55

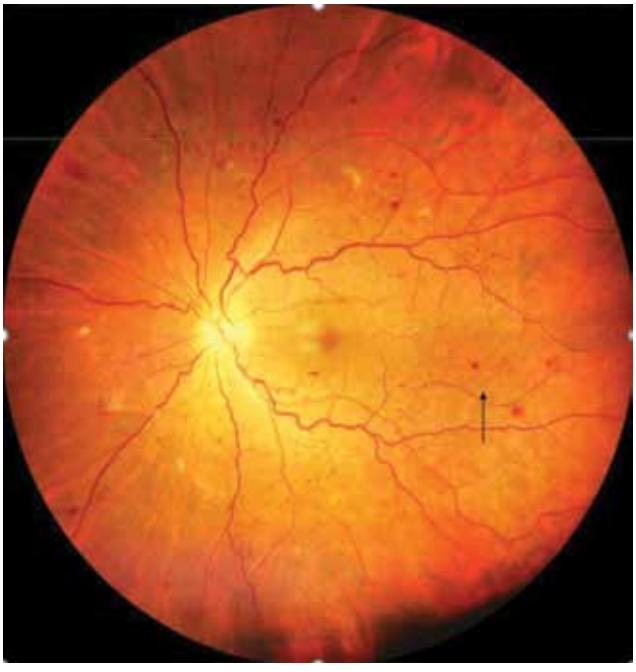

Figure 9. Dot-blot hemorrhages (*black arrow*).

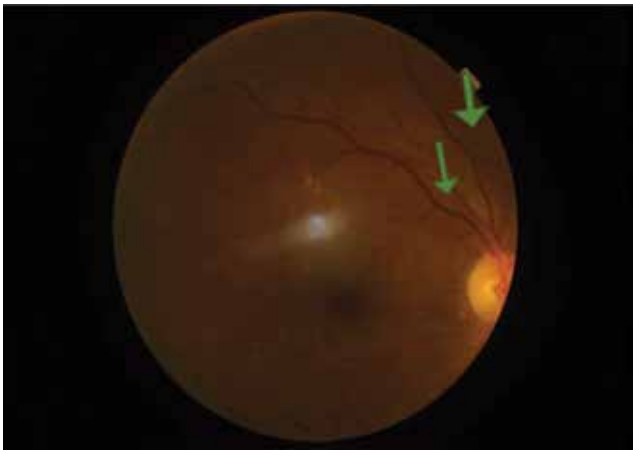

Figure 10. Multiple microaneurysms (*green arrows*) at 7 O'clock and 11 O'clock positions.

Other Retinal Vascular Changes

One patient, who had coexisting hypertension along with GDMA2, had Grade 1 hypertensive retinopathy

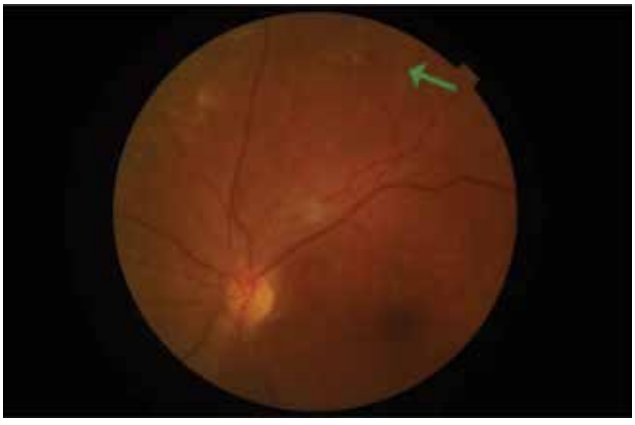

Figure 11. Evidence of microaneurysm (*green arrow*).

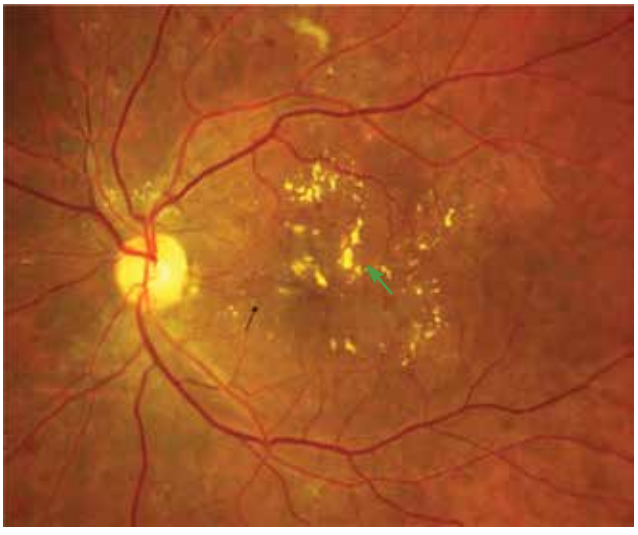

Figure 12. Hard exudates (*green arrow*) along with microaneurysms (*black arrow*) over entire retina.

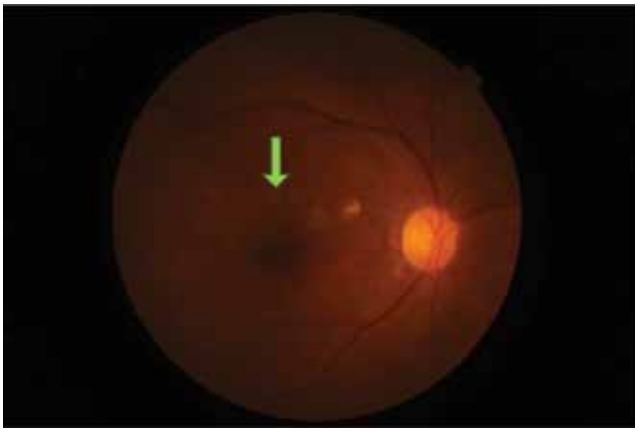

Figure 13. Microaneurysm (*green arrow*) at 10 O'clock position to foveal reflex.

(Keith and Wagner classification) on fundus examination, but no DR changes were observed.

Factors Contributing to Retinal Vascular Changes in Pregnant Women with GDMA2

Factors contributing to retinal vascular changes are shown in Table 13 and Table 14.

There was equal distribution of DR across all age groups. All the cases of DR were found in women with obesity and multiparous women. Significant association was found with respect to parity. One patient with coexisting hypertensive disease had DR changes.

Three women who developed DR were diagnosed with abnormal GTT at 24-28 weeks of gestation. Out of 138 women who had all three abnormal values, 4 had developed DR and 1 woman with 2 abnormal values had DR. Three cases of DR were seen in women who were on insulin and 2 cases were reported in women

Table 13. Baseline and Obstetric Factors Contributing to Retinal Vascular Changes

Characteristics		Frequency	P value
Age category (years)			
19-34	No DR	178	0.76
	DR	3	
≥35	No DR	13	
	DR	2	
BMI			
Overweight	No DR	7	0.663
	DR	0	
Obese	No DR	184	
	DR	5	
Coexisting medical disorders			
HDP	No DR	25	0.653
	DR	1	
CVD	No DR	14	0.53
	DR	0	
Parity			
Nulliparous	No DR	91	0.744
	DR	0	
Multiparous	No DR	100	0.034
	DR	5	

Table 14. GDM Factors Contributing to Retinal Vascular Changes

Factors		Frequency	P value
Gestational age at diagnosis of GDM (weeks)			
20-23^{+6}	No DR	106	0.65
	DR	1	
24-28	No DR	77	0.88
	DR	3	
>28	No DR	8	0.66
	DR	1	
GTT values			
One abnormal value			
Fasting	No DR	2	0.23
	DR	0	
1st hour	No DR	1	0.36
	DR	0	
2nd hour	No DR	2	0.27
	DR	0	
Two abnormal values			
Fasting and1st hour	No DR	8	0.56
	DR	0	
Fasting and 2nd hour	No DR	9	0.26
	DR	0	
1st and 2nd hour	No DR	35	0.38
	DR	1	
Three abnormal values	No DR	134	0.30
	DR	4	
Antidiabetic drugs			
Insulin	No DR	53	0.295
	DR	3	
Metformin	No DR	134	
	DR	2	
Insulin + Metformin	No DR	2	
	DR	0	
Blood glucose profile (mg/dL)			
Fasting glucose ≥95	No DR	71	0.43
	DR	1	
Postprandial glucose (2-hour) ≥120	No DR	73	0.32
	DR	3	

on metformin. No cases of DR were observed in women who were on both insulin and metformin. Three cases of DR were reported in women with uncontrolled postprandial blood sugar compared to one case of DR with uncontrolled fasting blood sugar.

DISCUSSION

Gestational diabetes mellitus with its onset or first recognition during pregnancy is one of the most common pregnancy complications. The prevalence of GDM has considerably increased all over the globe across several racial and ethnic groups. It has been observed that Asian women are at a relatively higher risk of developing GDM even at low BMI cut-offs. We, at a tertiary care center, studied the primary outcomes of proportion and grade of retinopathy in 196 women with GDMA2, and secondary outcome related to the factors contributing to the development of diabetic retinopathy.

Primary Outcomes

Proportion and grade of retinopathy

In our study population, 2.5% of our study participants had mild NPDR on dilated fundus examination. This is similar to a UK based study[15] done in 222 women with GDM, which found a prevalence of 1.3% on fundal imaging. However, the participants of this study differed from ours as the 61 women (27.47%) included in their study had GDMA1. Although only microaneurysms were observed in the index study, other changes have been observed in women with GDM in other studies.

Retinal assessment by fundoscopic examination carried out in 88 women with GDM at 26-28 weeks of gestation has shown arteriolar changes, such as narrow caliber, decreased fractal dimension and larger branching angle when compared to non-GDM group suggesting that small vessel dysfunction might be caused by transient hyperglycemia during pregnancy.[9] Specifically, larger branching angle present in diabetic women has been linked to atherosclerosis and endothelial damage.[6]

Preclinical changes of retinopathy have been observed using OCT-A[10] including significant reduction of vascular density in superficial capillary layer, but an increased density in deep capillary layer in pregnant women compared to nonpregnant women. In spite of the similar changes in both GDM and non-GDM groups, capillary "dropout" changes in superficial capillary layer were found more in GDM group, but there were no other abnormal microvascular changes pertaining to DR. Also, central macular thinning and foveal avascular zone enlargement was found to be better in GDM mothers when compared to non-GDM mothers.

Apart from fundus imaging and OCT-A, Doppler blood flow of retinal vessels can add further information about microvascular changes such as seen in a cross-sectional study of 65 GDM women of which 10 were GDMA2 and 55 were GDMA1. It was observed that the GDMA2 group had significant reduction of flow velocity in central retinal artery and ciliary artery and higher resistance index in ciliary artery compared to GDMA1.[11]

However, whether these changes persist after pregnancy and their association with long-term risk of developing T2DM has not been well studied. Addressing this, a prospective cohort study found that second trimester retinal venular widening in digital retinal photographs was associated with a 9.2% incidence of 5-year metabolic syndrome in 142 mothers with GDM independent of the obesity status and maternal sugar control.[12] Another study[13] used fundus images to study the structure and function of retinal vessels in 127 women with history of GDM at a 5-year follow-up visit. When compared to non-GDM group, they found a reduction in retinal venular dilation in GDM group. This was more significant in women with recurrent GDM than in women who had history of single episode of GDM. A population-based cohort study observed 9,888 women with history of GDM and found more ophthalmic morbidities such as glaucoma, DR and retinal detachment in a mean follow up of 12 years.[14]

Other retinal vascular changes seen in our study was Grade 1 hypertensive retinopathy in a woman with GDMA2 on insulin with coexisting gestational hypertension although there were no DR changes.

Secondary Outcomes

Factors contributing to retinal vascular changes

Baseline factors

The mean age of our study population was 27 years, which is lesser than the participants in other studies[9,10,12,15] in which mean age was above 30 years. The lesser age of our participants could be because of younger age at marriage in Indian population.

Almost half of our study population had completed graduation, which was similar to a study assessing the 5-year incidence of metabolic syndrome in women with GDM.[12]

However, another study showed a lower proportion of graduates (25%) in their study.[9]

In our study, we had no patients belonging to the upper socioeconomic class and majority of the study population (66.33%) belonged to lower middle class. Two studies done in Singapore analyzed the socioeconomic status of their study population as a risk factor for retinal vascular changes in GDM women and found that 26% to 30% of them belonged to upper class.[9,12] The significance of the socioeconomic status is that obesity is generally prevalent in upper class population, which in turn is a risk factor for diabetes.

Majority of our study population (96%) were either overweight or obese in spite of belonging to lower middle class. This can be attributed to ethnicity of Indian population that predisposes to higher BMI despite low socioeconomic status. In two other studies,[9,12] which analyzed BMI as a risk factor for retinal vascular changes; only about 4% of their population were overweight. Higher BMI has been associated with increase in the 5-year incidence of metabolic syndrome in GDM women.[12] In contrast, the higher prevalence of obesity in our population was not significantly associated with retinal vascular changes.

Obstetric factors

There was equal distribution of nulliparous and multiparous women similar to one prospective cohort study.[12] Nevertheless, all cases of DR (n = 5) were found in multiparous women in our study, out of which, 3 had history of GDM in previous pregnancy, which suggests that recurrent GDM might be a major risk factor for development of DR. This finding of our study is consistent with a prospective cohort study done in Singapore,[13] which concluded that women with recurrent GDM had significant reduction in retinal venular vasodilatory response and lower retinal venular dilation (4.5%) when compared to a single episode of GDM.

One-fifth of our study participants had coexisting medical disorders (HDP and CVD). No significant association has been found with coexisting hypertension and GDM associated retinal vascular changes similar to other studies.[9,10]

GDM factors

In our study, 54% of the study population underwent the 75 g GTT between 20-24 weeks in contrast with all other studies where 75 g GTT was done later at 27-28 weeks.[9,11,12,15] It is because of the current practice in India due to high prevalence of GDM to offer testing at 1st visit, 24-28 weeks and 32-34 weeks. There was no significant association of gestational age of diagnosis of GDM with DR.

We analyzed number of abnormal GTT values in our study and found that two-thirds of women had all three values abnormal. We found there was no significant association between these values and the development of DR. Individual GTT values has not been mentioned in the aforementioned studies.[9-15] However, higher FBG was proposed to be risk factor for development of 5-year metabolic syndrome in women with history of GDM.[12] In our study, the 2 women who had only abnormal FBG did not develop DR, though the number is not high enough to draw a conclusion in this regard.

About 70.4% and 28.7% women in our study on metformin and insulin respectively had developed DR, while the 2 participants taking both metformin and insulin did not develop DR. There was no significant association between the treatment modality and the development of DR ($p = 0.29$).

Around 62% of study participants had their blood sugar levels within normal range with medication, diet and exercise at the time of fundus examination in our study. There is no mention of blood sugar profile in the other studies except for one study,[9] which found no association of FBG with retinal vascular changes. Overall, we found significant association between parity and DR, all 5 women with DR were multiparous ($p = 0.034$). However, there was no significant association between age, BMI, coexisting medical disorders, gestational age at diagnosis of GDM, number of abnormal GTT values, antidiabetic drugs, blood sugar control at fundus examination and DR in our study. Other studies have not examined the association of these risk factors with retinal vascular changes in women with GDM.[9-15]

CONCLUSION

This is the first study in South Indian population to evaluate retinal vascular changes and contributing factors in pregnant women with GDMA2 where there is lack of published data. Mild proliferative diabetic retinopathy was seen in 2.5% of pregnant women with gestational diabetes on treatment with either metformin or insulin but not on combination of metformin and insulin. One woman with gestational diabetes on insulin and coexisting gestational hypertension had Grade 1 hypertensive retinopathy with no DR changes.

Multiparity was the only factor significantly contributing to DR. There was no association of age, BMI, 75-g GTT values and glycemic control with DR. Future prospective studies with larger sample size incorporating baseline and frequent assessments will help to understand better about the retinal vascular changes in pregnant women with GDMA2.

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Smartwatch Therapy: A Boost for Depression Treatment

A Northeastern University study in the *New England Journal of Medicine* revealed the potential of wearable tech, like smartwatches, to monitor depression symptoms.

The study aimed to gauge if passive sensor data could anticipate shifts in depression severity or symptomatology. Experts stated that the study showed very individualized ways depression manifests in people.

