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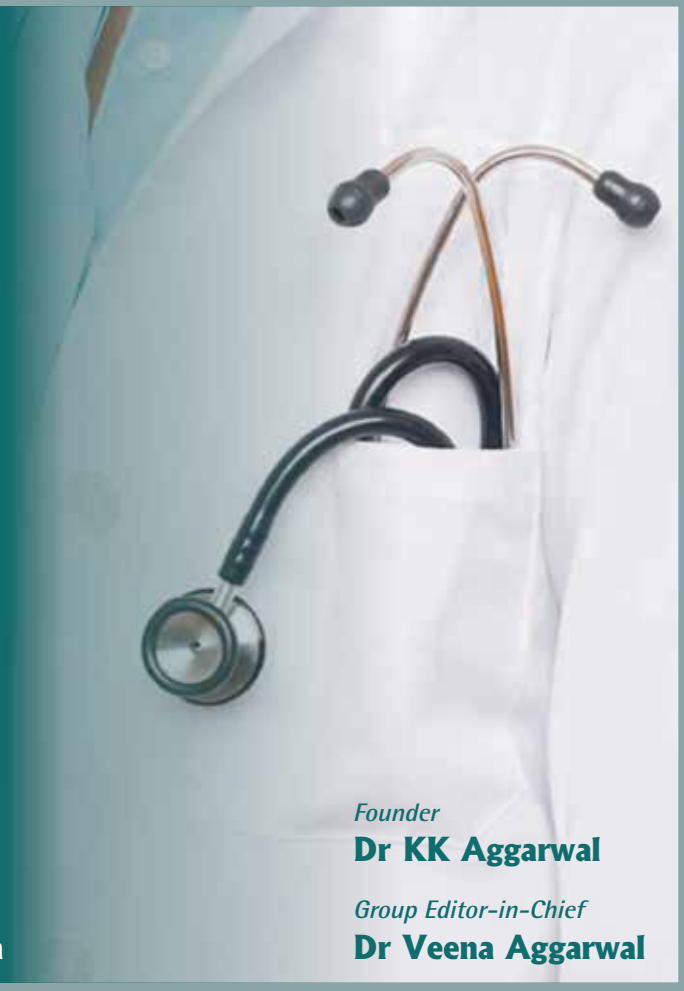

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Physician Suicide: An Emerging Public Health Crisis

Medicine is quite a demanding and stressful profession. It requires tremendous devotion and sacrifice. Doctors are literally stretched to their limits, both physically and mentally, almost every day. Statistics show that doctors are at 2.5 times higher risk of suicide compared to the general population. Female doctors are more vulnerable.

In March, Medscape published its annual Physician Suicide Report for 2023, based on a survey of 9,100 physicians across 29 specialties that was conducted in 2022. According to the report, 9% of those surveyed reported having suicidal thoughts, while 1% admitted to having attempted suicide. More female doctors (11%) than male doctors (9%) reported having suicidal thoughts. Younger physicians between the ages of 27 to 41 were more likely to have suicidal thoughts than those in the age group 57 to 75 years, where just 8% had suicidal thoughts.

When individual specialties were examined, ENT topped the list followed by psychiatry, family medicine, anesthesiology and obstetrics-gynecology. These specialties, according to the report, are marked by physician shortages. Specialties at least risk were rheumatology, orthopedics, oncology, nephrology and pulmonary medicine.

The risk of suicide among doctors is influenced by several factors, which include emotional exhaustion, long working hours, sense of failure, mood disorders, anxiety, substance use disorders, financial stress, impaired relationships, low resilience and depression. One-quarter of the physicians in the Medscape Survey had clinical depression, which was not due to a grief event, while 67% reported feeling sad or feeling down or "blue". Self-destructive tendency has also been cited as a risk factor by the American Medical Association (AMA). Media trials and rising litigations have added to the stress. All these come at a great cost to their health and well-being. The COVID-19 pandemic only added to the predicament. Though it increases the risk, burnout does not necessarily lead to suicidal thoughts.

Yet, physicians are disinclined to seek help; at least 40% of the physicians in the survey did not tell anybody about their suicidal thoughts. Concerns about privacy and confidentiality, lack of time, associated stigma of being thought of as weak and inefficient are some of the reasons that have been alluded to for this reluctance. Often, they are unaware of the available facilities where they can seek help. Adding to this is the culture of "patient comes first", which has been ingrained in doctors. The Medscape Survey threw up reasons for not seeking help along similar lines - 42% did not want to risk disclosure to the medical board, 33% were concerned about it being on insurance records, while 25% were concerned about their colleagues finding out.

There is a need to proactively address this crisis. Suicidal ideation and thoughts cannot be managed alone. Social support including peer support is crucial. Being self-reliant may be an admirable quality, but there are times when one needs to reach out. It is not a sign of weakness. It requires great strength to first recognize the need and then ask for help.

A little over half (52%) of the respondents said that they could deal with the problem on their own, but 60% confided in a family member or a friend/colleague and 38% spoke to a therapist, which is reassuring.

Acknowledging and talking about the problem is the first major step in this direction. Men were more likely to reach out to a family member, while women were more likely to confide in a friend or a colleague. A supportive working environment goes a long way in reducing work-related stress. Stress-management workshops, regular mental health check-ups, setting up a confidential physician helpline are some measures that may prevent physician suicides.

Connecting with others helps build resilience. Being resilient helps to bounce back and enhance coping skills. Self-awareness, mindfulness, self-care, positive relationships and purpose have been described as five resilience skills. A healthy work life balance effectively reduces stress. Spending time with family and friends was how 73% of the respondents chose to remain happy and have a positive mental health. Seventy percent had hobbies and activities, 67% engaged in regular exercise. Adequate sleep (53%), eating healthy (48%) and therapy (10%) were also other ways adopted for happiness and mental health.

Timely support can prevent a tragedy……

■■■■

Association of Childhood Obesity and Subtypes of Adult-onset Diabetes

Diabetes is typically described as type 1 and type 2 diabetes. However, in 2018, a study from Sweden defined five new subtypes of adult-onset diabetes based on the underlying mechanism: severe autoimmune diabetes (SAID), severe insulin-deficient diabetes (SIDD), severe insulin-resistant diabetes (SIRD), mild obesity-related diabetes (MOD) and mild age-related diabetes (MARD). SAID includes type 1 diabetes and latent autoimmune diabetes in adults (LADA), while the remaining four denote type 2 diabetes. The most prevalent subtype is MARD.[1] Whether the known modifiable risk factors for diabetes differ among these subtypes is not yet well-established.

A new study published in the journal *Diabetology* has for the first time shown that obesity during childhood is associated with higher risk of four out of the five subtypes of adult-onset diabetes.[2]

Researchers from Bristol University in the UK, Sun Yat-Sen University in China and the Karolinska Institute in Sweden collaborated on this study to investigate the impact of childhood obesity on different subtypes of adult-onset diabetes. Data for childhood body size were extracted from a genome-wide association study of 4,53,169 Europeans who self-reported body size (thinner, about average and plumper) at age 10 years in the UK Biobank study. More than 200 genetic mutations for childhood body size were identified and linked to the various subtypes of diabetes. Data from two genome-wide association studies from Europe involving adults newly diagnosed diabetes, or without diabetes was used to identify the genetic mutations. The Mendelian randomization method was used to analyze the association of genetically predicted childhood body size with different diabetes subtypes.

Results showed that being overweight or obese in childhood was associated with 62% higher risk of LADA with odds ratio (OR) of 1.62. The risk of SIDD was doubled with OR of 2.11, while the risk of SIRD increased nearly 3 times with OR 2.76. The odds of having MOD increased sevenfold with OR of 7.30. However, MARD showed no such association with childhood obesity (OR 1.06).

Childhood obesity is known to predispose to type 2 diabetes in adulthood characterized by insulin resistance. This study shows that childhood obesity is a risk factor for all subtypes of adult-onset diabetes, including those due to autoimmunity and insulin deficiency, except age-related diabetes. Hence, prevention of obesity during childhood is of utmost importance for better long-term health.