Leveraging anonymized patient data from Massachusetts General Hospital, participants wore Empatica E3 wristbands, tracking sleep, movement and heart rate variability.

Results showed shifts in sleep patterns, decreased physical activity and social withdrawal as potential indicators of depression. Additionally, clinicians could monitor text messaging app usage through the gathered data. While passive sensor data enhances information acquisition, it's stressed that clinical judgment remains essential.

Furthermore, the study emphasized how passive sensor data alleviates the need for extensive patient self-reporting, streamlining symptom assessment and facilitating rapid evaluation of new patients' mental health status.

(*Source: https://www.tribuneindia.com/news/health/smartwatch-may-help-boost-treatment-for-depression-593787*)

CLINICAL STUDY

Clinical Outcomes of Slow versus Rapid Enteral Feeding Advancement in Very Low Birth Weight Neonates at a Tertiary Care Center

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ABSTRACT

Background: In India, every year around 3.5 million babies are born premature, accounting for almost 13% of total live births in the country as compared to 5% to 7% incidence in the West. Preterm is defined as babies born before 37 weeks of pregnancy. The rapidity of feed volume increments involves controversies like faster weight gain, shorter hospital stays, the risk of necrotizing enterocolitis and vice versa. **Methods:** The present study was a randomized controlled trial conducted from June 1, 2018 to October 31, 2019. All infants in the study were randomized to slow and rapid feeding protocols by a stratified block randomization sequence of 2, 4, 6 blocks. Group 1 or the slow advancement group included 64 newborns babies and Group 2 or the rapid advancement group included 69 newborns babies. **Results:** The average weight gain in Group 1 was 4.41 ± 0.9 g and in Group 2 it was 6.33 ± 1.3 g, the difference was statistically significant ($p < 0.02$). Sixty out of 64 newborns regained birth weight within 16.87 ± 0.9 days in Group 1, while 64 out of 69 newborns regained birth weight within 13.63 ± 0.9 days in Group 2. The difference was statistically significant. Increment in the mean occipitofrontal circumference per week was 0.29 ± 0.27 cm Group 1, while in Group 2 it was 0.42 ± 0.05 cm; the difference was statistically significant. Mean average length increment per week was found to be 0.55 ± 0.04 cm and 0.69 ± 0.05 cm in Group 1 and Group 2, respectively, the difference was statistically significant ($p < 0.005$). The mean duration of hospital stay was 27.47 ± 3.33 days in Group 1 while in Group 2, the duration of stay was 23.15 ± 2.22 days, the difference was statistically significant. **Conclusion:** Our study supports enteral nutrition by rapid enteral feeding regimen in stable preterm neonates with very low birth weight.

Keywords: Very low birth weight, nutrition, feeding, enteral feeding, preterm

Globally, every year, an estimated 15 million babies are born preterm (before 37 completed weeks of gestation). Preterm birth complications are the leading cause of death among children under 5 years of age, responsible for approximately 1 million deaths in 2015.[1]

In India, every year almost 3.5 million babies are born premature, accounting for nearly 13% of total live births in the country as compared to 5% to 7% incidence in the West. Preterm birth is defined as babies born alive before 37 weeks of pregnancy are completed. There are subcategories of preterm births, based on gestational age.[2] Complications of prematurity include necrotizing enterocolitis (NEC), feed intolerance, exaggerated physiological jaundice, sepsis and prolonged hospital stay, etc. The duration of hospital stay may be reduced if feed can be rapidly built up thereby significantly reducing morbidity and mortality in these newborns. The appropriate goals of low birth weight feed include ensuring adequate short-term growth, preventing feeding-related morbidities, optimizing long-term outcomes including its impact on adult-onset diseases (e.g., coronary artery disease [CAD], diabetes mellitus, etc.). Over the last 2 decades, the concept of minimal enteral nutrition has evolved and is defined as starting a small amount of enteral feeding (exact volume not defined) usually 5-25 mL/kg as soon as possible after birth. This approach has numerous positive impacts on the development and maturation of gut function, hormonal and digestive enzyme surge.[3,4] Numerous studies have shown the beneficial effects of minimal enteral nutrition; however, none have demonstrated an

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increase in the incidence of NEC. However, larger trials are required regarding safety in very immature and critically ill babies.[5,6]

The rapidity of increments in feed volume has been beset with controversies. A more rapid increase should result in faster weight gain and a shorter hospital stay. The proponents of slow feed advancements have cited the risk of NEC in their defense, while those in favor of rapid advancements have cited better growth in their defense. Controlled trials prior to the 1990s had observed an association between rapid feed advancement and increased risk of NEC.[4,6] However, many randomized controlled trials have not demonstrated any increased risk of NEC.[7-11] The lack of effect on NEC could be a result of differences in study design, improved neonatal care resulting in a decrease in NEC risk factors, and a shift in feeding protocols. The present study was aimed to compare the effects of slow rates of enteral feed advancement versus rapid advancement on the incidence of NEC in very low birth weight (VLBW) infants and to compare the effects of slow enteral feed advancement versus rapid advancement on the weight of VLBW infants. The *primary outcome* was the duration to reach full enteral feeds (days). The s*econdary outcomes* were to study the incidence of feed intolerance, to find duration of hospital stay (days), to calculate average weight gain, length and head circumference and to find incidence of NEC.

MATERIALS AND METHODS

The present randomized controlled trial included 133 stable newborn babies, having a birth weight between 1,000 to 1,500 g, admitted in neonatal intensive care unit (NICU) in the Department of Pediatrics, SMS Medical College, and Attached Group of Hospitals, Jaipur during a period of 16 months from June 1, 2018 and October 31, 2019 after obtaining informed written consent of parents. Newborns with major congenital cardiac or other malformations contraindicating initiation of enteral feeds as per existing guidelines; with hypotension requiring dopamine ≥10 μg/kg/min or more than one inotrope support, persistent metabolic acidosis (pH <7.25 or base deficit of ≥10 mmol/L for >4 hours), abdominal distension, gastrointestinal bleeding and absent bowel sounds were excluded. All infants in the study were randomized into slow and rapid feeding protocols by a stratified block randomization sequence of 2, 4, 6 blocks. The slow advancement group (Group 1) comprised of 64 newborn babies and the rapid advancement group (Group 2) included 69 newborn babies. Both the study group newborns were thoroughly examined clinically on daily basis. The patients were monitored for weight gain, time to achievement of full feed, the occurrence of complications like NEC and sepsis. The findings and data were recorded on a predesigned proforma (Fig. 1).

The serial weight of the baby was recorded daily. Serial data of the length were recorded weekly. Abdominal girth was measured by using a nonstretchable tape, at the level, just above the umbilicus. Serial data of abdominal girth were recorded daily.

Feeding protocol: All neonates of both the groups were given gastrointestinal priming feeding (Trophic feeding) on Day 1 with expressed breast milk (EBM) at the rate of 10 mL/kg/day. All newborns were given feeding through a nasogastric tube.

Group 1 (Slow advancement group): All infants were given gastrointestinal priming feeding on Day 1 with EBM at the rate of 10 mL/kg/day, thereafter the feeds increased by 15-20 mL/kg/day till the maximum volume of 180 mL/kg/day was achieved.

Group 2 (Rapid advancement group): All infants in Group 2 were also given gastrointestinal priming as in Group 1 infants. The feed was advanced by 30-40 mL/kg/day till the maximum volume of 180 mL/kg/day was achieved.

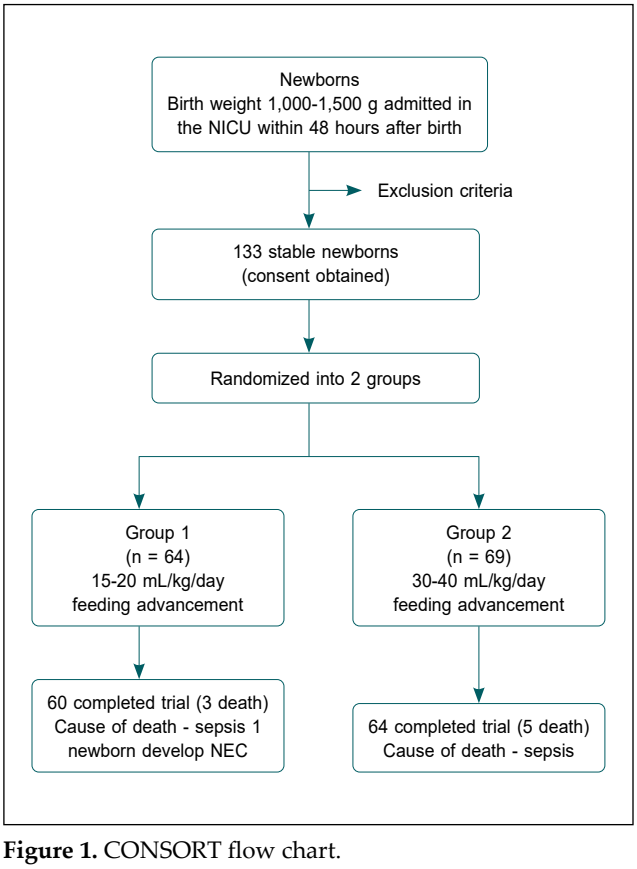

Figure 1. CONSORT flow chart.

All stable VLBW neonates were thoroughly examined clinically daily and the finding were duly recorded on a predesigned proforma.

The pre-feed abdominal girth was measured. If pre-feed abdominal girth increased >2 cm between consecutive feeds, then gastric aspiration was done. If the pre-feed gastric aspirate volume was >30% or 3 mL/kg (whichever is greater) then the further increment of feed was deferred for the next 24 hours and one feed was omitted. If gastric aspirate volume was >50% of pre-feed, the feeding was discontinued temporarily for the next 24 hours.

During this period, the baby was investigated for evidence of sepsis and NEC. If sepsis was confirmed, the feed was discontinued and if sepsis screen was negative, feed was restarted at half the volume of last feed. In the event of the occurrence of severe sepsis or NEC, the patient was excluded from this study and managed for this complication.

RESULTS

In these VLBW babies, feed intolerance was observed clinically in relation to abdominal distension and gastric residue. We found that there was no statistically significant difference between the slow and rapid advancement groups. Both the time for reaching full-feed and duration of regaining birth weight were less in rapid advancement group than in slow advancement group. In the present study, total 133 VLBW babies were included.

In Group 1, 36 babies (56.25%) were male and 28 (43.75%) were female and 60 (93.75%) were appropriate-for-gestational age (AGA) and 4 (6.25%) were small-for-gestational age (SGA).

In Group 2, 43 (62.31%) were male and 26 (37.68%) were female and 65 (94.20%) were AGA and 4 (5.79%) were SGA.

The overall mean gestational age of newborns in Group 1 was 31.8 ± 0.3 weeks and that of Group 2 newborns was 31.9 ± 0.3 weeks. It was 31.63 ± 0.32 and 32.8 ± 2.04 weeks in Group 1 AGA and SGA newborns, while it was 31.89 ± 0.29 and 32.8 ± 1.36 weeks in Group 2 AGA and SGA newborns.

The mean birth weight of Group 1 newborns was 1,270.06 ± 38.2 g and those in Group 2 was 1,293.1 ± 36.2 g. It was 1,269.58 ± 38.58 and 1,299.69 ± 36.39 g in Group 1 AGA and SGA newborns, while it was 1,299.69 ± 36.39 and 1,263 ± 245.5 g in Group 2 AGA and SGA newborns (Table 1).

The mean time of starting minimal enteral feed in Group 1 was 25.6 ± 3.9 hours and 21.7 ± 3.8 hours in Group 2. It was 28.15 ± 5.42 and 27.0 ± 31.4 hours in Group 1 AGA and SGA newborns; while in Group 2 it was 21.35 ± 3.98 and 22.8 ± 21.12 hours in AGA and SGA newborns.

The mean time to achieve full feeds was 11.37 ± 1.36 days in Group 1, while in Group 2 was 6.59 ± 0.62 days. It was 10.75 ± 1.55 and 12.4 ± 8.76 days in Group 1 AGA and SGA newborns, while in Group 2 it was 6.63 ± 0.66 and 7.2 ± 3.44 days in AGA and SGA newborns. Feeding was interrupted in about 4.68% newborns in Group 1 and in 5.79% in Group 2.

The mean time of regaining birth weight was 16.87 ± 0.9 days in Group 1, while it was 13.63 ± 0.9 days in Group 2 (Table 2). It was 13.87 ± 1.88 and 16.0 ± 1.96 days in Group 1 AGA and SGA newborns, while in Group 2 it was 13.03 ± 1.16 and 11.0 ± 8.0 days in AGA and SGA newborns.

The average weight gain in Group 1 was 4.41 ± 0.9 g and 6.33 ± 1.3 g in Group 2 (Table 2). It was 3.61 ± 0.86 and 2.175 ± 2.09 g in Group 1 AGA and SGA newborns,

Table 1. Socio-demographic Profile

Variable	Group 1 (n = 64)	Group 2 (n = 69)	P value
Male:Female	36:28	43:26	>0.05
Birth weight (in grams)	1,270.06 ± 38.2	1,293.1 ± 36.2	0.39
Gestational age (In weeks)	31.8 ± 0.3	31.9 ± 0.3	0.42
AGA:SGA	60:4	65:4	>0.05

Table 2. Outcome Measures in Both Groups

Outcome	Group 1 (n = 64)	Group 2 (n = 69)	P value
Average weight gain per day (grams)	4.41 ± 0.9	6.33 ± 1.3	0.02
Regain of birth weight (days)	16.87 ± 0.9	13.63 ± 0.9	0.005
Average occipitofrontal circumference increment per week (cm)	0.29 ± 0.27	0.42 ± 0.05	<0.005
Average length increment per week (cm)	0.55 ± 0.04	0.69 ± 0.05	<0.005
Duration of hospital stay (Days)	27.47 ± 3.33	23.15 ± 2.22	0.03

while it was 5.66 ± 1.29 and 4.04 ± 6.22 g in AGA and SGA newborns in Group 2.

The mean occipitofrontal circumference increment per week was 0.29 ± 0.27 cm Group 1, while in Group 2, it was 0.42 ± 0.05 cm (Table 2). It was 0.28 ± 0.03 and 0.32 ± 0.14 cm in Group 1 AGA and SGA newborns, while in Group 2 AGA and SGA newborns, it was 0.42 ± 0.06 and 0.32 ± 0.18 cm, respectively.

The mean length increment per week was found to be 0.55 ± 0.04 cm and 0.69 ± 0.05 cm in Group 1 and Group 2, respectively (Table 2). It was 0.53 ± 0.05 and 0.56 ± 0.03 cm in Group 1 AGA and SGA newborns, while it was 0.70 ± 0.05 and 0.54 ± 0.28 cm in Group 2 AGA and SGA newborns.

The mean duration of phototherapy was 92.04 ± 9.22 hours in Group 1 and it was 77.42 ± 7.54 hours in Group 2. It was 67.7 ± 12.8 and 67.2 ± 48.97 hours, respectively in Group 1 AGA and SGA newborns, while in Group 2 it was 62.28 ± 9.6 in AGA and 76.8 ± 64.6 hours SGA newborns.

In Group 1, NEC was found in 1 baby, while none of the newborns in Group 2 suffered from NEC.

In Group 1, sepsis was found in 3 babies, while it was seen in 5 babies in Group 2.

The mean duration of hospital stay was 27.47 ± 3.33 days in Group 1 while in Group 2, the duration of stay was 23.15 ± 2.22 days (Table 2). It was 27.9 ± 3.5 and 25.2 ± 14.86 days in Group 1 AGA and SGA newborns, while in Group 2 it was 23.37 ± 2.31 and 19.4 ± 9.48 days in AGA and SGA newborns.

Four newborns in Group 1 had adverse outcomes (expired/NEC), while 5 newborns in Group 2 had adverse outcomes (expired).

DISCUSSION

In the present study, study subjects included 64 newborns in Group 1 and 69 newborns in Group 2. The profile of patients was almost similar to that seen in other studies.[7-13] In the present study, 93.75% newborns were AGA and 6.25% newborns were SGA in Group 1, while 94.2% were AGA and 5.80% newborns were SGA. In a study conducted by Krishnamurthy et al, in 80% newborns in Group 1 were AGA and 20% were SGA, while in Group 2, 72% newborns were AGA and 28% newborns were SGA.[14] In a study conducted by Karagol et al, 65.21% newborns were AGA and 34.79% newborns were SGA in Group 1, while 63.04% newborns were AGA and 36.96% newborns were SGA in Group 2.[8]

In a study conducted by Krishnamurthy et al, the mean gestational age in Group 1 was 31.1 ± 1.2 weeks and 30.8 ± 1.1 weeks in Group 2.[14] While in the study conducted by Karagol et al, the mean gestational age in Group 1 was 28.2 ± 1.1 weeks and in Group 2, it was 28.3 ± 1 weeks.[8]

In the present study, mean birth weight in Group 1 was 1,270.06 ± 38.2 g and in Group 2 was 1,293.1 ± 36.2 g. It was 1,269.58 ± 38.58 and 1,268 ± 250.6 g in Group 1 AGA and SGA newborns, while it was 1,299.69 ± 36.39 and 1263 ± 245.5 g in Group 2 AGA and SGA newborns. While in study conducted by Karagol et al, mean birth weight was in Group 1 was 984.3 ± 217.1 g and in Group 2 was 951.6 ± 196.4 g. The difference was because Karagol et al had selected newborns with weight ranging from 750 to 1,250 g.[8] The birth weight in the study conducted by Caple et al in 2004 was 1,000 to 2,000 g and <1,250 g in the study by Salhotra and Ramji in 2004 Krishnamurthy et al in 2010 reported a mean birth weight of 1,306.0 ± 129.2 g and 1,261.4 ± 121.6 g in Groups 1 and 2, respectively, which was similar to our study.[7,13,14]

In the present study, the mean time of starting minimal enteral feed in Group 1 was 25.6 ± 3.9 hours and 21.7 ± 3.8 hours in Group 2. It was 28.15 ± 5.42 and 27.0 ± 31.4 hours in Group 1 AGA and SGA newborns whiles in Group 2 it was 21.35 ± 3.98 and 22.8 ± 21.12 hours in AGA and SGA newborns. In Karagol et al, the mean time of starting minimal enteral feed was 36.4 (8-17) hours in Group 1 and 35.8 (11-22) hours in Group 2.[8] In our study, trophic feeding in almost all babies were started within 24 hours, while in Karagol et al, the average time of starting trophic feeds was 24 to 48 hours.

In present study, the volume increments in Group 1 ranged from 1,520 mL/kg/day, while in Group 2, the increment in volume was 30-40 mL/kg/day. In Karagol et al, the volume increment in Group 1 was 20 mL/kg/day and 30 mL/kg/day in Group 2.[8] In Rayyis (1999),[12] the volume increment was 15 mL/kg/day in Group 1 and 35 mL/kg/day in Group 2. It was 20 mL/kg/day (Group 1) and 35 mL/kg/day (Group 2) in Caple et al (2004);[13] 15 mL/kg/day (Group 1) and 30 mL/kg/day (Group 2) in Salhotra and Ramji in 2004[7] and 20 mL/kg/day (Group 1) and 30 mL/kg/day (Group 2) in the study by Krishnamurthy et al.[14]

In the present study in Group 1 were given gastrointestinal priming feeding for first 24 hours with EBM at the rate of 10 mL/kg/day 4-hourly thereafter the feeds increased by 15-20 mL/kg/day till maximum achievement that was 180 mL/kg/day and similarly all

the infants of Group 2 were also given gastrointestinal priming as Group 1 infants and feeds were advanced by 30-40 mL/kg/day till maximum of 180 mL/kg/day was achieved. Salhotra and Ramji in 2004,[7] and Krishnamurthy et al in 2010[14] and Karagol et al in 2013[8] also used the same maximum advancement of 180 mL/kg/day.

The method of feeding in the present study was nasogastric tube feeding similar to the other trials.[9,11,12,14]

Caple et al in 2004[13] used full strength commercial formula or human milk for feeding infants, Salhotra and Ramji in 2004[7] used human milk for feeding infants; Krishnamurthy et al[14] used EBM and formula milk, while Karagol et al[8] used EBM and formula milk for feeding. In the present study, we used EBM for the feeding of all infants.

In the present study, feeding was interrupted in 6.25% newborns in Group 1, whereas in Group 2, feeding was interrupted in 5.79%, newborns, which was statistically not significant. In Salhotra and Ramji in 2004,[7] feeding was interrupted in 65.38% in Group 1 and in 51.62% in Group 2; in Krishnamurthy et al in 2010,[14] feeding was interrupted in 24% in Group 1 and 16% in Group 2 newborns, while in Karagol et al in 2013,[8] feeding had to be interrupted in 28% newborns in Group 1 and 23.9% in Group 2.

In the present study, no association was found between advancement of feed and feed intolerance. Salhotra and Ramji in (2004),[7] Caple et al (2004)[13] and Krishnamurthy et al (2010)[14] also reported no significant difference in feed intolerance with slow and rapid advancements of feeds. It further strengthened the belief that adverse events related to rapid advancement of feeding were not so common as previously feared.

In present study, the fast advancement group reached full enteral feeds significantly earlier (mean 6.59 ± 0.62 days) than in the slow advancement group (mean 11.37 ± 1.36 days), which was statistically highly significant. It was 10.75 ± 1.55 and 12.4 ± 8.76 days in AGA and SGA newborns in Group 1, while it was 6.63 ± 0.66 and 7.2 ± 3.44 days in Group 2 AGA and SGA newborns. In Karagol et al, the mean duration to reach full enteral feed in Group 1 was 18.1 ± 5.8 days and 15.5 ± 8.4 days in Group 2.[8] In Salhotra and Ramji in 2004, the fast advancement group (30 mL/kg/day) attained full enteral feeds of 180 mL/kg/day by the 10th day and the slow advancement group (15 mL/kg/day) by the 15th day (mean 14.8).[7] In Rayyis et al, the rapid advancement group (35 mL/kg/day) attained full enteral feeds of 180 mL/kg/day by the 11th day and the slow advancement group (15 mL/kg/day) by the 15th day.[12] In Krishnamurthy et al, the median time taken to reach full enteral feed was 9 days in Group 1 and 7 days in Group 2.[14] But in the present study, the rapid advancement group (30-40 mL/kg/day) reached full feed by the 6.59 days (mean), while slow advancement group (15-20 mL/kg/day) reached full feed by 11.37 days (mean). Our results were similar to the studies by Salhotra and Ramji in 2004[7] and Krishnamurthy et al in 2010[14] in reaching full feeds early by rapid advancement of feeds without complications.

In the present study, the mean time to regain birth weight was shorter in the rapid advancement group (13.63 ± 0.9 days) compared to the slow advancement group (16.87 ± 0.9 days); this difference was statistically significant ($p < 0.005$). It was 13.87 ± 1.88 and 16.0 ± 1.96 days in Group 1 AGA and SGA newborns while in Group 2 it was 13.03 ± 1.16 and 11.0 ± 8.0 days in AGA and SGA newborns.

Salhotra and Ramji in 2004[7] also showed early regain of birth weight in slow advancement feeding group in 23 days, while in rapid advancement group, regain in birth weight occurred in 18 days. In the study conducted by Krishnamurthy et al, median time to regain birth weight was 22 days in Group 1 while it was 16 days in Group2.[14] This study also supports our results of early regain of birth weight. Similar results were observed by Karagol et al.[8] In which, mean time of regaining birth weight was in Group 1 19.3 (14-17) days and in Group 2 was 16.0 (12.3-20) days.

In our study, the average increment in length per week was 0.55 ± 0.04 cm in Group 1 and 0.69 ± 0.05 cm in Group 2. It was 0.53 ± 0.05 and 0.56 ± 0.03 cm, respectively in Group 1 AGA and SGA newborns, while it was 0.70 ± 0.05 and 0.54 ± 0.28 cm in Group 2 AGA and SGA newborns.

The mean duration of phototherapy was 92.04 ± 9.22 hours in Group 1, and 77.42 ± 7.54 hours in Group 2. This difference was due to slow enterohepatic circulation in slow advancement group, and in Group 1 AGA and SGA newborns, the mean duration of phototherapy was 67.7 ± 12.8 and 67.2 ± 48.97 hours, while in Group 2 AGA and SGA newborns, it was 62.28 ± 9.6 and 76.8 ± 64.6 hours.

In the present study, mean increment in occipitofrontal circumference per week was 0.29 ± 0.27 cm in Group 1, while in Group 2 it was 0.42 ± 0.05. It was 0.28 ± 0.03 and 0.32 ± 0.14 cm in Group 1 AGA and SGA newborns, and in Group 2 AGA and SGA newborns, it was 0.42 ± 0.06 and 0.32 ± 0.18 cm.

In present study, average weight gain per day was 4.41 ± 0.9 g in Group 1 and 6.33 ± 1.3 g, respectively. According to gestational age, in Group 1 it was 3.61 ± 0.86 and 2.17 ± 2.09 g in AGA and SGA newborns, while it was 5.66 ± 1.29 and 4.04 ± 6.22 g in Group 2 AGA and SGA newborns.

In the present study, the incidence of culture proven sepsis in Group 1 was 3.12% and 4.34% in Group 2. In Salhotra and Ramji 2004,[7] 38.46% newborns in Group 1 and 18.51% in Group 2 developed sepsis. In Krishnamurthy et al in 2010,[14] sepsis was seen in 10% and 8% of Group 1 and Group 2 patients, respectively. In Karagol et al (2013)[8] sepsis was seen in 13.04% in Group 1 and 6.52% newborns in Group 2, respectively.

In the present study in Group 1 (slow advancement group), 1 male AGA newborn developed NEC. None of the newborns in the rapid advancement group developed NEC. Earlier studies have shown almost equal incidence of NEC in male and female newborns. In Caple et al in 2004,[13] 2.38% newborns in Group 1 and 5.40% in Group 2 developed NEC. In Salhotra and Ramji (2004),[7] 7.40% newborns in Group 2 developed NEC compared to none in Group 1. The incidence of NEC in Krishnamurthy in 2010[14] was 2% in Group 1 and 4% in Group 2, which showed similar ratio of NEC patients as present study. In Karagol et al,[8] 10.86% newborns in Group 1 and 8.69% newborns in Group 2 developed NEC. These studies show that is not a common adverse event in relation to feed advancement.

In the present study, mean duration of hospital stay was 27.47 ± 3.3 days in Group 1 and 23.15 ± 2.2 days in Group 2; it was 27.9 ± 3.5 and 25.2 ± 14.86 in Group 1 AGA and SGA newborns, and 23.37 ± 2.31 and 19.4 ± 9.48 in Group 2 AGA and SGA newborns. In Karagol et al,[8] the mean duration of hospital stay was 26.2 ± 1.1 days in Group 1 and 21.5 ± 1.3 days in Group 2.

The adverse events related to rapid advancement of feeding, i.e., gastric residuals, abdominal distension and feeding interruption were comparable in the slow advancement and rapid advancement group. The benefits of rapid advancement of feeds were early regaining of birth weight, shorter hospital stay and early achievement of full feed. Similar conclusion was also found in earlier studies by Salhotra and Ramji in 2004[7] and Caple et al in 2004[13] and Krishnamurthy et al 2010.[14]

Feed intolerance (abdominal distension, gastric residue, feed interruption) related to advancement of feeding were almost equal in slow advancement and rapid advancement group indicating that rapid advancement of feeding is beneficial in VLBW babies and refutes the old fear about the rapid advancement of feeding in low birth weight and premature babies.

CONCLUSIONS

In conclusion, rapid advancement of feeding up to 40 mL/kg/day is safe and well-tolerated in VLBW babies, including SGA and AGA. It leads to early regaining of birth weight and reduces the total duration of hospital stay of newborns, which can indirectly decrease the risk of hospital-acquired infections and other complications. It fulfills the required nutrition and prevents undernutrition and future growth retardation of VLBW babies.

It lessens the physical and psychological stress of parents and reduces the extra work load of the medical personnel and hospitals and also cuts short the financial burden on hospitals, families and heath personnel by shortening hospital stay in developing countries like India. But further long-term studies are required with large numbers of premature and low birth weight babies, to recommend universal rapid advancement of feeding in these babies.

Declarations

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Code availability: Not applicable.

Authors' contributions: RKM & DRB drafted the study design, collected data, contributed in statistical analysis and inference of results. RM & JS supervised the entire work, drafted the study design, collected data, contributed in statistical analysis and inference of results. CKM did critical analysis of all data, counseled the parents and hypothesized the study, drafted the study design, collected data, contributed in statistical analysis and inference of results. RKM, DRB, JS, CM & RM drafted the conclusions, reviewed the literature, drafted the study design, collected data, contributed in statistical analysis and inference of results.

Ethics approval: Taken.

Consent to participate: Consent of parents was taken.

Consent for publication: Yes.

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The Association of Iron Deficiency Anemia and Diabetes

A study published in the journal *Cureus* has shown that iron deficiency anemia (IDA) may have an impact on diabetes management and glycemic control.[1] Diabetes patients with anemia had higher glycated hemoglobin (HbA1c) levels, indicating poorer diabetes control. In this cross-sectional study, the main objective was to examine the relationship between IDA, HbA1c levels and glycemic parameters in patients with diabetes, both type 1 and type 2. For this they enrolled 143 adult patients diagnosed with diabetes attending OPDs. Their mean age was 55 years and over half of the study group was male. Serum ferritin levels below 100 ng/mL, transferrin saturation below 20% and other hematologic parameters were used to define IDA. Additionally, a subgroup of patients underwent continuous glucose monitoring (CGM) to obtain daily glucose profiles and assess glycemic dynamics. The aim of the study was to determine how IDA may impact HbA1c levels and glycemic control in individuals with diabetes. Nearly 80% had type 2 diabetes. The duration of diabetes ranged from less than 5 years in 43.4% of the participants, 5 to 10 years in ~33% and over 10 years in ~24%. None of the selected participants had any known hematological disorders other than IDA. Results showed that the prevalence of IDA among the diabetic cohort was 39.9%. The mean HbA1c levels were higher among the anemic diabetes patients compared to those who did not have IDA; 7.2% versus 6.8% suggesting a potential influence of IDA on HbA1c values. Moreover, CGM data showed that the patient with IDA spent more time in hyperglycemic ranges and exhibited greater glucose variability. Other parameters of iron deficiency including low ferritin levels and high red cell distribution width (RDW) were also found to have a correlation, albeit weakly positive, with HbA1c levels.

This study illustrates the high prevalence of IDA in patients with diabetes and may be linked to inaccurate HbA1c values and poor short-term glycemic control. The authors however caution that further larger controlled studies are needed to fully comprehend the mechanisms connecting IDA to changes in HbA1c levels and glycemic dynamics. By implementing optimized screening and treatment strategies for IDA, it is possible to enhance the accuracy of diabetes monitoring and potentially improve outcomes for patients.

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CASE REPORT

Unveiling the Eschar: A Mite's Mark in Scrub Typhus

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ABSTRACT

Scrub typhus is an acute febrile illness caused by *Orientia tsutsugamushi*, a Gram-negative intracellular organism transmitted by *Leptotrombidium* mites, with wild rats serving as natural reservoirs. The disease is more common in the Tsutsugamushi Triangle, often afflicting travelers and creating diagnostic challenges in clinical practice. We present the case of a diabetic patient who acquired the infection while visiting an agricultural farm. Our discussion covers clinical manifestations, diagnostic markers and treatment modalities, emphasizing the significance of early recognition and the benefits of prompt treatment. The importance of searching for an eschar, a key physical sign, is underscored and potential serious outcomes are discussed. Recent advances and preventive measures are also highlighted. This synthesis of research and clinical insights aims to enhance global awareness, prompt diagnosis and effective management of scrub typhus.