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Gauging the Antiobesity Potential of Oral Semaglutide in Type 2 Diabetes in the Indian Context

ABSTRACT

"Diabesity", which combines type 2 diabetes (T2D) and obesity has emerged as a global epidemic in the modern world. Indeed, diabesity contributes significantly to increased morbidity, and the prevalence of this global health burden has steadily increased in India over the past three decades. Importantly, only a few pharmacological agents are currently available across the world, and India in particular has access to only a limited number of such agents. However, with the advent of oral glucagon-like peptide-1 receptor agonist (GLP-1RA) after its launch in India recently as an antidiabetic agent, the horizon to combat diabesity has expanded. With the available evidence from several phase 3 trials of oral GLP-1RA (PIONEER, Peptide Innovation for Early Diabetes Treatment), it is increasingly becoming apparent that oral semaglutide could have some potential to fulfil the US Food and Drug Administration criterion of an antiobesity agent.

Keywords: Obesity, oral GLP-1RA, semaglutide, weight loss

Type 2 diabetes (T2D) is one of the largest global health emergencies of this century, ranking among the 10 leading causes of mortality along with cardiovascular disease, respiratory disease and cancer.[1,2] According to the World Health Organization (WHO), noncommunicable diseases (NCDs) accounted for 74% of deaths globally in 2019, of which, diabetes resulted in 1.6 million deaths, thus becoming the 9th leading cause of death globally.[2] Diabetes has steadily increased around the world including in India over the last decades and India's contribution to the global burden is markedly increasing the overall disease burden and mortality.[3] The past three decades have witnessed a global increase in overweight (body mass index [BMI] ≥25 kg/m^2) from 28.8% to 36.9% in men and from 29.8% to 38.0% in women.[4] Similarly, age-standardized obesity (BMI ≥30 kg/m^2) has increased from 3.2% to 10.8% in men and from 6.4% to 14.9% in women.[5] Studies from different parts of India have provided evidence of the rising prevalence of overweight/obesity, and indeed overweight/obesity has been found to be the most important contributor to the rising prevalence of diabetes in the country.[6] Obesity is associated with a decreased life expectancy of 5 to 20 years depending upon its duration both due to the magnitude of excess weight and the emergence of associated comorbid diseases. Besides, obesity increases the prevalence of psychological, neurological, pulmonary, gastrointestinal, renal, musculoskeletal and endocrine diseases.[7] To this end, antiobesity medications, when combined with lifestyle intervention, produce larger weight loss than behavioral treatment alone.[8] Available evidence clearly suggests that even a modest loss of 5% to 10% is often associated with a significant reduction in obesity-related complications and increases the quality of life.[9]

In 2007, the United States Food and Drug Administration (US FDA) laid down certain criteria to qualify as an effective antiobesity drug. The criteria require

at least one of the following to be met after 1 year of treatment. First, the "mean" efficacy criterion wherein the difference in mean weight loss between the active product and placebo-treated groups is ≥5%, and the difference should be statistically significant. Second is the "categorical" efficacy criterion where the proportion of subjects losing ≥5% of baseline body weight in the active-product group should be ≥35%, and it should be approximately double the proportion in the placebo-treated group, and the difference between groups should be statistically significant.[10] To date, the US FDA has approved six pharmacological agents for chronic weight management as an adjunct to a reduced-calorie diet and increased physical activity. These include orlistat, phentermine/topiramate ER, naltrexone ER/bupropion ER, high-dose liraglutide (3.0 mg), injectable high-dose semaglutide (2.4 mg) and recently a dual glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 receptor agonists (GLP-1RAs), injectable tirzepatide (5 mg, 10 mg, 15 mg).[11]

On the other hand, the European Medicines Agency (EMA) has approved all of them except phentermine/topiramate and tirzepatide. Orlistat, phentermine/topiramate ER, naltrexone ER/bupropion ER and liraglutide 3.0 mg produce placebo-subtracted weight losses varying from 2.6 kg (orlistat) to 8.8 kg (phentermine-topiramate) at 1 year.[12,13] Interestingly, among the six approved antiobesity drugs, randomized controlled trials (RCTs) of only tirzepatide, semaglutide 2.4 mg and phentermine + topiramate have so far fulfilled both the "mean efficacy" and "categorical efficacy" criteria of antiobesity drugs across all the phase 3 trials, as per US FDA mandate of 2007. For liraglutide 3.0 mg, 3 out of the total of 4 RCTs fulfilled both the "mean efficacy" and "categorical efficacy" criteria. Notably, only 1 RCT of naltrexone + bupropion (COR-II) fulfilled both the "mean" and "categorical" efficacy criteria, while none of the RCTs of orlistat and lorcaserin (earlier approved but recently withdrawn) fulfilled both criteria. Thus, it is apparent that some of these antiobesity drugs that only fulfilled the "categorical" efficacy criterion have also received US FDA approval as antiobesity drugs for long-term use.[13,14]

GLP-1RAs have been the most effective weight-lowering agents in people with T2D. This finding led to examination of higher strength GLP-1RA formulations in people with obesity regardless of T2D. Surprisingly, a significant reduction in body weight was noted. For example, injectable liraglutide 0.6-1.8 mg once daily is approved for the treatment of T2D, while liraglutide 3.0 mg is approved for obesity regardless of T2D. Similarly, injectable semaglutide 1.0 mg, a once-weekly subcutaneous GLP-1RA was first approved as a treatment for T2D in 2017, while higher strength injectable semaglutide 2.4 mg once-weekly has been approved for obesity by the US FDA, United Kingdom Medicine and Health Products Regulations Agency, and EMA in 2021 and 2022, respectively.[12] Notably, the reduction in body weight was quite larger with injectable semaglutide 1.0 mg (-6.5 kg) compared to dulaglutide 1.5 mg (-3.0 kg) (Estimated treatment difference [ETD] -3.55 kg; 95% confidence interval [CI], -4.32 to -2.78 kg; $p < 0.0001$) in SUSTAIN-7 (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) trial.[15] Higher strength semaglutide 2.4 mg lowered mean body weight to approximately 15% after 68 weeks of treatment (relative to about 2.4% in placebo).[16] Tirzepatide at the dose of 10 mg and 15 mg dose led to a nearly 20% weight reduction in SURMOUNT-1.[14]

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are another class of antidiabetic agents that has shown a modest weight loss in T2D. However, weight loss with SGLT2 inhibitors has been generally lesser compared to GLP-1RAs. For example, in the SUSTAIN-8 trial, once-weekly injectable semaglutide 1.0 mg had a significantly greater weight loss compared with canagliflozin 300 mg once daily (ETD -1.06 kg; 95% CI, -1.76 to -0.36; $p = 0.003$).[17] Similarly in the PIONEER-2 trial, oral semaglutide 14 mg daily had a higher weight loss compared with empagliflozin 25 mg daily at Week 52, as evaluated by the trial product estimand (-4.7 vs. -3.8 kg, respectively; ETD -0.9 kg; 95% CI, -1.6 to -0.2; $p = 0.01$).[18] Unfortunately, neither the injectable semaglutide (1.0 mg and 2.4 mg) nor tirzepatide is currently available in India. The currently available GLP-1RAs available in India that include the injectable form of dulaglutide (1.5 mg) and liraglutide (1.8 mg) have shown a significant but only modest weight loss in people with T2D. Thus, it is of interest to gauge the weight-lowering potential of oral semaglutide 14 mg available in India for the treatment of T2D.

The available evidence from some of the head-to-head, active comparator trials of GLP-1RAs (for example-AWARD-6 between liraglutide vs. dulaglutide, PIONEER-4 between oral semaglutide vs. injectable liraglutide, and PIONEER-10 between oral semaglutide 14 mg vs. dulaglutide 0.75 mg) suggest that amongst the three agents available in India, weight reduction is largest with oral semaglutide 14 mg followed by injectable forms of liraglutide 1.8 mg and dulaglutide 1.0 mg, respectively. Moreover, in PIONEER-1, 44% of patients on oral semaglutide 14 mg had ≥5% weight loss at 26 weeks compared with 16% of patients on placebo

(trial-product estimand), which satisfies the US FDA "categorical" efficacy criterion (≥35% of participants on active drug having ≥5% weight loss). Since PIONEER-1 was conducted for only 26 weeks it did not fulfil the 52 weeks trial duration criteria laid down by the US FDA. However, in the PIONEER-4 trial, the percentage of patients with ≥5% weight loss at 52 weeks was 49.3% versus 12% in the placebo arm, alike SUSTAIN-1 of injectable semaglutide 1.0 mg once weekly (Fig. 1). These findings hint towards an antiobesogenic potential of oral semaglutide 14 mg similar to injectable semaglutide 1.0 mg. Indeed, both ≥5% and ≥10% weight reduction with oral semaglutide 14 mg is almost like the injectable semaglutide 1.0 mg, despite a relatively lesser baseline body weight in the former trial (Fig. 2). Finally, in a post-hoc analysis of PIONEER 1-5 and PIONEER-8 that evaluated the composite 3 (glycated hemoglobin [HbA1c] reduction ≥1% and body weight loss ≥5%), found 1% to 8% of patients on placebo, 11% on sitagliptin 100 mg, 18% on liraglutide 1.8 mg, 20% on empagliflozin 25 mg and 27% to 41% on oral semaglutide having achieved this composite. Moreover, the odds of achieving this composite 3 with oral semaglutide 14 mg were significantly ($p < 0.0001$) greater versus all other comparators.[19]

In summary, oral semaglutide has been approved by the Drugs Controller General of India (DCGI) in 2020 and has been introduced in the Indian market in January 2022 as an antidiabetic agent.[20] Despite a potential antiobesogenic effect, it was not launched in India as an antiobesity agent. However, it does appear to fit into the US FDA "categorical" efficacy criterion as an antiobesity agent based on the findings from the PIONEER-1 and PIONEER-4 trials. Notwithstanding, amongst all antidiabetic agents available in India, oral semaglutide seems to have the highest potential for weight loss in

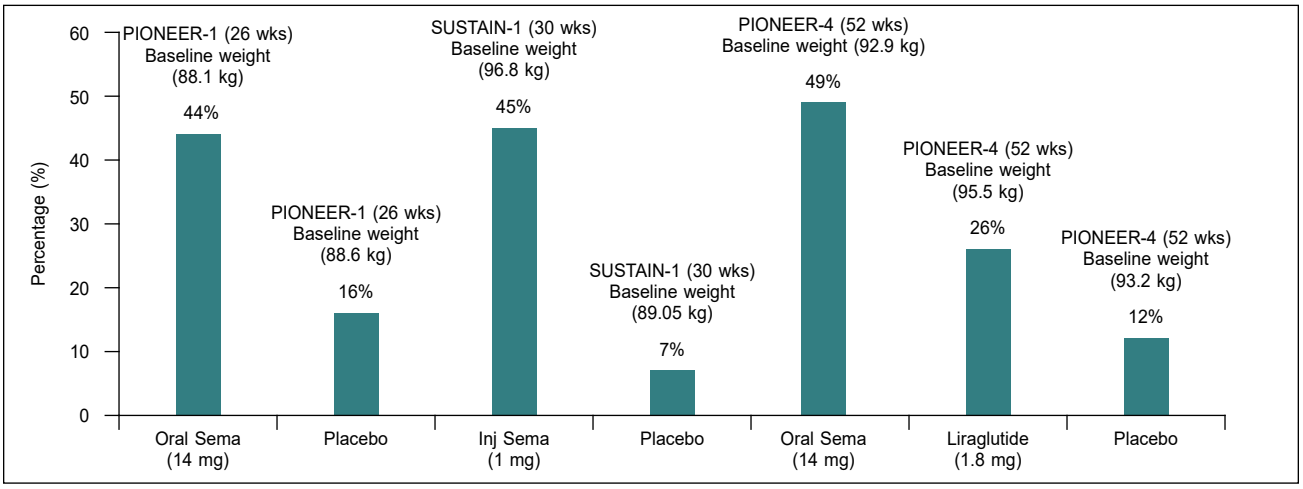

Figure 1. Comparative weight loss (≥5%) with oral (14 mg) and injectable semaglutide (1 mg) vs. placebo.

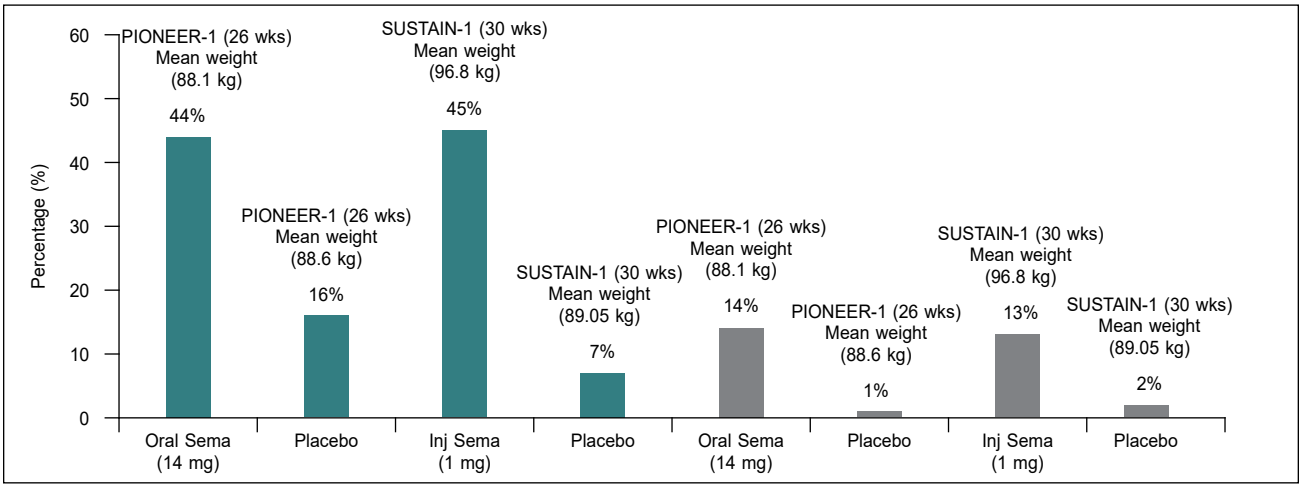

Figure 2. Comparative weight loss of ≥5% (green color) and ≥10% (grey color) with oral (14 mg) and injectable semaglutide (1 mg) vs. placebo.

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people with T2D. Further phase 3 global trials of higher strength oral semaglutide such as 25 mg and 50 mg in people with obesity (OASIS-1 and OASIS-2) are currently ongoing,[21,22] while a top line result from a similar study recently conducted in people with T2D with obesity (PIONEER-PLUS) found both higher strength of oral semaglutide to have superior efficacy not only in terms of glucose-lowering but with an excellent weight lowering effect compared to oral semaglutide 14 mg with an acceptable side effects.[23]

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REVIEW ARTICLE

Vitamin D in Clinical Practice: Current Perspectives

SANJAY KALRA*, ABDUL HAMID ZARGAR†, AG UNNIKRISHNAN‡, ARUNDHATI DASGUPTA#, RAKESH SAHAY¥, SHEHLA SAJID SHAIKH§, NITIN KAPOOR£, SAMBIT DAS^

ABSTRACT

India is a heliophobic country; despite ample sunshine, almost 490 million people are vitamin D deficient in the country. Additionally, the Indian diet has not been successful in providing the daily need for vitamin D, leading to a vitamin D deficiency. The need to fortifying food with vitamin D has been raised several times. Besides, there have been discussions about whether vitamin D is a hormone or a vitamin? In this review, the authors have reviewed vitamin D deficiency and its status in India, assessment and screening, the role of vitamin D in various disease conditions, dosage recommendation and regimen.

Keywords: Vitamin D, heliophobic, vitamin D deficiency, hypervitaminosis

With approximately 490 million people deficient in vitamin D in a sun-rich country like India, it is important to emphasize the significance of vitamin D sufficiency. Besides, the Indian diet generally fails to provide the daily need for vitamin D, resulting in a deficiency. There is a need to fortify various foods with vitamin D through national health programs and raise awareness about the importance of diet, lifestyle and vitamin D supplementation. Another ongoing discussion is whether vitamin D is a vitamin, prohormone or hormone precursor. Hence, this silent epidemic needs to be addressed appropriately. In this article, the authors have reviewed the present status of vitamin D deficiency in India, its positioning as a vitamin or hormone, clinical implications in various conditions, and given recommendations on the use, dosage and duration of vitamin D use. An algorithm has also been suggested for managing the population's vitamin D deficiency and sufficient conditions.