Keywords: Eschar, fever-mite, tsutsugamushi, scrub typhus, international travelers

Scrub typhus is an acute febrile illness caused by infection with *Orientia tsutsugamushi*, an intracellular obligate Gram-negative organism. It is transmitted to humans by the bite of the infected chigger, the mite of *Leptotrombidium*. Wild rats serve as the natural reservoir, with humans as accidental victims. Chiggers, measuring 0.2 mm, are challenging to visualize with the naked eye. They typically inhabit scrubs, the transitional area between woods and clearings, hence the term "Scrub Typhus". In tropical regions, infections can occur year-round, while in the Far East, infections peak from July to September.[1]

The geographical distribution of this disease forms a triangular area extending from northern Japan in the east to eastern Russia in the north, Afghanistan and Pakistan in the west and northern Australia in the south, known as the Tsutsugamushi Triangle. Approximately half of the human population resides in this area. Scrub typhus is often acquired during occupational or agricultural exposure.[2] An estimated 1 million cases occur annually and around 1 billion people in the endemic areas are possibly being infected at some point. In India, although clear statistics are lacking, a literature search from the past 10 years reported 18,781 confirmed cases.[3]

The incubation period ranges from 6 to 20 days, with an average of 10 days. Patients commonly present with high fever, cough, malaise, anorexia, ocular pain, lymphadenopathy and splenomegaly. Severe cases may involve pneumonitis, encephalitis, myocarditis, hepatitis, renal failure and, rarely, complications such as acute respiratory distress syndrome, circulatory failure and disseminated intravascular coagulation. A diagnostic sign is the presence of an eschar at the chigger bite site, with a maculopapular rash potentially developing on the 5th to 8th day. Mortality rates vary from 1% to 60%, depending on the strain and geographical area, with poor prognostic factors including age over 60, high initial leukocyte count, elevated C-reactive protein (CRP), abnormal liver function tests and the absence of an eschar.[4]

Doxycycline is the preferred treatment, and alternatives include azithromycin, rifampin and chloromycetin. Chemoprophylaxis with weekly doxycycline starting a week before and continuing for 6 weeks after exposure is advisable. Wearing appropriate clothing or using repellent to prevent mite bites and employing a cloth barrier while in the scrubs are recommended preventive measures.[5]

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CASE SUMMARY

A 54-year-old male was admitted to the hospital on 24th July, 2023 with an 8-day history of fever with chills. He had an ulcer with surrounding erythema on the left thigh (Fig. 1), and vaguely recalled being bitten by an insect in the same area a week before the ulcer developed. This incident occurred during an outdoor party at a friend's farmhouse in a suburban area. The patient developed an erythematous maculopapular rash on the day of admission (Fig. 2). He had a 20-year history of diabetes treated with a combination of insulin aspart and insulin aspart protamine and had taken an antibiotic (amoxicillin clavulanate) initially but discontinued it due to gastrointestinal side effects. He had taken cefuroxime for 3 days before admission. The patient was febrile with a temperature of 103°F (Fig. 3), normal blood pressure and a pulse rate of 101/min. Physical examination revealed clear lungs, tachycardia, mild abdominal distension with no tenderness and restlessness. Laboratory investigations are detailed in Table 1.

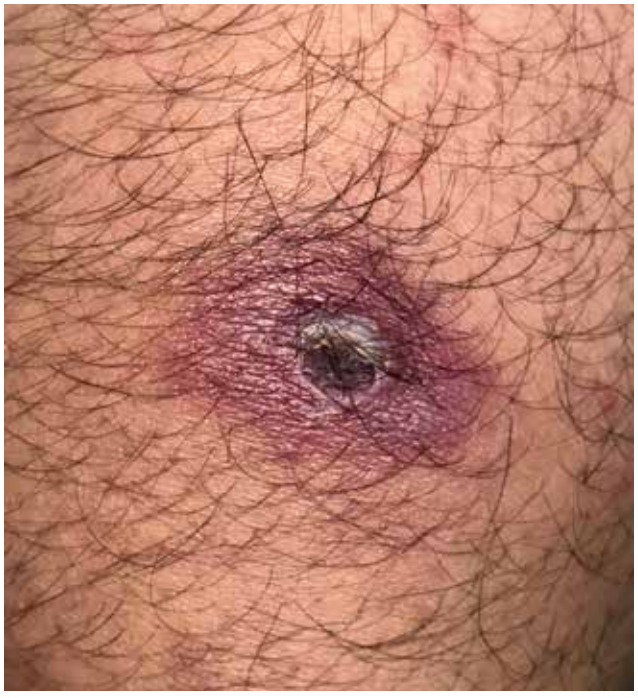

Figure 1. Eschar, consisting of a central tough black scab surrounded by dull red areola. It is neither pruritic nor painful.

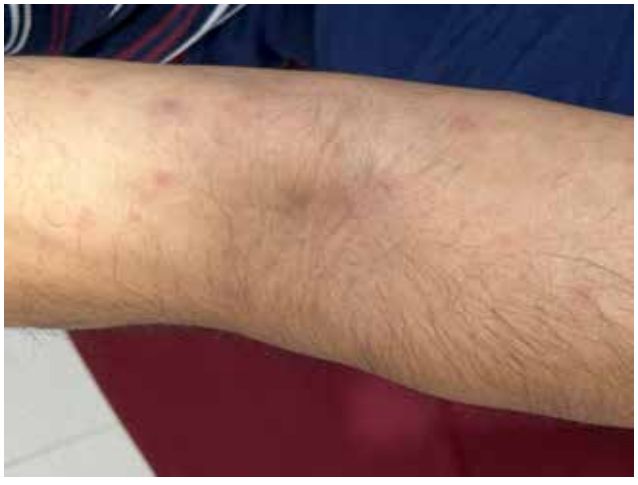

Figure 2. Maculopapular rash usually appearing first on the trunk and spreading (centripetal) to limbs between 5th to 8th day illness

Based on clinical presentation, the presence of an eschar and a positive rapid immunochromatographic test for IgM against *O. tsutsugamushi*, a diagnosis of scrub typhus was established. The patient was treated with doxycycline and azithromycin and showed a favorable response by the 3rd day, with the fever resolving and ulcer healing by the 5th day. The patient was discharged on a regimen of doxycycline and azithromycin, and after a 10-day follow-up, the patient was healthy with complete healing of the ulcer.[6]

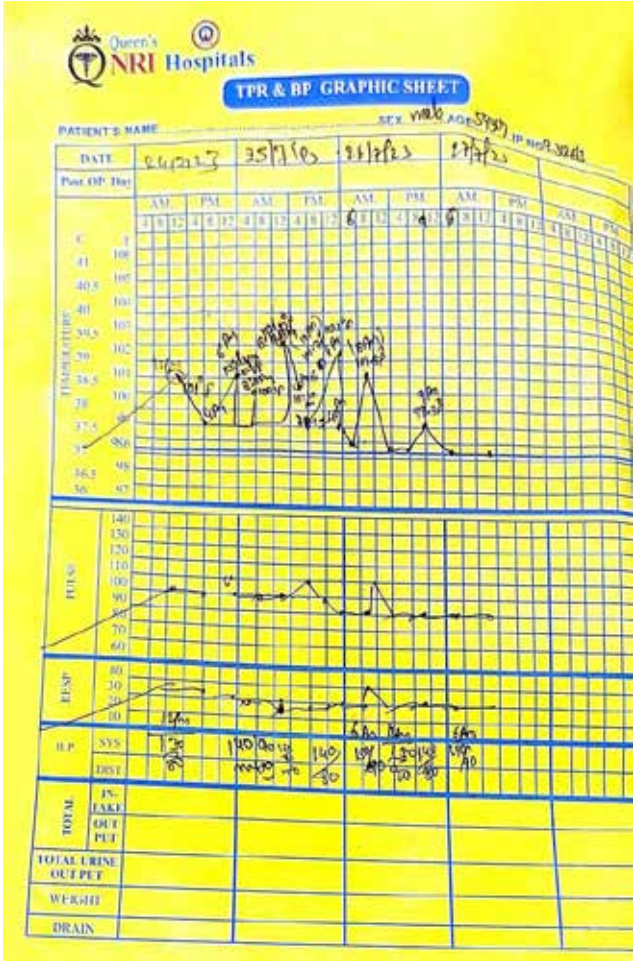

Figure 3. Patient's temperature chart showing fever spikes.

Table 1. Laboratory Investigations

TWBC: 7,000/µL
Hb%:14.0 g
CRP: 23.71 mg
Peripheral smear: Normal
LDH: 364 Unit/L
Urine microscopy: 6-8 pus cells
Dengue serology: Negative
QBC malaria: Negative
IgM typhoid: Negative
HBsAg: Negative
HCV: Negative
HIV: Negative
IgM scrub typhus: Positive
Ultrasound abdomen: Cholelithiasis
Chest X-ray: Normal
ECG: Normal
Urine culture and sensitivity: No growth
Blood culture and sensitivity: No growth

TWBC = Total white blood cells; Hb = Hemoglobin; CRP = C-reactive protein; LDH = Lactate dehydrogenase; QBC = Quantitative buffy coat; IgM = Immunoglobulin M; HbsAg = Hepatitis B surface antigen; HCV = Hepatitis C virus; HIV = Human immunodeficiency virus; ECG: Electrocardiogram.

DISCUSSION

The patient likely contracted scrub typhus while visiting an agricultural farm, commonly associated with activities in scrubs or agriculture. The presence of a typical eschar at the insect bite site supported the diagnosis, although its absence does not exclude the disease. The patient exhibited high-grade spiky fever, a common symptom in scrub typhus cases. The maculopapular rash on the 8th day aligned with the typical presentation, and although the patient had a normal leukocyte count, literature suggests initial lymphopenia followed by lymphocytosis is common. Poor prognostic indicators, such as increased CRP, were present in this case. A positive rapid test for IgM is a common method for diagnosing scrub typhus in developing countries. Pulmonary involvement, often seen as patchy pneumonia, did not manifest radiologically in this patient.[7]

Differential diagnoses include leptospirosis, dengue, malaria, typhoid, anthrax, rickettsial pox, tularemia and viral fevers with thrombocytopenia. Diagnosis may be challenging in the absence of a typical eschar.

Interestingly, in human immunodeficiency virus (HIV)-positive patients infected with certain strains of scrub typhus, a dramatic decrease in viral load has been observed, sparking research interest.[8] Treatment choices involve doxycycline and azithromycin, either individually or in combination, depending on the clinical scenario. Our patient responded favorably to treatment, emphasizing the importance of timely intervention. If a patient does not respond, re-evaluation of the diagnosis or consideration of drug resistance is crucial.[9]

CONCLUSION

Scrub typhus can be fatal if not diagnosed early and treated appropriately. Clinical presentations and laboratory parameters may mimic other febrile illnesses, necessitating a thorough search for an eschar as a vital diagnostic clue. Scrub typhus should be considered in the differential diagnosis, particularly when treating febrile illnesses in travelers from endemic areas.

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Declarations

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Ethical approval: Not required.

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Characteristics of Hyperosmolar Hyperglycemic State in Diabetes Patients

Patients with type 1 diabetes are more likely to experience hyperosmolar hyperglycemic state (HHS) compared those with type 2 diabetes, as per a new study reported in *Diabetes Care*,[1] which also states that HHS is considered a spectrum of hyperglycemic crises and can be further categorized into two subgroups: pure HHS and HHS-DKA (diabetic ketoacidosis).

Researchers from the Copenhagen University Hospital and the University of Copenhagen sought to evaluate the incidence of HHS and also examine the clinical and biomarker profiles of patients with HHS, including those with acidosis and acute kidney injury (AKI). For this they conducted a descriptive cohort study using Danish registry data from 2016 to 2018. Patients having a glucose level of ≥33 mmol/L and an osmolarity (calculated as 2 × sodium + glucose) of ≥320 mmol/L were included in the study. A total of 24,196 had type 1 diabetes, while the number of adults diagnosed with type 2 diabetes was 2,51,357.

A total of 634 adult patients with an average age of 69 years and who met the criteria for HHS among a population of 4.80 million individuals were included in the study. The incidence rate of HHS in patients with known type 1 diabetes was 16.5 per 10,000 person-years and in patients with known type 2 diabetes, the incidence rate was 3.9 per 10,000 person-years. Interestingly, 32% of the patients diagnosed with HHS had not previously been diagnosed with diabetes.

The researchers further categorized the total HHS patients into two groups: 394 had pure HHS, while 240 had combined HHS and DKA. Patients in the pure HHS group were older than the HHS-DKA group. Sixty-five percent of patients in the pure HHS group had AKI at the time of hospitalization. Of these, just 6.2% had a chronic renal disease. "Among the patients with pure HHS who did not receive a DKA diagnosis during hospitalization, 39% still had an acidosis". The in-hospital mortality rate for patients with pure HHS was found to be 17% compared with 9% among those with HHS-DKA

HHS is a rare but acute condition and carries a high mortality rate. This study illustrates the incidence and characteristics of HHS in patients with diabetes. It is important to characterize HHS to help physicians to promptly recognize and diagnose this acute illness and take appropriate measures so that effective and rapid treatment can be initiated upon arrival at the hospital. Here, it also becomes important to note that it can sometimes be the initial indication of underlying diabetes, as was the case in this study, where HHS was actually the first presentation of their diabetes diagnosis.

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CASE REPORT

Dyke-Davidoff-Masson Syndrome: A Rare Presentation

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ABSTRACT

Introduction: Dyke-Davidoff-Masson syndrome (DDMS) is characterized by seizures, facial asymmetry, contralateral hemiplegia and mental retardation. The characteristic radiological features are cerebral hemiatrophy with homolateral hypertrophy of skull and sinuses. **Case report:** We report a case of DDMS in a 41-year-old female who presented with generalized tonic-clonic seizures, hemiparesis of the right upper and lower limb with deviation of the mouth to left. Noncontrast computed tomography (NCCT) head and magnetic resonance imaging (MRI) revealed hemiatrophy of the right cerebral hemisphere. **Conclusion:** DDMS is a rare disease; hence, diagnosing and managing such patients may be challenging. Our aim is to draw attention of the treating physicians towards this disease with the help of this case report.

Keywords: Tonic-clonic seizures, hemiparesis, facial asymmetry, cerebral hemiatrophy, homolateral hypertrophy of skull, NCCT head

Dyke-Davidoff-Masson syndrome (DDMS) was initially identified in 1933 by Dyke, Davidoff and Masson. They reported the pneumoencephalographic and plain skull radiography abnormalities in a group of 9 individuals.[1] Nearly 100 cases have been reported since it was first characterized in 1933,[2] although only 21 cases involving adults have been documented.[3] Recurrent seizures, facial asymmetry, contralateral hemiplegia, mental retardation or learning difficulty, and speech and language problems are the most prevalent presentations. Sensory loss and mental health issues like schizophrenia are seldom reported.[4,5] Cerebral hemiatrophy with ipsilateral compensatory enlargement of the skull and sinuses are characteristic radiological findings. Most cases of the syndrome in adults and adolescents have been reported.[6,7]

In this article, we present a case of DDMS as it is a rare disorder and therefore it is important to draw attention towards such cases.

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CASE REPORT

A 41-year-old right-handed woman, presented in emergency ward with 3 to 4 episodes of sudden-onset of abnormal movements (tonic-clonic) since 2 days involving all 4 limbs associated with deviation of angle of mouth to left side and frothing from mouth and urinary incontinence. This was followed by altered sensorium, which was nonprogressive, slurring of speech and weakness in right upper and lower limb, which was maximum at the time of onset and nonprogressive (Fig. 1).

Patient had a past history of similar complaint of abnormal body movement and poor scholastic performance since childhood. She was receiving tablet phenytoin 100 mg thrice a day but there was no computed tomography (CT)/magnetic resonance imaging (MRI)/electroencephalogram (EEG) report available. Patient was born with normal vaginal delivery with no history of complication following it. Patient had history of delayed developmental of milestones and poor scholastic performance.

On examination, patient was conscious and not oriented to time, place and person initially because of postictal confusion but later she regained her orientation within a day. Mental status examination revealed a score of 22/30. Cranial nerve examination revealed right upper motor neuron type of facial palsy. Patient's muscle tone was markedly reduced and power was 3/5 in right upper and lower limb, while left upper and lower limb

Figure 1. Patient was able to stand only with support and had circumduction gait.

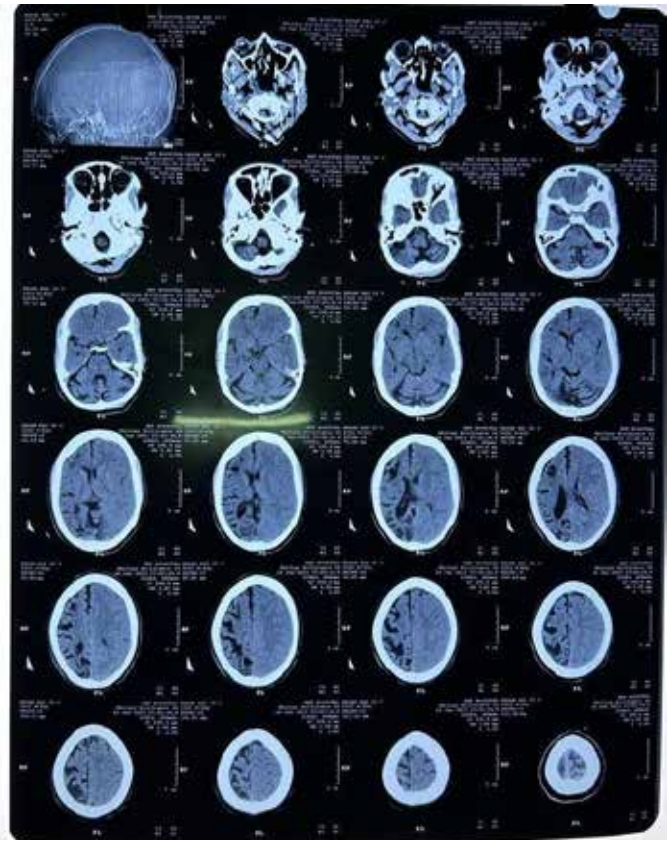

Figure 2. NCCT head - Second row images showing nonpneumatization of left frontal sinus with enlarged right frontal sinus. Fifth row image showing mild cortical hyperostosis on the right side compared to left; atrophy of the right cerebral hemisphere with prominent sulcal spaces and dilated right ventricle and the right occipital region showing cystic encephalomalacia.

motor examination was normal. Deep tendon reflexes were brisk and plantar response was extensor. Sensory examination was normal.

Lab biochemistry was unremarkable. A provisional diagnosis of sudden-onset generalized epilepsy with motor hemiparesis and mental retardation was made.

Noncontrast computed tomography (NCCT) (Fig. 2) head and MRI (Fig. 3) brain was performed, which revealed atrophy and prominent sulci and gyri of right cerebrum and cerebellum, with dilation of right lateral ventricle. There was mild cortical hyperostosis on the right side compared to the left. Nonpneumatization of left frontal sinus with enlarged right frontal sinus was seen. The left occipital region showed cystic encephalomalacia. EEG revealed epileptiform discharges in the form of paroxysmal generalized spike and wave having amplitude of 100-200 μV. Histopathology could not be done as the attendants were not willing. The patient was treated with tablet phenytoin 300 mg HS and tablet valproate 500 mg BD.

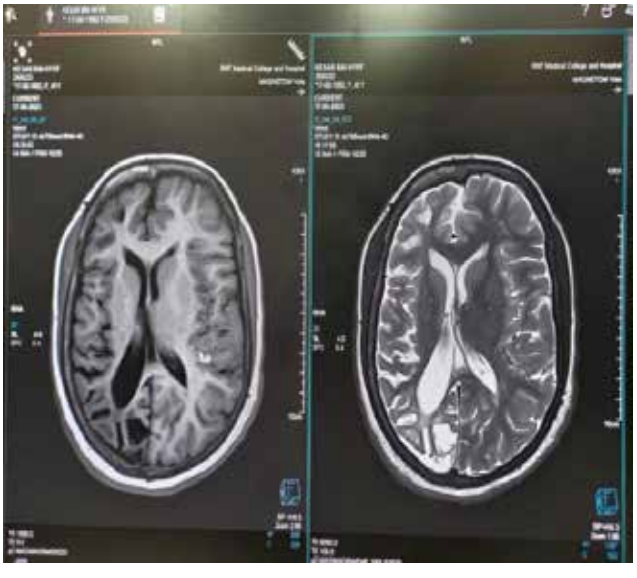

Figure 3. MRI Brain showing atrophy of the right cerebral hemisphere with prominent sulcal spaces, dilated right ventricle and right occipital region showing cystic encephalomalacia.

DISCUSSION

The uncommon neurological disorder known as DDMS was first identified in 1933 in 9 patients presenting with hemiparesis, facial asymmetry, seizures, intellectual disability and skull radiography findings of pneumatoencephalographic changes.[8] The exact cause of Down syndrome is still unknown, but prior research has linked the disorder to a brain injury that occurred either during pregnancy (congenital subtype), which manifests in infancy or in early childhood (acquired subtype), which may have resulted from a variety of causes including trauma, ischemia, hemorrhage or infection.[2] While DDMS is commonly thought of as a childhood illness, adult occurrences have been documented; a recent review found only 21 cases in the adult population.[2]

When the injury happens *in utero*, it results in congenital hemiatrophy, which is characterized by a shift of midline structures to the side of the illness and the absence of the sulcal prominence that would normally replace the gliotic tissue.[9] This characteristic sets it apart from early-life cerebral hemiatrophy. Trauma, inflammation or vascular malformations, and occlusions have all been proposed as the etiological factors of DDMS. Gestational vascular occlusion, which mainly affects the middle cerebral vascular territory, may be the cause of the insult when it happens *in utero*. Several Indian studies have reported a potential etiological relationship between seizures and cerebral hemiatrophy.[10,11]

The following conditions are included in the differential diagnosis of DDMS: Rasmussen encephalitis, Fishman syndrome, linear nevus syndrome, Sturge-Weber syndrome and basal cell germinoma.[12] The accurate diagnosis is given by a complete clinical history and the results of a CT or MRI. Treatment for convulsions, hemiplegia, hemiparesis and learning disabilities is symptomatic. If hemiparesis develops after the age of 2 years and there are no prolonged or recurrent seizures, the prognosis is better. Hemispherectomy has an 85% success rate in carefully chosen cases and is a potential treatment option for children with hemiplegia and intractable disabilities.[13]

CONCLUSION

DDMS stands as a rare neurological condition first identified in 1933. While its prevalence remains low, with nearly 100 cases reported to date, it presents with distinct clinical features including recurrent seizures, facial asymmetry, contralateral hemiplegia and cognitive impairments. Despite its rarity, the syndrome warrants attention due to its potential impact on patient quality of life. By presenting a case of DDMS in this article, we contribute to the growing body of knowledge surrounding this condition, emphasizing the importance of recognizing and addressing rare disorders in clinical practice. Increased awareness and understanding of DDMS may facilitate earlier diagnosis and intervention, ultimately improving outcomes for affected individuals.

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BRIEF COMMUNICATION

Prediabetes: Correlating the Ancient and Modern Schools of Medicine

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ABSTRACT

Modern medicine has recognized prediabetes as a well-characterized syndrome only in the last two decades. However, Ayurveda has clearly described distinct stages of diabetes thousands of years ago. The Ayurvedic classification represents the entire clinical spectrum of diabetes that we encounter today. In this article, we present the Ayurvedic perspective on prediabetes with regard to etiology, clinical features and management, which emphasizes lifestyle modification as the key approach to manage the dysglycemia.

Keywords: Ayurveda, dysglycemia, *kapha prameha, pitta prameha, vata prameha, shadakriyakaal*

PREDIABETES IN MODERN MEDICINE

The first use of the word 'prediabetes' dates back to 1918, when it was used[1] to describe dogs with partial damage to the pancreas. The term was used in clinical medicine, mostly in obstetric medicine, intermittently, with only 6 more PubMed citations in the next 30 years.[2] Interest has spiked in the last two decades, and prediabetes is now a well-characterized and well-described, clinical syndrome.

PREDIABETES IN AYURVEDA

Ayurveda, however, has clearly described distinct stages of diabetes thousands of years ago. *Charaka Samhita*, Nidanasthanam, Chapter 4, lists 20 types of *prameha* or urinary disorders.[3] These are further classified into 10 types of *kapha prameha*, 6 types of *pitta prameha* and 4 types of *vata prameha*.

While there is controversy regarding the appropriateness of this classification, *kapha prameha* seems equivalent to prediabetes, and *pitta prameha* appears to allude to early uncomplicated diabetes. The various types of *vata prameha* suggest a catabolic or advanced state of diabetes with vascular or visceral complications. Put together, the Ayurvedic classification represents the entire clinical spectrum of diabetes that we encounter today.

Murthy et al[4] present a comprehensive analysis of the classification, pathophysiology and clinical features of *prameha*. We must note that this opinion piece was written at a time when modern diabetology was not well developed, and when the concept of prediabetes had not been established.

DIVERSITY OF DYSGLYCEMIA

Atreya clearly mentions that the disease can present in asymptomatic or symptomatic manner, with varied natural trajectories and combination of clinical features. Many of the symptoms and complications of diabetes are listed in the narrative. There is a rightful emphasis on the relationship of fat and *prameha*. A step-wise progression of dysfunction is delineated, with various stages being described. The etiopathogenesis of diabetes is shared, as are the precipitating and aggravating factors for worsening. In fact, the concept of diabetes remission is alluded to as well.

The particular etiology, *dosha* and *dhatu* (tissue strength), in combination, decide the response of the body to diabetes. Asymptomatic, mild, late-onset, partial or full-blown manifestations may occur based upon various permutations and combinations of etiopathogenesis. This implies that Ayurveda understood the epidemiological triad (host, etiological factor and environment) as well as

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Table 1. Etiology of *Prameha*

Food
• Excessive and prolonged use of new grains, new legumes, meat, rice preparations
Beverages
• Excessive and prolonged use of sugarcane products, milk, fresh wine
Hygiene
• Abstinence from cleanliness
Physical activity
• Abstinence from physical exercise
• Indulgence in sleep, lying down, sitting

the epidemiological quartet (including time) that have been postulated in modern medicine. The multifaceted causation is clearly mentioned, in a way similar to that of the ominous octet.[5]

ETIOLOGY

The etiological factors listed by Charaka are mentioned in Table 1.

Prameha approaches immediately like a bird to its nest-tree, the person who is greedy in eatables and has dislike for bath and walking.

Death, in the form of prameha, takes away immediately the person who is dull in activities, over-obese, over-uncted and voracious eater.

(*Charaka Samhita*, Nidanasthanam, Chapter 4:50-52.)

CLINICAL FEATURES

Clinical features that are mentioned in Nidanasthanam, Ch. IV are listed in Table 2. Rastogi et al[6] classify symptoms and signs of prediabetes as anatomical, physiological and neurocognitive. While some of these are symptoms and signs of hyperglycemia and its neurological complications, others may be associated with micronutrient malnutrition, urinary tract or skin infection. While this approach encourages astute clinical observation, it would be fallacious to create a separate clinical symptomatology for prediabetes.

MANAGEMENT

Prediabetes is best managed by lifestyle modification. This is taught in *Charaka Samhita*. It is noteworthy that the following verse discusses "happy life" in diabetes, a concept that is now termed as glycemic happiness or euthymic euglycemia.[7]

Table 2. Clinical Features of *Prameha*

Kapha and *Pitta Prameha*
• Obesity
• Boils
• Abnormal urine, in term of quantity, color, smell, taste, consistency, precipitants
Vata Prameha: Urinary Symptoms
• *Vasameha*: muscle fat in urine = albuminuria
• *Majjameha*: marrow in urine
• *Hastimeha*: increased frequency
• *Madhumeha*: sugar in urine
Vata Prameha: Systemic Symptoms
• Osmotic symptoms: thirst, "morbidities in urine", crawling of bees and ants on body and urine
• Skin: matting of hair, dirt in the body, smearing in body orifices
• Oral cavity: sweetness in mouth, dryness of mouth, palate, throat
• Nervous system peripheral: numbness, burning over hands and feet
• Nervous system, central: lassitude, frequent sleep and drowsiness
• Complications: fleshy smell in body (ketosis), diarrhea, fever, anorexia, indigestion, boils due to sloughing of muscles (muscle necrosis)

The person who takes food which maintains the equilibrium of dhatus and also practices various physical activities enjoys happy life.

(*Charaka Samhita*, Nidanasthanam, Chapter 4:50-52.)

Ayurveda also enjoins us to practice prevention at all levels, from primordial to tertiary. These concepts are worded in Ayurveda as the six stages of *shadakriyakaal*.[6] While *sanchaya* refers to the stage of primordial prevention, *prakopa* and *prasaara* call for primary prevention. *Sthaana samshraya* is a stage where both primary and secondary prevention can be practiced. *Vyakti* and *bheda* are full blown clinical stages in which secondary and tertiary prevention are required.

Khirodkar et al[8] reinforce this concept, calling for preventive action during the phase of *purva rupa* or predisease. They point out the importance of managing *atisthaulya* (obesity) as a means of managing prediabetes as well as preventing diabetes and its complications.

SUMMARY

A rational reading of Ayurvedic texts demonstrates the clarity of thought with regards to multifactorial etiology and multifaceted presentation of diabetes. The natural

history of dysglycemia is well delineated, with an emphasis on possible remission of diabetes through a healthy lifestyle. While frank diabetes is thought to be incurable, this does not hold true today. With modern management diabetes can easily be managed, even though it may not be cured. Use of physio-friendly pharmacotherapy and lifestyle interventions can help achieve diabetes remission, provided that therapy is instituted in a timely manner. Prediabetes management holds the promise of preventing establishment of diabetes.

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Impaired Awareness of Hypoglycemia in Pediatric Type 1 Diabetes

The prevalence of impaired awareness of hypoglycemia (IAH) in children with type 1 diabetes is high and it is associated with episodes of severe hypoglycemia and an increased fear of hypoglycemia, says a study from Norway published January 13, 2024 in the journal *Diabetes Research and Clinical Practice*.[1]

The aim of this study was to investigate the prevalence and associations of IAH in children with type 1 diabetes using data from the Norwegian Childhood Diabetes Registry. The study included a total of 1,329 participants, with 53% being males. The ages of the participants ranged from 2 to 19 years, with a median age of 13.3 years. The participants had been diagnosed with type 1 diabetes for at least 6 months, with a median duration of 4.6 years.

Awareness about hypoglycemia was checked with the help of the Clarke questionnaire, which was self-assessed. For the 235 participants below the age of 9 years, parents responded on their behalf. The study also examined the associations between impaired awareness of hypoglycemia and clinical data from the Norwegian Childhood Diabetes Registry.

The overall prevalence of IAH was found to be 22%. But this prevalence declined gradually from 53% in preschoolers to 12% in adolescents aged 16 years and older. The study also identified several factors associated with IAH. These included a history of severe hypoglycemia with adjusted odds ratio (aOR) of 6.0 and diabetic ketoacidosis (aOR: 3.45) in the preceding year, increased fear of hypoglycemia (highest quartile vs. lowest: aOR: 2.27), female sex (aOR 1.41) and glycated hemoglobin (HbA1c) levels ≥8.5% (vs. 7.5-8.4%) (aOR 1.48). However, the study did not find an association between IAH and duration of diabetes, use of insulin pump or continuous glucose monitoring or HbA1c levels below 7.5%.

To conclude, IAH is indeed prevalent in pediatric type 1 diabetes, with a higher likelihood of being reported in young children. However, it is important to note that good metabolic control can still be achieved without an increased risk of developing IAH. This suggests that with proper routine evaluation and education on hypoglycemia awareness, pediatric patients with type 1 diabetes can maintain stable blood sugar levels while minimizing the risk of impaired awareness of hypoglycemia.

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Medication Errors and Drug-related Issues

Medication errors are a major cause of avoidable harm in health care systems globally and can occur at various stages of their use. In 2006, a report from the Institute of Medicine (IOM) titled 'Preventing Medication Errors' said, "In hospitals, errors are common during every step of the medication process—procuring the drug, prescribing it, dispensing it, administering it, and monitoring its impact—but they occur most frequently during the prescribing and administering stages."[1] Although medication errors are usually minor; but sometimes they can be serious. Since these errors can result in severe harm, disability and even death their timely detection is of the essence. In order to better understand medication errors, it is important to define the terms that describe them and classify them.[2]

SOME DEFINITIONS

- **Medical error:** "The failure of a planned action to be completed as intended or use of a wrong inappropriate or incorrect plan to achieve an aim."[3]
- **Sentinel event (major accidents):** "An unexpected occurrence involving death or serious physical or psychological injury or the risk thereof." Serious injury specifically includes loss of limb or function.[4,5]
- **Adverse event:** "An unintended injury or complication caused by medical management resulting in death, measurable disability or prolonged hospital stay."[6]
- **Adverse drug reaction: "**Any response that is noxious, unintended or undesired, which occurs at doses normally used in humans for prophylaxis, diagnosis, therapy of disease or modification of physiological function."[5]
- **Near miss (benign error):** "Any event or situation that could have resulted in an adverse outcome (accident, injury or illness), but did not, either by chance or through timely intervention."[7]
- **Medication error:** "A failure in the treatment process that leads to, or has the potential to lead to, harm to the patient."[2]

NEVER EVENTS

Never events are events, which should never happen in a health care setting. Examples include surgery performed on the wrong patient or wrong site surgery. They have been described as "the most egregious of patient safety incidents".[8] Although rare, they are very distressing to the patient with a substantial impact on the morbidity and mortality. Furthermore, they increase treatment costs due to prolonged hospitalization not only for the patient and also cause loss of revenue to the hospital.