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EPIDEMIOLOGY OF VITAMIN D DEFICIENCY

Vitamin D deficiency has been cited for having assumed pandemic proportions, despite being the most under-diagnosed and under-treated nutritional deficiency globally.[1] In the general population across the world, vitamin D deficiency ranges from 20% to 80% and in critically ill patients, the prevalence increases with a simultaneous rise in disease severity.[2] With an exponential rise in prevalence, recent observational studies have revealed that almost 40% of Europeans are vitamin D deficient, while 13% are severely deficient.[3] Vitamin D deficiency or insufficiency has been reported from several countries across the globe, including the United States, South America, Canada, the Middle East, Australia, South Asia, Europe and Africa. Studies from India have reported a wide range of vitamin D deficiency, from 30% to as high as 100%. Other parts of the world, like the Middle East, China and South America, have also reported an alarmingly high prevalence of vitamin D deficiency.[4]

Several countries worldwide report a very high prevalence of low vitamin D status. Vitamin D [25(OH)D] levels below 30 nmol/L occur commonly in India, Tunisia, Pakistan and Afghanistan in over 20% of

the population. Studies have shown that 490 million individuals have vitamin D deficiency in India.[3]

Another study amongst South Asian adults revealed a high (68%) and variable prevalence of vitamin D deficiency among the adults of different South Asian countries, which was hypothesized to be linked to the high prevalence of several other health issues in this region. A country-wise comparison revealed that Sri Lanka had the lowest prevalence of vitamin D deficiency (48%), while Pakistan had the highest prevalence (73%). Bangladesh and the Indian population had about 67% prevalence of vitamin D deficiency.[5]

Community-based studies conducted in the last 10 years have shown a prevalence range of 50% to 94% of vitamin D deficiency in India. A high prevalence of vitamin D has been noted in the country.[6] A study conducted in South India showed a high prevalence of vitamin D deficiency among pregnant women, attributed to reduced physical activity, sun exposure, darker skin complexion, lower socioeconomic status and lack of awareness.[7] A single-center cross-sectional study in North India revealed a prevalence of vitamin D deficiency of 55.55% and inadequacy of 38.46%.[8]

While sun exposure can suffice for vitamin D sufficiency, it is a frequently witnessed nutritional deficiency. Even though India is a tropical country with abundant sunshine, it seems to be a heliophobic country as vitamin D deficiency has been prevalent. Vitamin D deficiency is commonly present in individuals of all ages, gender, race and geography.[1]

As per a report by the International Osteoporosis Foundation in 2009, 96% of neonates, 91% of healthy school girls, 78% of healthy hospital staff and 84% of pregnant women in North India were diagnosed with hypovitaminosis D.[9]

A cross-sectional multicenter study has demonstrated a high prevalence of vitamin D deficiency across India in healthy, middle-aged health care professionals.[10] Vitamin D deficiency is particularly pronounced in special categories of patients, including patients with chronic renal failure and on hemodialysis, renal transplant recipients affected with liver disease or after liver transplantation, ranging from 85% to 99%.[3]

Besides, critically ill patients have an extremely high prevalence of vitamin D deficiency, and low vitamin D levels are also associated with increased illness severity, morbidity and mortality in patients admitted to intensive care units (ICUs) and medical and surgical ICUs.[3] In a study conducted in South India, vitamin D deficiency was present in all patients with active tuberculosis despite adequate sunlight exposure in 72% of the cases.[11]

The Eradication of Vitamin D Deficiency

Vitamin D deficiency is a global issue manifesting several clinical signs and symptoms with major consequences. Vitamin D deficiency has a high global prevalence and leads to many health risks, including bone health, chronic pain in cancer, musculoskeletal, fibromyalgia, autoimmune conditions, cardiovascular diseases (CVDs) and even neurological system disorders. The benefits of vitamin D are undisputable in bone health. An early application of vitamin D is further supported by extraskeletal benefits.[12] Considering the high prevalence of vitamin D and its overarching consequences, it is important to take steps toward eliminating vitamin D deficiency.

Iodine deficiency, at one point, was the world's single most important preventable cause of brain damage and mental retardation. Thirty-eight million newborns in developing countries remain unprotected from the lifelong impact of brain damage associated with iodine deficiency disorders. A massive worldwide effort led to a dramatic rise in the proportion of people consuming iodized salt, from under 20% in the 1990s to about 70% by 2000.[13] The Iodine Deficiency Disorder Control Programme in India is a public health success story. The successful translation of research to policy to program, sustained political commitment, the increased production of iodized salt and involvement of the private sector, the institution of legislation to ensure iodization of salt and the catalytic role played by academic institutes, civil society and international agencies are key factors in establishing the success of Iodine Deficiency Disorder Control Programme.[14] Taking cues from the successful programs implemented to eradicate iodine deficiency, measures such as nutritional replenishment of iodine, robust health and nutrition education activities to create demand for iodine insufficiency and developing monitoring information systems for ensuring that iodine is sufficiently available to the population,[14,15] we can facilitate evidence to policy transition to eradicate vitamin D from India.

IS VITAMIN D A VITAMIN OR HORMONE?

There has been a discussion amongst clinicians and researchers about whether vitamin D is a prohormone or hormone precursor, as it has to be synthesized by the sunlight for activation. Unlike other vitamins such as A, B and C, vitamin D is the only vitamin that the body can

make. It plays an important part in the neurobiological pathways and cascading effects associated with mental health. Other evidence has also shown that it has a crucial role in various endocrine pathways, reiterating that vitamin D deficiency is a hormonal deficiency. Besides, vitamin D is also involved in brain development on a hormone level. Hence, vitamin D fits more appropriately in the criteria of a hormone replacement rather than a vitamin supplement.[12]

Technically, the term vitamin D is misleading, as it cannot be considered a true vitamin. The body has the capacity to synthesize its own cholecalciferol (D3). Hence, it is more accurately referred to as a steroid hormone or an oxysterol. The International Union of Pure and Applied Chemistry's Commission on the Nomenclature of Biological Chemistry defines vitamin D3 as a 'steroid or secosteroid'[16] (Refer Box).

Box. Vitamin D: Vitamin vs. Hormone

Evidence suggesting that vitamin D is a hormone	
Prohormone	Vitamin D is a prohormone, the body converts the substance Vitamin D into a hormone for it to be used.[12] It is a key regulator of bone metabolism and calcium and phosphorus homeostasis through negative feedback with the parathyroid hormone.[17]
Hormone precursor	Vitamin D is a hormone precursor, as it must be synthesized by the sunlight for activation.[16]
Synthesized by the body	The only vitamin that can be made by the body, unlike other vitamins.[18] The endogenous synthesis occurs by ultraviolet light exposure of 7-dehydrocholesterol within the microvessels of the skin resulting in its conversion into cholecalciferol.[18]

Vitamin D Formulations

Vitamin D preparations may be administered orally, subcutaneously, intraperitoneally or intravenously. They may be administered daily, sometimes in divided doses or intermittently in large bolus doses, usually 3 times per week. The timing of the dose is also important which may be at night, as the gut calcium load is at a minimum at night.[19]

Vitamin D is available in two forms in India: Vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). A market assessment in India has shown that over 99.9% of the preparations contain vitamin D3 in the form of alfacalcidol, calcitriol or cholecalciferol. Most of the preparations have vitamin calcitriol or alfacalcidol. About 10% of preparations contain cholecalciferol.[20]

The most common formulation for oral administration is in the form of tablets and capsules. Alfacacidiol and calcitriol are commonly available as tablets and capsules; cholecalciferol is in the form of granules in sachets. Other dosage forms include syrups and soft gel capsules. More than 75% of alfacalcidol preparations also contain calcium. Most of the calcitriol preparations are combined with zinc or zinc sulfate. Several vitamin D preparations also contain various other minerals/vitamins such as magnesium, cupric, boron, methylcobalamin, vitamin E, vitamin K, vitamin C, pyridoxine, folic acid, beta-carotene, glutamic acid, manganese, omega-3 and docosapentaenoic acid.[20]

Tablets and capsules contain 10-10,000 IU of vitamin D and are usually administered on a daily basis. Cholecalciferol soft gel capsules, syrup and sachets containing granules of vitamin D (60,000 IU) are given weekly. Vitamin D2 preparation is available in tablet form in two formulations containing 20 IU and 100 IU, respectively.[20]

The parenteral route has been shown to be effective and safe in patients with hypovitaminosis D caused by severe intestinal malabsorption. Intramuscular vitamin D is the preferred treatment for malabsorption disorders like intestinal bowel disorders, pancreatic insufficiency, short-bowel syndrome, gluten enteropathy, post-bariatric surgery and any need to total parenteral nutrition.[21] Table 1 depicts the different preparations of vitamin D formulations available in India.