The term "never events" now also encompasses in its scope, adverse events that are unambiguous (clearly identifiable and measurable), serious (resulting in death or significant disability), and usually preventable. There are now 29 "serious reportable events" that have been divided into 7 categories:[4]

1. Surgical or procedural events
2. Product or device events
3. Patient protection events
4. Care management events
5. Environmental events
6. Radiologic events
7. Criminal events

TYPES OF MEDICATION ERRORS

Medication errors can take myriad forms. Some common types of mistakes in medication are described below.

- **Prescribing:** Errors in prescribing include irrational, inappropriate and ineffective prescribing, underprescribing and overprescribing (prescribing faults) and errors in writing (illegible prescription).[2]
- **Omission errors:** Failure to give a scheduled medication dose.
- **Incorrect timing:** Medications should be administered at their scheduled times; failure to give a medication dose on time may cause either underdosing or overdosing. Food may also alter the absorption of some medications.[5]
- **Incorrect duration:** Taking medications for shorter or longer duration than has been prescribed.[5]
- **Administration errors:** Improper route of administration, giving the drug to the wrong patient, giving an extra dose of the drug, or administering drugs that are given IV at the incorrect rate, which may cause severe adverse drug reactions.[5]

- Use of inappropriate abbreviations, confusion of metric and other dosing units.
- Confusion between sound-alike drug names.
- Prescribing contraindicated drugs.
- **Monitoring errors:** Failure to follow-up or to consider the patient's liver and renal function or allergies or potential for drug-drug or drug-food interactions or not reviewing repeat prescriptions.
- **Compliance errors:** Not adhering to the protocol or rules or dispensing and prescribing medications.
- **Expired product:** Use of expired medications may occur because of their improper storage.[5]

CAUSES OF MEDICATION ERRORS

- **Distraction:** Physicians more often than not are multitaskers. Prescription writing is one among the several tasks they carry out every day such as examining their patients, prescribing investigations, taking daily rounds, assuring family members, etc. They may lack support staff. Overwork and the ensuing fatigue may sometimes cause a lapse of judgment leading to a medication error. Also, carrying out all these duties leaves them with insufficient time to counsel patients about medications.[5]
- **Environment:** Lack of proper lighting, heat/cold, and other environmental factors can cause distractions resulting in errors.
- **Memory lapses:** When the doctor knows that a patient is allergic, but fails to recall. This is often caused by distractions.
- **Distortions:** These occur from poor writing, use of abbreviations, misunderstood symbols or incorrect translation.
- **Lack of knowledge:** Lack of complete and up-to-date knowledge about the pharmacology of a drug, including its various names (generic and brand).
- **Incomplete patient information:** Lack of information about which medications a patient is allergic to, other medications the patient is taking, previous diagnoses or current lab results.
- **System problems:** Inappropriately labeled medications, lack of bar code scanning system, placing sound-alike drugs adjacent to one another.

PREVENTION OF MEDICATION ERRORS IN PRACTICE

Physicians must be encouraged to report medication errors. But this can be done only by providing a nonpunitive environment.[2] Measures that may reduce the odds of errors include use of electronic prescription systems, education and training, improving communication and involving clinical pharmacists.[9]

Pharmacovigilance

Pharmacovigilance or adverse drug reaction reporting is crucial to delivering quality patient care. The World Health Organization (WHO) has defined pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems".

In 1986, adverse drug reaction monitoring system was set-up in India under the direction of the Drug Controller of India. This marked the beginning of pharmacovigilance in the country. In 2005, the National Programme of Pharmacovigilance was launched, which was given the name Pharmacovigilance Programme of India (PvPI) in 2010.[10] PvPI is run by the Indian Pharmacopoeia Commission (IPC) as its National Coordination Centre (NCC) under the aegis of the Union Health Ministry.

The objective of establishing the PvPI was to generate country-wide data about adverse drug reactions by promoting reporting of adverse drug reactions. It encourages reporting of "all types of suspected adverse reactions with all pharmaceutical products irrespective of whether they are known or unknown, serious or nonserious and frequent or rare" (*Indian Pharmacopoeia Commission*). Its effectiveness, though is hampered by several challenges; under reporting is one such challenge.

Here are some examples of common prescription errors and how to avoid them.

- **Always spell the drug:** Sound-alike drugs can cause confusion. Always spell the drug if you are giving telephonic instructions.
  - E.g., the patient received Isoprin IV in place of Isoptin and nearly died.
  - E.g., Amlopress AT/80 mg; a hypertensive called up his family physician who asked him to take Amlopress AT but the patient took Amlopress 80 mg. After sometime he developed dizziness, flushing, palpitation, nausea, abdominal pain.
- **Never write 'U' to abbreviate the word 'units':** Do not write 'U' for units when writing prescription. Always write the complete word 'units'. It may be mistaken as zero. E.g., never write 4U insulin.

The patient may be given 40 units of insulin when the doctor actually meant just 4 units (4 U).

- **Misinterpreting decimal points**
  - **Never write the numeric after a decimal point:** The use of a trailing zero after a decimal point when writing prescription may lead to medication errors. For example, do not write 5.0 mg. There are chances that the patient may get 50 mg; 5.0 mistaken as 50 mg if the decimal point is overlooked.
  - **Always write the numeric 0 before the decimal point:** Always add a leading zero when writing dose of a drug, which is less than one. Lack of a leading zero may lead to a decimal point being missed. For example, never write .25 mg; instead write 0.25 mg. Otherwise there are chances the patient may take 25 mg in the first instance itself.
- **8-2-8 mistake:** The time interval should be written more clearly as 8 am 2 pm 8 pm. This may be mistaken as the number of tablets to be taken: 8 in the morning, 2 in the afternoon and again 8 at night.
- **Taking medicines with inadequate quantity of water or lying down immediately after taking the drug** can cause pill esophagitis by direct esophageal mucosal injury. It is commonly seen with drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), tetracycline, doxycycline, alendronate, antiviral drugs, iron supplements.
- **Prescribing liquid medications in teaspoons and tablespoons:** A teaspoon (tsp) can be confused with a tablespoon (tbsp). Their sizes may vary. Hence, all liquid medications should be prescribed in milliliters (mL) and they should be taken with a dosing device such as a small cup with mL markings.
- **Pill splitting:** Tablets that are not scored should not be split into two. They can crumble or are divided into unequal halves affecting the dose strength. Sustained or extended-release tablets and enteric- or film-coated tablets are generally not considered appropriate for tablet splitting. Film coating masks taste; therefore, splitting film-coated tablets may unmask the taste.
- **Some medicines need to be taken "before meals" or "on an empty stomach"** because food can prevent absorption of some medicines and reduce their effectiveness. For example, levothyroxine and rifampicin should be taken on an empty stomach.
- **Taking medicines with fruit juices:** Grapefruit, orange, and apple juices decrease the absorption of many drugs such as fexofenadine, cancer chemotherapy (etoposide), antibiotics (ciprofloxacin, levofloxacin), itraconazole, antihypertensives (atenolol), immunosuppressant (cyclosporine).

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HCFI Dr KK Aggarwal Research Fund

Minutes of an International Weekly Meeting on "Approach to a Patient with Palpitations"

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- Palpitations are very common. Studies have found that at least one-third are due to anxiety or panic disorders; ~40% can be due to some serious cause such as cardiac disorder and one-tenth are due to drugs or medications, which may include sympathomimetics, drug abuse, substance abuse. This is an important but often missed cause of palpitations. This history should be elicited in people complaining of palpitations.
- There can be noncardiac causes of palpitations as well. Palpitation is awareness of one's heartbeat, normal or abnormal. Normal can be after exertion or fright. Abnormal but physiological causes are pregnancy, anemia and fever. But there can be abnormal unphysiological situations for which different mechanisms exist such as cardiac (electrical and mechanical problems), vascular issues and extracardiac mechanisms (thyroid, drugs).
- The approach to a patient with palpitations depends on the setting of the patient contact, whether in the emergency room (ER) or the outpatient department (OPD).
- Patient who comes to the ER with palpitations should be considered serious. Assess ABC first and then rule out serious causes. Quickly do an ECG (electrocardiogram) and focused history to rule out heart disease. The basic aim of palpitation workup is to differentiate between benign and serious causes for triage, cardiac and extracardiac causes, assess structural status of heart. To find out who requires assurance/clinical follow-up, who requires further cardiac testing and who requires treatment.
- The overall prognosis and treatment is to a large extent dependent on the presence or absence of structural heart disease.
- Palpitations with a history of syncope, history of heart disease, extreme ages, hemodynamic instability, heart murmur and abnormal ECG should be considered serious. Syncope is a sign of severe arrhythmia or structural heart disease.
- Elicit a history of what happened before palpitations, i.e., what event triggered the palpitation (such as exertion, sleeping, posture, fever, stress) and what happened during the palpitations (onset, other symptoms, mode of termination).
- A family history of sudden death is important. This is true for channelopathies like long QT syndrome, etc. where the symptoms are very atypical and since the heart function is normal and the ECG look almost normal, these patients are treated as psychological disorder or are put on antiepileptics. They are more prone to sudden death.
- Palpitations during exercise are mostly serious. Ventricular arrhythmia, long QT syndrome, atrial fibrillation (AF) are all serious diseases and are brought on by exertion. Often symptoms are a clue to the etiology. If palpitations are associated with anxiety or panic, there are overlapping or multiple symptoms especially in young women.
- History of the episode should include details about the rate, irregularity, termination, long duration episode, long history, dizziness/presyncope/syncope.
- In paroxysmal supraventricular tachycardia (PSVT), at extremes of age (geriatric) or compromised heart function, even a simple AF can cause dizziness.
- In 50% of patients, the ECG may not provide any clue. A short PR interval and a delta wave indicate Wolff-Parkinson-White (WPW) syndrome and the associated arrhythmia is PSVT.
- Presence of epsilon wave and incomplete right bundle branch block (RBBB) are diagnostic of arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC). Long QT is associated with polymorphic ventricular tachycardia (VT).
- Anxiety or panic disorder may occur in 15-305 of patients with palpitations. Typically seen in younger people especially in women. A clue to this is lot of somatization, emotional distress. There are multiple symptoms related to multiple organs. A simple question can help in diagnosis: "Have you experienced brief periods, for seconds or minutes, of an overwhelming panic or terror that was accompanied by racing heartbeats, shortness

of breath or dizziness?" Never brand someone as anxiety disorder without ruling out cardiac causes.

- If structural heart disease or arrhythmic cause of palpitations is suspected or there is history of syncope, then do an echo. If there are almost daily symptoms or AF is suspected, then do a Holter. Ectopics are a very common cause for palpitations.
- Premature ventricular complexes (PVCs) are often not sensed by the pulse oximeter in the periphery. Even if no symptoms, the oximeter shows a very low pulse rate.
- Refer the patient to a cardiologist if there is history of syncope, abnormal ECG/echo, family history of sudden death, documented tachycardia on ECG/monitor and recurrent palpitations of likely arrhythmic etiology despite management.
- There are certain pitfalls to be avoided such as syncope does not have tonic-clonic movement or incontinence, a person with palpitations and no tachy or bradycardia on ECG can be safely discharged, a cardiac patient with palpitations but no hemodynamic problem is safe, a stable patient with wide QRS tachycardia is likely to have SVT and that patient on anxiolytics should not be investigated further.
- If there is no history of significant heart disease or on examination and the ECG is normal (rate and morphology), then the patient can be considered for discharge, e.g., in long QT syndrome, the ECG looks absolutely pristine except QT is prolonged but is often missed by people.
- Keep cardiac patients with palpitations for an extended period of time in the ER as they have high chances of recurrence of arrhythmia.
- Atrial flutter is a common reason in the elderly. This can occur in either the left or the right atrium, more commonly in the right atrium. It often looks like sinus tachycardia. The sawtooth pattern on ECG is characteristic of atrial flutter.
- In atrioventricular nodal re-entrant tachycardia (AVNRT), the ECG shows pseudo S waves in the inferior leads because of inverted P wave at the end of QRS. This also causes pseudo R' pattern in V1, which is typical of AVNRT. ST depression is one sign of AVNRT.
- Presence of delta wave and slurred onset of QRS which is wider, then this is WPW syndrome.
- FBI (fast broad irregular) tachycardia is a very serious rhythm. If this is seen on the ECG, then shock to the heart must be given.
- Atrial ectopics appear as sinus rhythm but the preceding P wave has abnormal morphology. This gives a clue that the ectopics can be due to atrial tachycardia or AF. A fragmented P wave may be a clue that the palpitation is due to AF. Atrial tachycardia can be easily demonstrated in most patients by showing AV dissociation. Lead V1 is good for seeing P waves.
- ARVC is a very common cause of sudden death in young people. It is a very common cause of exercise related sudden death in young people. The characteristic feature is overall the voltage of the complexes is low, there is RBBB pattern and a notch at the end of QRS. This notch causes the epsilon wave, which is a pathognomonic sign of ARVC. The QT interval and size of P wave is varying with every beat, this is called QT alternans and is a sign of risk of sickle cell disease in these patients.
- If there are PVCs on ECG, it is highly suggestive that these may be the cause for palpitations.
- Another important cause in young people is hypertrophic cardiomyopathy. It can be due to AF which is very common as well as ventricular ectopics and VT. In such patients, if VT occurs, there is good enough chance that the VT will recur in the next 24 hours. So, prolonged monitoring of these patients is required.
- People with long QT syndrome and Brugada syndrome will always have palpitations that are followed by presyncope and syncope.
- In catecholaminergic polymorphic ventricular tachycardia (CPVT), classically there are bidirectional complexes. The treatment is beta-blocker. Stable VT can become unstable as the rate picks up. These patients require hospitalization.
- Always think of the context and the physiological situation in which you are seeing the patient. When reading the ECG, also look at the morphology in addition to the rate and rhythm.

Member – National Medical Associations: Dr Yeh Woei Chong, Singapore, Chair of Council-CMAAO; Dr Wasiq Qazi, Pakistan Immediate Past President, CMAAO; Dr Akhtar Hussain, South Africa

Invitees: Dr Monica Vasudev, USA; Dr EC Ng; Dr Surendra Singh; Dr Anjali Agarwal; Dr KL Prajapati; Dr NK Gupta; Dr Nidhi Dhawan; Dr Monika Khanna; Dr Narinder Batra; Dr Manisha Kukreja; Dr Meena Bajaj; Dr Rajani Kant; Dr Sanchita Sharma, Editor-IJCP Group

Moderator: Mr Saurabh Aggarwal

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

LTx FOR ACUTE-ON-CHRONIC LIVER FAILURE: DON'T RUSH IT!

Dr Dharmesh Kapoor, Hyderabad

Acute-on-chronic liver failure (ACLF) is a dynamic syndrome associated with very high short-term mortality. Until 2013, there was no evidence-based definition of ACLF. However, a definition was later proposed based on the results of a large prospective observational European study, called "European Association for the Study of the Liver (EASL)–Chronic Liver Failure (CLIF) Consortium Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC)" study.

The CANONIC study also found that: Identifiable precipitating events (e.g., bacterial infection, active alcoholism) are found in only 50% of cases of ACLF. Precipitating events may be initiators of ACLF but do not drive the outcome. ACLF is associated with systemic inflammation even in patients who do not have identifiable precipitating events.

When it comes to the treatment of ACLF stage 2-3, liver transplantation (LTx) has been shown to improve the survival of patients. It has been recommended that patients who recover from ACLF should also be listed for LTx, as the rate of mortality at 6 months is 40% to 50%. However, some of the factors can lead to escalation of care or futility of care after LTx, such as:

- Standard ICU consideration: Age, comorbidities, functional/nutritional status, severity of acute illness
- Liver-specific considerations: Severity of disease, indication of admission.

REDUCING DEATHS FROM ACLF IS A REALISTIC GOAL

Dr Rajiv Jalan, UK

- Patients with acute decompensated cirrhosis have high morbidity/mortality.
- Liver transplantation can save the lives of patients with ACLF.
- New therapies are under development for managing ACLF, like CARBALIVE, PRECIOSA, TLR4 antagonist, G-TAK, DIALIVE APACHE.
- Cirrhocare is a decompensated cirrhosis management in the community that provides early diagnosis, allows rapid intervention and reduces hospitalization; thus improving the quality of life.
- CARBALIVE are adsorbent beads whose unique physical structure gives functionality to remove macromolecules such as endotoxins which reduce inflammation and improves gut health.
- DIALIVE modifies the pathophysiological process involved in the pathogenesis of ACLF.

MANAGEMENT OF PATIENTS WITH HEPATIC ENCEPHALOPATHY

Dr Sunil Taneja, Chandigarh

- For the management of recurrent or persistent hepatic encephalopathy (HE), use a medical treatment like nonabsorbable disaccharides + rifaximin and avoid precipitating factors.
- In patients refractory to treatment, consider spontaneous portosystemic shunts (SPSS) (abdominal CT/MRI).
- In the presence of SPSS and model for end-stage liver disease (MELD) score ≤11, no significant PH-related complications and technical feasibility of embolization = consider embolization.
- In the presence of SPSS and MELD scores 12-14, consider each case individually. In the presence of SPSS and MELD score ≥15, significant PH-related complications, and technical difficulties for embolization = consider liver transplant.

NEWER THERAPIES IN HBV

Dr Anil Arora, New Delhi

- Complex hepatitis B virus (HBV) life cycle and current treatment are dependent on nucleos(t)ide analogues (NAs).
- A partial or functional cure is not enough, hence is crucial to target covalently closed circular DNA (cccDNA) for a complete cure.
- Entry inhibitors are approved for chronic hepatitis D virus (HDV), however, they do not address cccDNA.

- Attractive options for targeting cccDNA are – Inhibition of mini chromosomes and silencing transcription. Concerns over genomic stability are still hindrances.
- Post-transcriptional control – Antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs). Do not eliminate cccDNA, rebound post-treatment.
- Capsid assembly modulators (CAMs) are the best among the present novel therapies. They cause long-term suppression of HBV DNA and RNA.
- S-antigen transport-inhibiting oligonucleotide polymers (STOPS) and nucleic acid polymers (NAPs) have given promising results, however, need further studies.
- Good results have been obtained for TLR7, the combination of RIG with IFN, and promising results of vaccination in the phase III trial.
- Multiple combination strategies under investigation need larger and longer trials.

HBV RNA AND HBcrAg: BIOMARKERS OF DISEASE ACTIVITY IN CHB

Dr Norah Terrault, South California

HBV RNA and HBcrAg (Hepatitis B core-related antigen) are both biomarkers that are used to assess disease activity in chronic hepatitis B (CHB) infection. These biomarkers can help in determining the criteria to cess NA therapy. According to the Japanese HBV guidance, the criteria to cess NA therapy are: At least 2 years of administration of NAs. Undetectable serum HBV DNA level. Negative serum hepatitis B e-antigen (HBeAg) at the time of treatment cessation.

However, in case, when these criteria are met, hepatitis B surface antigen (HBsAg) and HBcrAg levels can be used to estimate the risk of relapse at the time of cessation. Some of the additional points to note about HBcrAg in CHB management are:

- HBcrAg and HBV RNA offer measures of cccDNA transcriptional activity, but not the amount of cccDNA.
- Limited diagnostic application – HBcrAg is strongly influenced by HBeAg status and the presence of PC/core mutations.
- Potential prognostic applications – Prediction of hepatocellular carcinoma risk in Indian patients and after HBsAg seroclearance; prediction of HBsAg loss in a subset of patients.
- Shedding new light on HBsAg seroclearance and liver-related risk that may occur after HBsAg loss. Most likely concept that will be useful in predicting outcomes after NA withdrawal. However, the only limitations are: Need to standardization, improve dynamic range and increase access/ease of use.

REFRACTORY ASCITES – NEWER CONCEPTS IN THE MANAGEMENT

Dr Rakhi Maiwall, New Delhi

Refractory ascites is a challenging condition where the accumulation of fluid in the abdominal cavity (ascites) does not respond to standard medical therapies. It is often associated with advanced liver cirrhosis and is a significant complication that can lead to poor quality of life and increased mortality.

Over the years, several newer concepts in the management of refractory ascites have been explored to improve patient outcomes. Transjugular intrahepatic portosystemic shunt (TIPS) prevents further decompensation and improves survival in patients with cirrhosis and portal hypertension. But some of the challenges associated with this method are: Patient selection; timing; risk of liver failure and HE; post-TIPS cardiac decompensation.

Another new concept is the alfapump system for patients with refractory ascites when TIPS is not feasible. This device is also used for patients with previously failed TIPS, portal thrombosis and associated cardiac dysfunction. This battery-operated device is subcutaneously implanted in the peritoneal cavity and drains ascitic fluid from the peritoneal cavity and into the urinary bladder. However, it has several limitations, such as cost, availability and risk of infection.

A liver transplant is the first treatment of choice for refractory ascites. Some of the other points that should be considered for managing refractory ascites are:

- Patients with low MELD scores should be considered.
- Patients with spontaneous bacterial peritonitis or hepatorenal syndrome should be prioritized.
- All other measures should be considered as bridge to transplant in the presence of refractory ascites.
- Simultaneous liver-kidney transplant for patients with concomitant chronic kidney disease stage 3b.
- Lastly, remember, other than these interventions, nutritional, frailty and palliation form an integral part of refractory ascites management.

News and Views

The Case for Fludrocortisone + Hydrocortisone in Septic Shock

Administration of a combination of fludrocortisone and hydrocortisone reduced mortality by 12% among patients with septic shock compared to hydrocortisone alone, according to a study published in the *American Journal of Respiratory and Critical Care Medicine*.[1]

The objective of this study was to compare the effectiveness and safety of fludrocortisone + hydrocortisone versus hydrocortisone alone versus placebo/usual care in adult patients with septic shock. The researchers conducted a systematic review and Bayesian network meta-analysis of randomized trials published in peer-reviewed journals. All-cause mortality at the last follow-up was set as the primary outcome of the study. The reference treatment used for comparison was placebo/usual care.

Based on the analysis of 17 trials involving 7,688 patients, the combination of fludrocortisone + hydrocortisone demonstrated the lowest all-cause mortality at last follow-up, with a relative risk (RR) of 0.85 and a high probability (98.3%) of being superior, supported by moderate-certainty evidence. Hydrocortisone alone had a slightly higher RR of 0.97 and a lower probability (73.1%) of superiority, based on low-certainty evidence.

The authors note that the comparison between fludrocortisone + hydrocortisone and hydrocortisone alone relied primarily on indirect evidence, with only two trials providing direct evidence. However, the combination therapy still showed a 12% lower risk of all-cause mortality compared to hydrocortisone alone, with an RR of 0.88 and a 94.2% probability of superiority, supported by moderate-certainty evidence.

In adult septic shock patients, the combination of fludrocortisone + hydrocortisone was found to be associated with a lower risk of all-cause mortality at last follow-up compared to both placebo and hydrocortisone alone. However, it is important to note that owing to the paucity of head-to-head trials comparing fludrocortisone + hydrocortisone versus hydrocortisone alone; this network meta-analysis relied mainly on indirect evidence for this comparison, as per the authors. Although several sensitivity analyses and assessments were undertaken to ensure the robustness of our findings, it is crucial to consider these results while also acknowledging the heterogeneity of the included trials.

Fludrocortisone is a very potent mineralocorticoid, while hydrocortisone has mineralocorticoid and glucocorticoid activity. The comparative activity of hydrocortisone to fludrocortisone is approximately 1 to 125-150; this ratio is mainly derived from the effects of hydrocortisone and fludrocortisone on sodium retention in the kidneys.

There is evidence to suggest that in patients with sepsis, the production of mineralocorticoids is impaired considerably more than the synthesis of glucocorticoids. This deficiency in mineralocorticoid synthesis has been found to be associated with a higher risk of sepsis-related mortality.[2]

Earlier studies have elucidated on the potential role of mineralocorticoids in septic shock.

There are different isoforms of the mineralocorticoid receptor. Some of these isoforms can bind to both glucocorticoids and mineralocorticoids, while others specifically bind to mineralocorticoids. The deactivation of glucocorticoids ensures that mineralocorticoids have a strong interaction with mineralocorticoid receptors. These receptors are also present in immune cells and when activated, they can enhance leukocyte adhesion, which can be beneficial in eradicating bacterial infections. Experimental sepsis studies have shown that mineralocorticoids, such as fludrocortisone, can reduce the levels of histamine, serotonin and bradykinin in the plasma, leading to a faster reversal of shock.[2]

Addition of fludrocortisone enhances the mineralocorticoid activity. By affecting salt and water balance in the body, mineralocorticoids may have a role in septic shock by restoring the effective blood volume through increased mineralocorticoid activity. On the other hand, glucocorticoids preferentially affect sugar metabolism and show sex hormone activities.[3]

These findings provide support for the beneficial effects of addition of fludrocortisone to hydrocortisone in lowering the risk of short-term mortality in these patients.

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Endometriosis and Pregnancy Outcomes

Pregnant women with stage III or IV endometriosis are likely to have a higher incidence of placenta previa compared to pregnant women with stage 1 or II endometriosis, suggests a study published in the *European Review for Medical and Pharmacological Sciences*.[1] But other pregnancy complications did not differ much in the two disease severity groups.

Through this retrospective study, Zhao-Zhen Liu, from the Dept. of Obstetrics and Gynecology at the College of Clinical Medicine for Obstetrics, Gynecology and Pediatrics at Fujian Medical University, China, and coauthors aimed to investigate the impact of endometriosis on pregnancy and assess any potential pregnancy complications and neonatal outcomes in patients with pregnancies complicated by endometriosis. Their goal was to contribute to a better understanding of the impact of endometriosis on pregnancy outcomes.

A total of 3,809 pregnant women who underwent cesarean section delivery at Fujian Maternity and Child Health Hospital in China between January 2014 and December 2020. Among them, 1,026 were diagnosed with endometriosis after the cesarean section, forming the endometriosis group. The control group consisted of 2,783 women without endometriosis.

The endometriosis group was further categorized into subgroups based on the disease severity; the first subgroup consisted of 882 subjects with stage I or II endometriosis, while the second subgroup comprised 144 parturients with stage III or IV endometriosis. During the study, general data of all patients and medical records of pregnancy complications and neonatal outcomes were collected and retrospectively analyzed. Age, gestational age, gestation and parity times were comparable between endometriosis and control groups.

Results showed no statistically significant differences in age, gestational age, gestation and parity times between all groups ($p > 0.05$). However, the incidence of pre-eclampsia and placenta previa in the endometriosis group was higher compared to the control group ($p < 0.05$). No significant between-group differences were observed with regard to other pregnancy complications such as chronic hypertension with pregnancy, pre-eclampsia with chronic hypertension, hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, gestational diabetes mellitus, pregestational diabetes mellitus, intrahepatic cholestasis of pregnancy, premature rupture of membranes and placental abruption.

When the two subgroups were analyzed, patients with more severe endometriosis, stage III/IV were found to have higher incidence of placenta previa compared to those with stage I/II endometriosis ($p < 0.05$). Additionally, the amount of postpartum hemorrhage (1,000-1,500 mL) was significantly greater in the endometriosis group compared to the control group. However, there was no significant difference in the incidence of postpartum hemorrhage among patients with pregnancies complicated by endometriosis at different stages.

These findings provide valuable insights into the potential risks and complications associated with endometriosis during pregnancy and suggest that endometriosis may contribute to an increased risk of certain pregnancy complications. They show that in pregnant women, endometriosis is associated with an increased incidence of placenta previa, and this correlation is influenced by the severity of the disease. Additionally, pregnant women with endometriosis have higher rates of pre-eclampsia and postpartum hemorrhage compared to women without endometriosis. It is important to consider these factors when managing and providing care for pregnant women with endometriosis.

Reference

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Prognostic Factors in Acute Exacerbation of Idiopathic Pulmonary Fibrosis

Long-term use of supplemental oxygen, the need for invasive mechanical ventilation upon admission, pre-exacerbation steroid use and increased neutrophils in bronchoalveolar lavage (BAL) are indicators of higher mortality risk in patients acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF). These findings from a systematic review and meta-analysis were published in *Respiratory Medicine*.[1]

To understand the factors that contribute to mortality in patients with AE-IPF, researchers from Canada, USA, UK, Norway and Australia conducted a systematic

review and pairwise meta-analysis of factors associated with mortality in these patients. For this they searched databases such as Embase, Medline and CINAHL for studies that reported on the association between any prognostic factor and AE-IPF in adult patients. A total of 35 studies, involving over 18,000 patients, published between 1990 and 2022 were included in the analysis. Over two-thirds of them were from Japan with other participants from South Korea, Canada, China and the US. Their mean age ranged from 64.6 to 78.5 years and majorities were male.

Review of these studies revealed several factors related to the risk of death in patients with AE-IPF.

Long-term use of supplemental oxygen at baseline more than doubled the risk of death in patients with AE-IPF with adjusted hazard ratio (aHR) 2.52 with moderate certainty of evidence. Additionally, a diagnosis of IPF compared to non-IPF interstitial lung disease (ILD) was associated with an increased risk of death (aHR 2.19) with moderate certainty of evidence. Mortality was also increased in patients aged ≥80 years versus younger patients (aHR 2.98).

Radiographic factors associated with higher risk of death in these patients were also identified. These included: a diffuse pattern on high-resolution computed tomography (HRCT) (vs. non-diffuse pattern) with aHR of 2.61 (with moderate certainty) and a higher CT score (aHR 1.14) with low certainty.

Use of steroids before hospitalization for exacerbation increased the odds of mortality with aHR of 2.19. Patients with neutrophilia (% increase) in BAL during the exacerbation were at an increased risk of death with aHR of 1.02 (moderate certainty). Risk of mortality was higher among patients who needed invasive mechanical ventilation upon admission (aHR 3.74).[2]

This study has defined factors that adversely affect prognosis in patients with AE-IPF. Identification of these factors can therefore help clinicians to define clinical management and treatment decisions and potentially improve outcomes in these patients. Nevertheless, the authors have called for further studies "to validate additional prognostic factors to inform IPF management".

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Common Household Cleaning Products and Asthma Control

Frequent use of household disinfectants and cleaning products in a week is strongly associated with uncontrolled asthma, says a study published in *The Journal of Allergy and Clinical Immunology: In Practice*. The risk increased with almost every day use.[1,2]

This study examined the impact of household disinfectants and cleaning products (HDCPs), including irritants and green products, sprays and disinfecting wipes and asthma control using 2018 data from the French Web-based NutriNet-Santé cohort. A standardized questionnaire was used to assess asthma control and the use of HDCPs at home. Factors such as sex, age, smoking status, body mass index (BMI) and educational level were considered. In the overall study population of 37,043 patients, the mean age was 47.5 years; three-fourth of them were women. In addition, 12.5% were current smokers, 32.2% were classified as overweight (BMI 25 kg/m^2), and ~64% participants had completed at least 2 years of university education. Sixty-two percent reported using at least 1 HDCP every week.

Participants with current asthma and uncontrolled asthma tended to be younger, female, current smokers and overweight. Those with current asthma had higher education levels and those with uncontrolled asthma had lower educational status.

Based on the analysis conducted on 37,043 adults, it was found that greater weekly use of HDCPs was strongly associated with uncontrolled asthma.

Those who used irritants and green products almost daily (4-7 days/week) were at least twice more likely to have uncontrolled asthma with odds ratios (ORs) of 2.81 and 2.40, respectively (vs. those who used them for 1-3 days/week with ORs of 1.65 and 1.49, respectively). A similar association was noted with use of sprays (OR 2.69) (vs. 1.49 for 1-3 days/week use). Those who used disinfecting wipes were 3.5 times more likely to have poorly controlled asthma (OR 3.51) (vs. 2.2 for 1-3 days/week use). Notably, even when not used together with irritants and sprays, both disinfecting wipes (OR 1.99) and green products (OR 1.59) still showed statistically significant associations with uncontrolled asthma.