Recommended Vitamin D Levels in the Body

Maintaining adequate serum levels of 25(OH)D for skeletal and extraskeletal physiologic effects is important. Studies have shown that the desirable and safe levels of serum 25(OH)D levels should be 30-100 ng/mL because, at the level of 30 ng/mL, the intestinal calcium

Table 1. Different Formulations of Vitamin D

Formulation	Vitamin D strength	Administration
Tablets/Capsules	10-10,000 IU	Daily
Sublingual tablets	10-10,000 IU	Daily
Soft gel capsules/ granules/syrup/tablet	60,000 IU	Weekly
Intramuscular injection	6,00,000 IU/mL	Weekly
Soft gelatin capsules/tablets	10-10,000 IU	Daily

absorption reaches its highest level and parathyroid hormone (PTH) levels are continually reduced until this level of 25(OH)D is reached.[6]

Vitamin D deficiency is described as a serum/plasma level of 25(OH)D below 75 nmol/L (or 30 ng/mL). A threshold of <25 or <30 nmol/L (or 10/12 ng/mL) can raise the risk of osteomalacia and nutritional rickets, thus determining severe vitamin D deficiency.[3]

The clinical practice guidelines of the Endocrine Society Task Force on vitamin D have described a cut-off level of 50 nmol/L as vitamin D deficient.[22] In addition, various societies and expert bodies worldwide define 50 nmol/L as the vitamin D requirement of all normal, healthy individuals, primarily considering bone health.

We recommend that desired serum level of vitamin D should be between 40 and 60 ng/mL, and hence, appropriate vitamin D dose should be administered.

INDICATIONS FOR VITAMIN D

Musculoskeletal Effects of Vitamin D Deficiency

Rickets and osteomalacia

Vitamin D, a secosteroid hormone, is crucial for calcium absorption and bone mineralization absorption, which positively associates with bone mineral density.[23] It is known that prolonged and severe vitamin D deficiency causes rickets in children and osteomalacia in adults. Results from several clinical studies have shown that vitamin D supplementation can improve muscle strength contributing to a reduction in the incidence of falls.[23]

It has been established that insufficient vitamin D intake over a prolonged period can result in bone demineralization. Vitamin D deficiency reduces calcium absorption, eventually reducing the calcium concentrations in the circulation. Vitamin D deficiency also causes secondary hyperparathyroidism, which structurally weakens the bone and increases the risk of fractures.[23]

Maternal vitamin D deficiency passes on to the infant who is at high risk of presenting in the first few days or months of life with hypocalcemic complications, including seizures, tetany and dilated cardiomyopathy. Vitamin D deficiency in older children can result in motor delay, proximal myopathy and dental complications. Osteomalacia in girls can result in pelvic deformities and lead to obstructed labor later in life.[24]

Vitamin D deficiency triggers the release of PTH, which enhances urinary phosphate excretion, resulting in hypophosphatemia and osteomalacia.[25] Low calcium intake and/or low vitamin are the primary reason for body calcium deprivation across the world, and their combined deficiency accelerated bone demineralization.[24]

Osteoporosis

Osteoporosis is defined as a bone mineral density (BMD) 2.5 standard deviations below the mean of healthy young individuals. Also, there is a direct relationship between BMD and fracture risk. Hence, vitamin D plays a key role in osteoporosis and fractures.[23]

The results of vitamin D deficiency are secondary hyperparathyroidism and bone loss, resulting in osteoporosis and fractures, mineralization defects, which may lead to osteomalacia in the long-term, and muscle weakness, causing falls and fractures. Several randomized controlled trials have shown that vitamin D and calcium showed a significant reduction in the incidence of fracture.[26]

Research has shown that vitamin D supplementation improves BMD and enhances muscle function, leading to reduced falls. It can also modulate the effect of pro-inflammatory cytokines on bone metabolism.[23]

Vitamin D sufficiency is, therefore, pivotal for normal skeletal development both *in utero* and in childhood and sustaining bone health in the adult population. A deficiency of vitamin D in mothers can lead to a considerable reduction in infant bone mineral acquisition, which is persistent in nature.[27]

Sarcopenia

Sarcopenia refers to a loss of skeletal muscle mass with aging. It is marked by the progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death. Studies have shown a positive correlation between serum 25(OH)D concentration and muscle function. A decline in serum 25(OH)D concentration with rising age leads to reduced bone density, leading to a higher risk of falling and bone fractures.[28]

Studies have shown that older people with vitamin D deficiency may be at risk of sarcopenia, a geriatric syndrome featured by the progressive loss of skeletal muscle mass and strength frequently complicated by adverse events, including falls, disability, hospitalization and death.[29]

MOAN syndrome

MOAN refers to the musculo-osteo-arthro-neuropathic syndrome. Osteoporosis is often related to sarcopenia and osteoarthritis and is attributed to calcium and

vitamin D deficiency, which may eventually result in metabolic neuropathy and myopathy. While conditions such as sarcopenia or loss of muscle mass or strength or function may occur as a primary condition, which may result in secondary such as osteoporosis and arthritis. Even though the associations have been shown to occur individually, it is important to address MOAN syndrome as one entity. Vitamin D may play an important role in preventing and managing the MOAN syndrome.[30]

Mitogenic Disorders

Strong preclinical data have demonstrated that vitamin D is linked with cell cycle control and cancer.[31] It was shown in a Cochrane systematic review that cancer mortality was modestly reduced by vitamin D supplementation in individuals receiving a mean daily dose of 1,146 IU compared to no supplementation during a mean follow-up for more than 6 years.[32] Several large randomized controlled trials, including the VITAL trial, showed that a vitamin D supplementation group had a nonsignificant trend of reduction in total cancer mortality.

The vitamin D endocrine system influences all cells and most cytokines of the immune system.[33] As per the results of the LUNG-ViDA trial, vitamin D supplementation may have a modest impact in improving expiratory lung function.[34]

Some studies have also shown a strong link between poor vitamin D status and increased risk of infection or autoimmune diseases such as multiple sclerosis, inflammatory bowel diseases, or type 1 diabetes mellitus.[35] A causal relationship between increased risk of multiple sclerosis and genetically low serum 25(OH)D levels has also been confirmed.

Besides, pregnant women frequently report poor vitamin D status compared to nonpregnant women of the same age. Studies have shown that vitamin D supplementation may lead to a considerable reduction in maternal mortality and improve the health of the baby.[36]

Psoriasis

Vitamin D has a significant role in the treatment of psoriasis, owing to its activity in the proliferation and maturation of keratinocytes. Significant associations between low vitamin D status and psoriasis have been systematically observed. A bi-directional relationship between low vitamin D status and psoriasis is also important for delineating the risk profile for comorbidities that may result from psoriasis, including type 2 diabetes and metabolic syndrome.[37] Clinicians should consider general vitamin D supplementation in individuals who are at high risk of vitamin D deficiency, such as psoriatic patients.

Glucometabolic, Cardiometabolic and Barometabolic Disorders

Cardiovascular diseases

Vitamin D deficiency has been implicated in cardiometabolic disorders, including obesity, type 2 diabetes mellitus, CVD and polycystic ovary syndrome.[38]

Epidemiologic studies have revealed that low vitamin D levels are linked with an increased risk of cardiovascular events. 25(OH)D plays a role in diabetic CVD, myocardial infarction (MI), heart failure and peripheral vascular disease. Decreased vitamin D levels are strongly associated with a high prevalence of coronary artery disease, a 3-times rise in the rate of myocardial ischemia among individuals with hypertension. Besides, the rate of cardiovascular complications, including MI and heart failure, was higher in individuals with vitamin D deficiency who were followed for about 5 years.[39]

It was seen in a clinical trial that vitamin D treatment may be effective in patients with cardiometabolic disorders having vitamin D deficiency.[40] Another study has shown that vitamin D supplementation given at a dose of 50,000 IU for 16 weeks brought about a considerable reduction in triglyceride level.[41]

Another Iranian study demonstrated an inverse link between plasma vitamin D levels and cardiometabolic risk factors in children and adolescents.[42] Supplementation also significantly reduces blood pressure in elderly women.[43] A systematic review and meta-analysis have shown that high vitamin D levels in middle-aged and elderly populations are related to a significant reduction in CVD, type 2 diabetes and metabolic syndrome.[44]

Vitamin D deficiency is highly prevalent and may lead to arterial hypertension. Vitamin D exerts its effect by suppressing renin and PTH levels and its anti-inflammatory and vasculoprotective properties. Low vitamin D levels may be an independent risk factor for incident arterial hypertension. Results of cross-sectional studies have shown that low vitamin D is linked with higher systolic blood pressure and a higher incidence of hypertension.[39]

Real-world data has shown that high vitamin D levels are associated with a favorable serum lipid profile. While there have been mixed results from different studies, some randomized controlled studies have

indicated that vitamin D supplementation provided a statistically significant rise in low-density lipoprotein cholesterol (LDL-C), with a tendency towards a rise in total cholesterol. Besides, the effect of vitamin D supplements on serum LDL-C levels is more pronounced in obese individuals.[45] Supplementation of vitamin D (1,000 mg) for a month in healthy school children demonstrated a significant improvement in the high-density lipoprotein (HDL) level.[46]

Type 2 diabetes

Poor vitamin D levels may act as one of the driving factors for the development of type 2 diabetes. This has been corroborated by the fact that low vitamin D status is linked with an increased risk of glucose intolerance or diabetes. Longitudinal studies have exhibited that poor vitamin D level is associated with an increased incidence of type 2 diabetes. Changes in calcium and vitamin D homeostasis are related to insulin resistance, decreased β-cell function, metabolic syndrome, glucose intolerance and diabetes.[39] Vitamin D supplementation (60,000 IU) for 1 year period significantly reduced the glycemic parameters, including fasting blood glucose (FBG), postprandial blood glucose (PPBG) and glycated hemoglobin (HbA1c).[47]

Obesity and overweight

Studies have shown that fluctuation in serum 25(OH)D concentrations may be associated with a myriad of problems. It has been shown that an increase in body mass index (BMI) levels per unit is associated with a 1.15% lower concentration of 25(OH)D, with adjusted age and sex. Other evidence points towards an association between obesity, high concentration of PTH and 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] with low serum 25(OH)D concentrations. Additionally, changes in behavior, low synthetic capacity, intestinal absorption and a changed metabolism play a major role in controlling vitamin D levels. Obese individuals are exposed to less sunlight, resulting in reduced synthesis of vitamin D. Besides, it has been suggested that weight loss is associated with improved serum vitamin D concentration in overweight or obese women.[39]

However, a few studies have also suggested that there are no evident benefits of vitamin D supplementation in cardiometabolic disorders.[38]

Miasma-related Disorders

Vitamin D deficiency has been shown to occur frequently in patients with chronic airway inflammatory and infectious diseases, correlated with increased disease severity. Research has shown that vitamin D modulates ongoing abnormal immune responses in chronic respiratory diseases and is shown to restrict bacterial and viral colonization into the lungs.[48]

Various studies have highlighted the association between low levels of vitamin D deficiency with increased risk of asthma and other respiratory disease symptoms, including lower lung function. Several studies involving clinical trials of vitamin D supplementation on asthma symptoms have reported positive results.[48]

Among the published clinical studies, a hospital-based cross-sectional study has reported that increased tumor necrosis factor (TNF)-α levels and low serum vitamin D concentrations are related with airway obstruction in chronic obstructive pulmonary disease (COPD) patients.[49] It has been assessed that around 40% to 90% of cystic fibrosis patients are vitamin D deficiency, with vitamin D serum levels below 30 ng/mL. Almost 15% to 20% have vitamin D levels below 15 ng/mL. While patients usually are given vitamin D supplementation when they present exocrine pancreatic insufficiency, but it normally appears at birth or during the first months of life. Hence, supplementation usually starts with the diagnosis.[50]

ASSESSMENT AND SCREENING

With the increasing awareness about the importance of vitamin D for maintaining musculoskeletal health, there has been a rise in vitamin D testing. However, uniform screening for vitamin D deficiency is not recommended in the general population as it is an expensive test. However, given that certain individuals are at high risk of vitamin D deficiency, it is important to perform targeted testing of the susceptible population.[51]

Once the treatment is initiated, timely retesting following 3 to 6 months of treatment must confirm adequate treatment and prevent potential toxic over-treatment. Vitamin D levels undergo seasonal variations and hence should be considered when tests and interpretations are conducted. In addition, risk factors for vitamin D deficiency should be considered to ensure targeted testing of patients.[52] The screening of vitamin D deficiency should be considered in the case of osteoporosis, osteomalacia, chronic kidney disease, hepatic failures, malabsorption syndromes, hyperparathyroidism, chronic treatment with medications that influence vitamin D metabolism, pregnant and lactating women, institutionalized or hospitalized patients, older adults (>65 years) in general, older adults with a history of falls or a history of nontraumatic fractures, granuloma-forming

disorders, chronic autoimmune diseases, obesity, dark skin pigmentation, different types of cancer, certain cardiovascular disorders, diabetes mellitus and its comorbidities, some neurological conditions and recurrent acute respiratory tract infections; in symptomatic patients with musculoskeletal pain; before initiating osteoporosis treatment with antiresorptive medications.[51]

Clinical Presentation of Vitamin D Deficiency

The common clinical presentations of vitamin D deficiency are listed in Table 2.[53]

Markers to Assess Vitamin D Deficiency

Total serum 25(OH)D concentration is the primary marker for assessing vitamin D status, reflecting vitamin D supply from all sources, including endogenous vitamin D synthesis in the skin, diet, supplements and mobilization from tissue stores. Patients suffering from vitamin D deficiency and other and other related health issues, such as bone diseases, require testing of additional laboratory parameters, including serum calcium, phosphate, alkaline phosphatase, PTH, creatinine and magnesium to guide further the diagnostics and treatment of these patients.[51]

Vitamin D deficiency is also accompanied by normal blood levels for calcium and phosphorus, high normal or increased levels of PTH, normal to high levels of total alkaline phosphatase, a low 24-hour urine calcium excretion rate and low levels of total 25(OH)D. Patients suffering from severe and chronic vitamin D deficiency may present with overt hypocalcemia and/or hypophosphatemia.[54] Based on risk factors and seasonal alteration in the serum levels of vitamin D, it is recommended that:

- Targeted testing based on risk factors is performed.
- Seasonal variations in vitamin D levels are considered before ordering testing for patients.
- Retesting for individuals on therapy is ordered after 3 months following the initiation of vitamin D treatment.

HYPERVITAMINOSIS D

An increased administration of vitamin D supplements may sometimes result in a higher risk of exogenous hypervitaminosis D, displaying symptoms of hypercalcemia, also referred to as vitamin D toxicity. Hypervitaminosis may develop as a result of using vitamin D analogs. Hypervitaminosis D with hypercalcemia may also be a manifestation of excessive production of $1,25(OH)_2D$ in granulomatous disorders, in lymphomas and during idiopathic infantile hypercalcemia.[55]

PREVENTION, TREATMENT AND MANAGEMENT

Sunlight

Insufficient sun exposure is the main reason for vitamin D insufficiency. The ultraviolet portion of the sunlight enters the skin and is converted to pre-vitamin D3. Pre-vitamin D3 rapidly converts within the plasma membrane to vitamin D3, which is released in the extracellular space. Factors affecting the cutaneous synthesis of vitamin D are sunscreen use, skin pigmentation, time of day, year's season, latitude and aging. Limited sensible exposure to sunlight or ultraviolet B radiation is more effective in raising blood levels of 25(OH)D than 1,000 IU vitamin D3 taken daily for most skin types.[56]

Vitamin D-fortified Foods

Vitamin D-fortified foods usually contain 100 IU per serving of vitamin D. It has been reported that consumption of vitamin D-fortified, especially milk, increased vitamin D intake and effectively increased 25(OH)D levels. Cereal, juices, other dairy products and margarine are other food items that can be fortified

Table 2. Clinical Manifestations of Vitamin D Deficiency

	Infants	Children	Adults
Symptoms	Difficult breathing, irritability	Repeated infection, bone pain, difficulty in squatting/standing/walking	Bone pain, muscle pain, muscle weakness, difficulty in squatting/standing/walking, frequent falls
Signs	Seizures, tetany stridor	Hypotonia, delayed dentition, enamel hypoplasia, dental caries, wrist widening, Rachitic rosary, knock knees, bowlegs	Waddling gait, anterior tibial weakness, rib cage tenderness, fractures, pelvic deformities, kyphoscoliosis
	Dilated cardiomyopathy, craniotabes, open anterior fontanelle and frontoparietal bossing		

with vitamin D.[1] Considering limited dietary sources of vitamin D, enhancing foods with vitamin D is a probable mode for ensuring increased consumption and improved vitamin D status.[57] Vitamin D food fortification is also an effective method to improve 25(OH)D levels, prevent vitamin D deficiency and improve the intelligence quotient in the pediatric population.[58] Besides, it has been seen that milk fortified with ergocalciferol has effectively eliminated rickets as an important health problem, and when used in high doses, ergocalciferol can effectively treat osteomalacia in adults.[59]