Subjects with overweight showed stronger association between use of irritants, sprays and green products and current asthma. Likewise, the association was also strong among participants who did not have any household help compared to those who had household help.

The use of irritants or sprays as household cleaning products are known to be associated with respiratory symptoms. Hence, green products and wipes are often used as alternatives to mitigate or minimize the potential respiratory risks while maintaining a clean and healthy household environment. By demonstrating an association between the weekly use of HDCPs, including green products or wipes and uncontrolled asthma, this study suggests that the use of HDCPs may have an impact on asthma symptoms and management.

This study draws attention to triggers other than the conventionally known ones such as upper respiratory infections, environmental allergens (like pollen, dust mite), cigarette smoke and air pollution. It is important for health practitioners to be aware of the impact of common household cleaning items on asthma and consider it when developing treatment plans for their patients to improve and maintain asthma control. While they may not entirely be preventable, they can be controlled for a good quality of life.

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Predicting Occurrence of Hypothyroidism in OSA Patients with Lymphocyte Count

A new study published in the journal *BMC Pulmonary Medicine* has suggested that the prevalence of hypothyroidism rises with increasing lymphocyte count in patients with obstructive sleep apnea (OSA).[1]

Xiaoyan Fang from the Dept. of Respiratory and Critical Care Medicine, Tianjin Medical University General Hospital, Tianjin in China and colleagues conducted this retrospective study to evaluate the association between lymphocytes and hypothyroidism specifically in patients with OSA. The study participants underwent routine blood tests, including thyroid profile and nocturnal sleep monitoring. The researchers used logistic regression analysis to identify independent predictors of hypothyroidism in OSA patients. Additionally, they determined the cut-off level of lymphocyte count using a receiver operating characteristic (ROC) analysis to determine the occurrence of hypothyroidism in these patients.

They selected 920 patients attending the Sleep Center at the Tianjin Medical University General Hospital. The prevalence of hypothyroidism was found to be 4.46% (n = 41), the prevalence in male patients was 3.4% and in female patients, it was 6.6%. Around 95.5% (n = 879) had normal thyroid function. The BMI of OSA patients with hypothyroidism was higher (34.78) than in controls (32.38). Epworth Sleepiness Scale (ESS) scores were significantly higher in OSA patients with hypothyroidism versus controls (10 vs. 6).

The researchers found that in the entire OSA population and male OSA patients, the lymphocyte percentage and lymphocyte count were significantly higher in the hypothyroid group compared to the control group. On subgroup analysis, the lymphocyte counts were markedly raised among OSA patients younger than 60 years old and those with mild to moderate OSA, the hypothyroid group had significantly higher lymphocyte counts compared to those with normal thyroid function.

The study identified lymphocyte count, ESS, and sex as independent predictors of hypothyroidism development in OSA patients. The ROC curve analysis indicated that the risk of hypothyroidism rose with increasing lymphocyte count in the overall patient population, with an optimal diagnostic cut-off point of 2.5×10^9/L.

This study demonstrates a correlation between the number of lymphocytes and the prevalence of hypothyroidism in patients with OSA, which includes subclinical hypothyroidism and not just overt. As the number of lymphocytes increased, the prevalence of hypothyroidism increased. A higher lymphocyte count therefore can be used as an independent predictor of the occurrence of hypothyroidism in this group of patients. The two conditions also share clinical features such as excessive sleepiness during the day, lethargy, obesity. Lymphocyte count is a simple and an easily available test and therefore can be undertaken to diagnose hypothyroidism in OSA patients followed by appropriate management resulting in better patient outcomes. Nevertheless, researchers advocate further research to corroborate their findings and to understand the mechanisms of this association.

Reference

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Low Self-Esteem

Low self-esteem is the opposite of ego. Supportive psychotherapy is often used to treat depression by improving self-esteem.

Low self-esteem always develops when one compares their skill or knowledge with somebody else. We often forget that for passing marks, we only need 50%. One who passes with 50% is a good student.

But the same person, when compares himself or herself with a student who has got 90%, he or she feels that his education was inferior as he was not as competent as others.

Remember that one is required to possess average degree of knowledge and skill and not the maximum degree of skill and knowledge. In the society, one needs to possess only average degree of skill and knowledge.

For example, if a person has passed MBBS with 50% marks, he or she is allowed to practice medicine with full powers and respect. There may be chances when a person who is 90 percentile may be able to take some better decisions but the same does not make him a superior doctor.

The fundamental principle in self-esteem is to make a person proud of his personal knowledge and skills and also to bring out his or her uniqueness.

Passion and profession are two different things. We should judge an individual from is passion and not profession.

■■■■

Benefits of Early Initiation of Exercise Training in Hospitalized COPD Patients

For patients who are hospitalized with a chronic obstructive pulmonary disease (COPD) exacerbation, early initiation of exercise training during hospitalization is safe, improves physical function and increases exercise capacity after hospital discharge. These findings from a systematic review and meta-analysis were published February 1, 2024 in the journal *Respiratory Medicine.*[1]

A systematic review and meta-analysis set out to investigate if starting exercise training early during hospitalization, as opposed to not starting it at all, would affect the outcomes measured at discharge for adults admitted with a COPD exacerbation.

Ten studies were identified for analysis after search of PubMed, the Cochrane Library, PEDro and EMBASE databases. The selected participants had a mean forced expiratory volume in 1 second (FEV1) ranging from 26% to 50% predicted. The 423 participants were divided into two groups: one which was assigned to exercise training within 48 hours of hospital admission (experimental) along with standard care and the second group that received standard treatment without exercise prescription (control). The study outcomes were exercise capacity, physical function, adverse events and participation in outpatient pulmonary rehabilitation programs.

At discharge, the experimental group outperformed the control group in terms of physical function (standardized mean difference [SMD] –0.54; four studies, moderate effect, low certainty evidence) and exercise capacity (SMD 0.58, five studies, moderate effect, low certainty evidence). No severe adverse effects were reported to occur. After discharge, no study documented the use of pulmonary rehabilitation.

This study demonstrates that exercise training administered within 48 hours of hospitalization was safe, enhanced physical function and increased exercise capacity in patients admitted to a hospital with a COPD exacerbation.

Reference

1. Lai Y, et al. Exercise training initiated early during hospitalisation in individuals with chronic obstructive pulmonary disease is safe and improves exercise capacity and physical function at hospital discharge: a systematic review and meta-analysis. Respir Med. 2024;223:107554.

INSPIRATIONAL STORY

Peace of Mind

Once, Buddha was walking from one town to another town with a few of his followers. This was in the initial days. While they were traveling, they happened to pass a lake. They stopped there and Buddha told one of his disciples, "I am thirsty. Do get me some water from that lake there."

The disciple walked up to the lake. When he reached it, he noticed that some people were washing clothes in the water and, right at that moment, a bullock cart started crossing through the lake. As a result, the water became very muddy, very turbid.

The disciple thought, "How can I give this muddy water to Buddha to drink!" So he came back and told Buddha, "The water in there is very muddy. I don't think it is fit to drink."

After about half an hour, again Buddha asked the same disciple to go back to the lake and get him some water to drink. The disciple obediently went back to the lake. This time he found that the lake had absolutely clear water in it. The mud had settled down and the water above it looked fit to be had. So, he collected some water in a pot and brought it to Buddha.

Buddha looked at the water, and then he looked up at the disciple and said, "See what you did to make the water clean. You let it be… and the mud settled down on its own – and you got clear water… Your mind is also like that. When it is disturbed, just let it be. Give it a little time. It will settle down on its own. You don't have to put in any effort to calm it down. It will happen. It is effortless."

■■■■

Persistent Hypertriglyceridemia and Risk of Incident Type 2 Diabetes among Young Adults

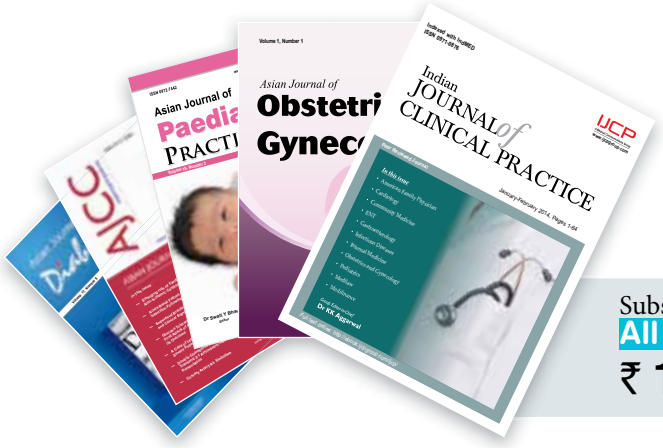
Young adults with persistent high triglyceride levels are thrice more likely to develop new-onset type 2 diabetes, suggests a recent study from South Korea published in the journal *Diabetes Research and Clinical Practice*.[1]

Researchers from the Hanyang University College of Medicine, Soongsil University, Konayng University Hospital, Republic of Korea conducted this study to investigate a potential connection between cumulative exposure to hypertriglyceridemia over a 4-year period and the risk of developing type 2 diabetes in young adults. They analyzed data of a large sample of 1,840,251 participants, aged 20 to 39 years, from the South Korean National Health Insurance Service (NHIS) database, who had undergone four consecutive annual health checkups and had no prior history of type 2 diabetes. These participants were divided into five groups (exposure score 0-4) based on the frequency of hypertriglyceridemia diagnosis. The primary outcome of interest was the occurrence of incident type 2 diabetes. During the 6.53-year follow-up period, 40,286 participants, who had cumulative exposure to fasting triglyceride levels of 150 mg/dL or higher, were found to have developed type 2 diabetes. The cumulative incidence of type 2 diabetes showed a significant increase with higher exposure scores for hypertriglyceridemia. The hazard ratio (HR) for incident diabetes, adjusted for multiple variables such as blood pressure, smoking, body mass index (BMI), among others, was 3.715 for participants with an exposure score of 4 vis-à-vis 1.674 for those with an exposure score of 1. The HRs for participants with exposure score of 2 and 3 were 2.192 and 2.637, respectively compared to those with an exposure score of 0.

This study has demonstrated a significant association between exposure to hypertriglyceridemia and an increased risk of type 2 diabetes. This association was found to be independent of lifestyle-related factors. Hence, maintaining healthy triglyceride levels is important in reducing the risk of developing type 2 diabetes in young adults as they are more likely to develop type 2 diabetes over time. Regular health checkups can help identify and monitor triglyceride levels, allowing for early intervention and management to mitigate the risk of developing type 2 diabetes.

Reference

1. Lee MK, et al. Cumulative exposure to hypertriglyceridemia and risk of type 2 diabetes in young adults. Diabetes Res Clin Pract. 2024;208:111109.



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Lighter Side of Medicine

HUMOR

OUTSTANDING

A man is driving down a country road, when he spots Santu standing in the middle of a huge field of grass.

He pulls the car over to the side of the road and notices that Santu is just standing there, doing nothing, looking at nothing. The man gets out of the car, walks all the way out to our Santu and asks him, "Ah excuse me sir, but what are you doing?"

Santu replies, "I'm trying to win a Nobel Prize." "How?" asks the man, puzzled. "Well I heard they give the Nobel Prize to people who are outstanding in their field."

JUMPING ON BEDS

Connie told her 4-year-old grandson, Dean, not to jump on the beds. After several warnings she punished him, explaining that should he fall, he would hurt himself badly.

Several minutes passed and he was back to jumping on the beds. Connie said, "Dean, you weren't jumping on the beds again, were you?"

He stood with his little head dropped low and said, "I'm trying, but it's so hard to quit."

GET ME A BATTLESHIP

After lunching at the Algonquin Hotel, Robert walked through the lobby, out the front door, and said to the uniformed man on the sidewalk, "My good man, would you please get me a taxi?"

The man immediately took offense and replied indignantly, "I'm not a doorman! I happen to be a rear admiral in the United States Navy."

Robert instantly quipped: "All right then, get me a battleship."

SPOON OUT FIRST?

Doctor, Doctor! I keep getting pain in the eye when I drink coffee! Doc: Have you ever tried taking the spoon out FIRST?

Four surgeons were taking a coffee break and discussing their work.

The first surgeon said, "I think that accountants are the easiest to operate on. You open them up and everything inside is numbered."

The second surgeon said, "I think that librarians are the easiest to operate on. You open them up and everything is in alphabetical order."

"The third surgeon said, "I think that electricians are the easiest to operate on. You open them up and everything is color coded."

The fourth surgeon said, "I think that lawyers are the easiest to operate on. They're heartless, spineless, gutless and their heads and their ass are interchangeable."

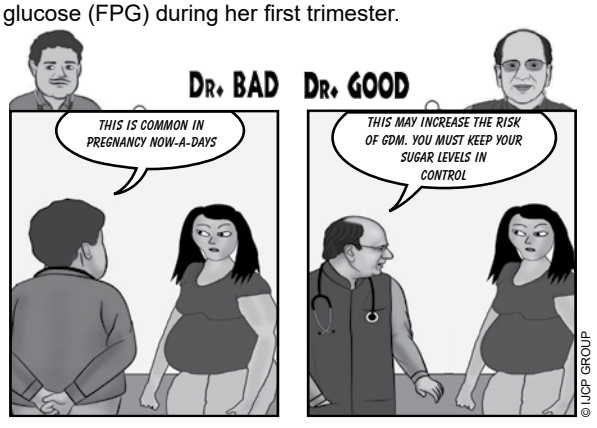
*****

While he was talking to me, his nurse came in and said, "Doctor, there is a man here who thinks he's invisible."

The doctor said, "Tell him I can't see him."

Dr. Good and Dr. Bad

SITUATION: A pregnant woman had high fasting plasma glucose (FPG) during her first trimester.



LESSON: A retrospective study revealed the active role of high FPG or body mass index (BMI), particularly in combination in pregnant women during the first trimester in predicting gestational diabetes mellitus (GDM).

Endocr J. 2017 Apr 14.

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

Books

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

Articles in Books

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

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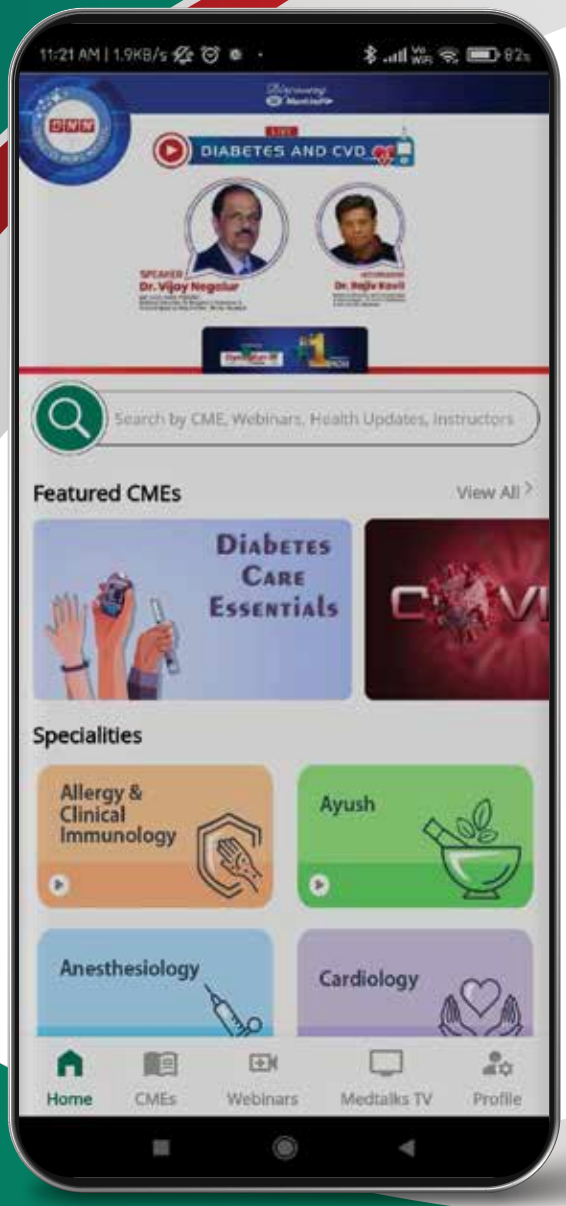

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