Pharmacological Therapy

Vitamin D supplementation

Sunlight and the skin are the primary sources of vitamin D; changes in sunlight exposure to the skin may alter vitamin D levels. There are several reasons for the low levels of vitamin D in the South Asian population, including dark skin, individuals whose skin is not exposed to sunlight because of clothing, sunscreen use or lack of outdoor activities. Besides, in winter, ultraviolet irradiation is reduced, particularly in temperate climates and air pollution leads to further vitamin D deficiency. Exclusive sunlight exposure is not adequate to achieve recommended vitamin D levels, and supplementation is necessary.[53] Vitamin D is included in the WHO Essential Medicines List 2021 and the Indian National List of Essential Medicines 2022 as micronutrient supplements.[60]

To ensure that non-specific symptoms of vitamin D insufficiency are not over-treated, patients are recommended to use over-the-counter vitamin D supplements or fortified food supplements such as cereals.[52] An empiric vitamin D supplementation without testing is suggested for patients without any risk factors or signs of deficiency but are suspected of having insufficient sun exposure or dietary intake.[54]

Vitamin D supplementation can be used to treat almost all individuals except those with an increased sensitivity to vitamin D treatment, a rare condition. Daily, weekly or monthly vitamin D supplementation at equivalent doses can adequately lead to a similar increase in 25(OH)D serum concentrations, while a daily vitamin D dosing is preferred.[51]

Individuals with an assessment of vitamin D level to be below 20 ng/mL should be treated with vitamin D supplementation. When aiming for a minimum 25(OH)D concentration of at least 30 ng/mL, a daily vitamin D supplement dose of about 1,000 IU per day is sufficient for all individuals, irrespective of the season. 100 IU of vitamin D per day increases serum 25(OH)D concentrations by about 1 ng/mL is one of the factors modulating the individual treatment response. Evaluation of treatment success should be considered in individuals with insufficient and deficient vitamin D levels after 3 months of treatment initiation.[51]

DOSAGE AND DURATION

Currently, bolus dosing with long dosing intervals is not used in the general population because of an increased risk of adverse effects such as falls and fractures related to them.[61] A 2017 metadata analysis showed that vitamin D leads to a significant benefit in case of acute respiratory infection with daily or weekly dosing but not with longer dosing intervals.[62] In the case of intensive care, an upfront loading dose, followed by a daily dose, is important to improve vitamin D levels quickly.[3]

Vitamin D dosing regimen should be such that it can maintain stable availability of several vitamin D metabolites. Vitamin D supplementation is necessary as only sunlight exposure and dietary intake are usually insufficient in most individuals. Currently, there is no international consensus on the standard level of vitamin D supplementation, and recommendations vary in different categories ranging from a daily dose of 400 to 2,000 IU.[3]

Endocrine Society has given a safe upper level for vitamin D supplementation as 10,000 IU, while the Institute of Medicine (IOM) and the European Food and Safety Authority recommend a value under 4,000 IU per day (100 μg). Most countries have recommended the upper level as 2,000 IU per day (50 μg) for adults.[3]

However, clinical studies on dose-response relationships or toxicity studies have shown that there are no adverse effects following an intake of 1,250 μg (50,000 IU) once every 2 weeks for several years. High doses do not cause hypercalcemia or other evidence of hypervitaminosis D.[63] Clinical studies conducted on smaller populations have also shown that even a daily consumption of up to 250 μg (10,000 IU) of vitamin D over long periods did not result in any adverse events in healthy adults.

Considering that the recommended daily dose of vitamin D supplementation of up to 2,000 IU may lead to severe side effects in the general population. Since, 800 IU is the lowest dose associated with a bone benefit, a recommended daily dose of 20 to 50 μg is reasonable.[64] A daily vitamin D of 800 IU is adequate to achieve a

Table 3. Daily Vitamin D Dosage Recommended by Different Societies and Organizations

Recommendation from	Vitamin D recommendation
United States RDA	200 IU/day in men and women ≤50 years
Vitamin D Council	2,000 IU vitamin D daily ≤60 years
IOF	800 to 1,000 IU/day in men and women
ICMR-NIN	600 IU/day in adult men and women 800 IU/day in men and women >60 years

RDA = Recommended Dietary Allowance; IOF = International Osteoporosis Foundation; ICMR-NIN = Indian Council of Medical Research-National Institute of Nutrition.

target of at least 20 ng/mL in most healthy individuals. However, 2000 IU is sufficient to achieve a level at least 30 ng/mL. Clinical data has also pointed out that a level higher than 20 ng/mL may be needed for optimal risk reduction in several cases.[3]

The results of a study showed that after a normal level of 25(OH)D is reached, the daily maintenance dose of 2,000 IU was inadequate to achieve and stabilize the level of 25(OH)D at ≤30 ng/mL. The daily dosage has increased from 400 to 2,000 IU per day to maintain normal levels. However, an adequate maintenance dose is required to prevent recurrent deficiency, irrespective of the initial dosage. National Health Service in the United Kingdom has recommended a daily dose ranging between 800 to 2,000 IU per day but opined to raise the dose up to 4,000 IU daily. However, the study supported the fact that supplementation is the only source of vitamin D, and obese individuals require 2 to 3 times higher doses compared to individuals with normal weight.[65] Table 3 shows the recommended doses of vitamin D by different societies and official bodies.

Based on several studies, it has been suggested that vitamin D deficiency is defined as 25(OH)D below 20 ng/mL, insufficiency as 25(OH)D of 21 to 29 ng/mL, and sufficiency as a level of 25(OH)D of 30 to 100 ng/mL.[22] Figure 1 gives an algorithm giving a step-by-step approach to assessing and managing vitamin D deficiency.

7 Ds of Vitamin D Supplementation

Demand

- Vitamin D deficiency has assumed pandemic proportions.
- Indian studies show prevalence ranging from 50% to 94%.

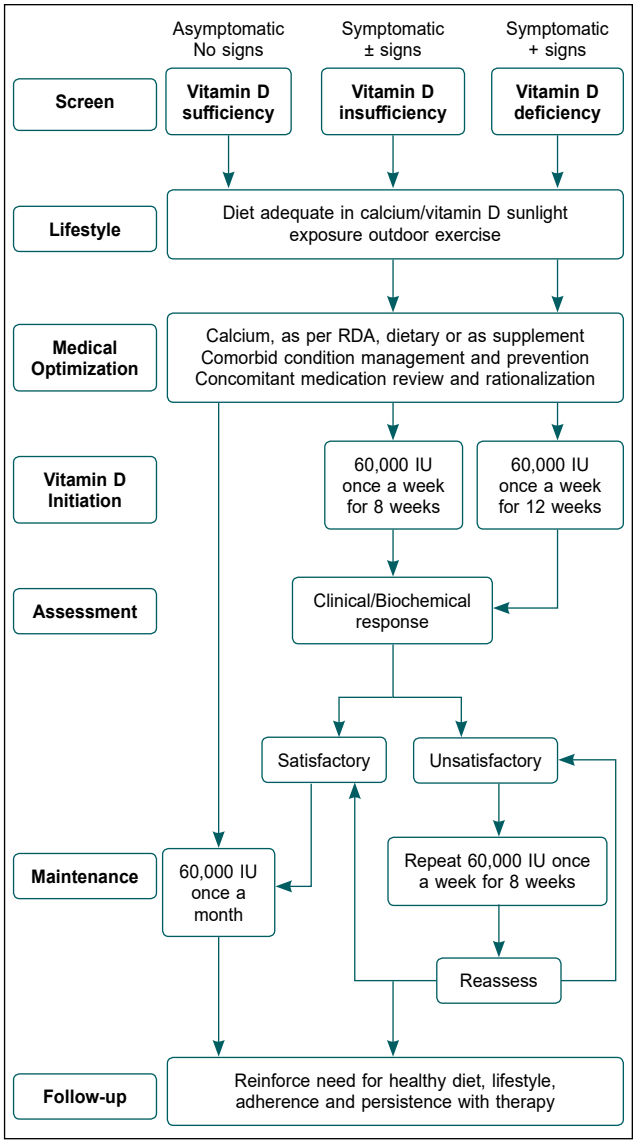

Figure 1. The clinical approach to managing individuals with vitamin D insufficiency.

- India is a heliophobic country leading to an inadequate exposure to sunlight, resulting in insufficient levels of vitamin D.
- Vitamin D deficiency has been implied in multiple systems; cardiometabolic disorders, essential for bone health in children and adults, and MOAN syndrome.
- Included in WHO Model List of Medicines 2021 and National List of Essential Medicines 2022.

Dosage

- Asymptomatic individuals: 800 to 2,000 IU per day.
- Symptomatic, vitamin D insufficient: Up to 60,000 once a week.

- Symptomatic, vitamin D deficient: Up to 60,000 IU once a week.

Duration

- Asymptomatic individuals: 800 to 2000 IU per day.
- Symptomatic vitamin D insufficient: Up to 60,000 IU
  - Initiation dose: Once a week for 8 weeks
  - If unsatisfactory, once a week for 8 weeks
  - Maintenance dose: Up to 60,000 IU, once a month.
- Symptomatic vitamin D deficient: Up to 60,000 IU
  - Initiation dose: Once a week for 12 weeks
  - If unsatisfactory, once a week for 8 weeks
  - Maintenance dose: Up to 60,000 IU, once a month.

Dynamics

- The recommendation for supplementation should be indication based.
- Vitamin D supplementation dependent on season, age, body weight and other risk factors including susceptible individuals including elderly >65 years, hospitalized individuals, women planning pregnancy and in patients with osteoporosis with an increased risk of falls. *OR*
- Patient should be referred for vitamin D supplementation
  - Lack of improvement
  - Malabsorption
  - Hypercalcemia
  - Associated kidney disease or hepatic disease
  - In individuals post-bariatric surgery.

Delivery

- Available in the form of tablet, capsules, soft gel capsules and syrups.
- Preferred drug formulation may be customized based on ease of administration and the patient compliance.

Desirability

- In the general population, desired serum levels following supplementation with initiation and maintenance dose should be 40 to 60 ng/mL.
- Vitamin D insufficient levels: ≥20 to <30 ng/mL.
- Vitamin D deficient levels: <20 ng/mL.

Direction

- Education and awareness of general practitioners on vitamin D deficiency
  - Desired serum levels, recommendations for indications, loading and maintenance dosages needed.
  - Reinforce need for healthy diet, lifestyle, adherence and persistence with therapy.
- Public awareness about
  - Importance of sunlight exposure for vitamin D production.
  - Lifestyle factors, diet, vitamin D-fortified food.
  - Vitamin D supplements availability, required dosage and formulations.

AWARENESS OF VITAMIN D DEFICIENCY

It is known that a lack of knowledge and awareness of vitamin D deficiency acts as a potential risk factor for vitamin D deficiency.[66] A study on children showed that most individuals with vitamin D deficiency are unaware of vitamin D sources.[67] There is a need for an improved campaign for awareness, knowledge and attitudes regarding vitamin D.

Several factors work at the heart of a successful eradication program. In case of vitamin D deficiency, it can be integrated with other programs running under the Ministry of Health and Family Welfare, such as maternal and child health programs (Janani-Shishu Suraksha Yojana, Janani Suraksha Yojana, Pradhan Mantri Surakshit Matritva Abhiyan, etc.), national program for health care of the elderly and noncommunicable disease control programs. Health care professionals need educational programs to create awareness about vitamin D assessment and supplementation.

CONCLUSION

Vitamin D deficiency could be symptomatic or subclinical, with a continuously rising prevalence. Hence, there is a clear need to educate the public and health care professionals about the prevention of deficiency through supplementation, diagnosis through targeted testing, especially in high-risk individuals, and adequate treatment, maintenance and monitoring.

Vitamin D is implicated in bone health, attributing to increased fractures and susceptibility to falls in individuals who are vitamin D deficient. Unarguably, vitamin D has also emerged as an independent risk factor for various CVDs, including MI and coronary heart disease.

Considering vitamin D prevalence in the general population and its clinical manifestations, we recommend the following dosage and duration of vitamin D: (a) Asymptomatic individuals – 800 to 2,000 IU per day, or 60,000 IU once every 30 days. (b) Symptomatic vitamin D insufficient – Up to 60,000 IU - initiation dose is once a week for 8 weeks and maintenance dose up to 60,000 IU, once a month. (c) Symptomatic vitamin D deficient – Up to 60,000 IU - initiation dose is once a week for 12 weeks and maintenance dose up to 60,000 IU, once a month.

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CLINICAL STUDY

An Open-label Prospective Noncomparative Clinical Study to Evaluate the Efficacy and Safety of Beliv: An Ayurvedic Medicine in Improving Liver Function

NARESH SAMUDRALA

ABSTRACT

An open-label prospective noncomparative study was conducted to examine the efficacy and safety of Beliv tablet, a polyherbal Ayurvedic medicine, in 30 adult patients suffering from liver disorders. Two tablets were administered daily for 56 days. Patients were evaluated at Day 0, Day 21, Day 42 and at Day 56. The primary end point of the study was a change in liver function test parameters measured by the levels of serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT) and total bilirubin at all assessment points. Results showed a significant reduction in the serum levels of SGOT, SGPT and total bilirubin from baseline to 21 days, 42 days and 56 days. The total icterus symptom score was also significantly reduced from 5.17 ± 2.26 (baseline) to 2.6 ± 1.48, 1.37 ± 1.13 and 0.77 ± 0.73 at Days 21, 42 and 56, respectively. The Subjective Global Assessment (SGA) decreased significantly from 3.33 ± 1.16 (Day 21) to 2.33 ± 1.16 and 1.80 ± 0.76 at Days 42 and 56, respectively. The Physician Global Assessment (PGA) score was also significantly reduced from 3.0 ± 1.02 (Day 21) to 2.07 ± 0.83 and 1.70 ± 0.79 at Days 42 and 56, respectively. A significant reduction in serum creatinine level was observed at Day 56. No adverse effects or serious adverse effects were observed during the study period. The study concluded that Beliv tablet was highly effective for the treatment of liver disorders, as evidenced by the reduction in serum levels of SGOT, SGPT, total bilirubin, icterus symptoms and PGA and SGA scores. No treatment-related side effects were reported by any of the study participants suggesting that it was safe for clinical use in humans for the treatment of liver disorders.

Keywords: Liver disorders, liver function tests, SGA score, PGA score, icterus symptom score

The liver is one of the largest organs in the human body, performing a variety of vital functions including metabolism, immunity, digestion, detoxification and vitamin storage.[1] Annually, approximately 2 million people die as a result of liver diseases worldwide.[1] Herbal products for liver disease have been used for a long time in India even though their therapeutic use has received considerable attention only recently.[2] In Indian systems of medicine, there are over 300 formulations for the treatment of jaundice and chronic liver diseases, and over 87 medicinal plants are used in various combinations for liver diseases.[3] Despite the significant numbers of preclinical studies, there is a lack of clinical trials and toxicological data on these plant products. Beliv is a polyherbal formulation. The constituent herbs include *Phyllanthus niruri, Tinospora cordifolia, Picrorhiza kurroa, Azadirachta indica, Eclipta alba, Boerhaavia diffusa, Andrographis paniculata* and *Aloe barbadensis*. The purpose of this phase IV post-marketing prospective study was to evaluate the safety and efficacy of the Beliv tablet in 30 adult volunteers suffering from liver disorders.

METHODS

This was a noncomparative open-label, single-arm clinical study for evaluating the efficacy and safety of Beliv tablets in subjects with mild to moderate liver dysfunction recruited from the outpatient clinics of the study center during their routine examination visit.

Male and female adults between the aged of 18 and 50 with abnormal liver function tests, based on

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complete medical history, physical examination and other laboratory tests, subjects with elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ≥1.5 times the upper limit of normal (ULN), subjects without life-threatening conditions and those who were willing to sign consent forms and were able to be present for follow-ups were included in the study.

The exclusion criteria were pregnant women or women with childbearing potential who were likely to be pregnant, subjects with severe alcoholic hepatitis with cirrhosis of liver or life expectancy less than 3 months or those with a history of severe renal failure (estimated glomerular filtration [eGFR] <60 mL/min per 1.73 m^2), liver disorders from cardiac causes, hereditary metabolic causes, hemochromatosis and Wilson's diseases or any other condition that, in the investigator's opinion, would adversely affect the ability of the subject to complete the study or its measurements. Subjects who had participated in another clinical trial with an active intervention or drug or device with the last dose taken within 60 days were also not included in the trial.

No concomitant medication was allowed during the study. However, if participants reported any clinical symptoms during the study, the study physician prescribed the appropriate medication, which was documented.

The primary end point of the study was a change in liver function test parameters from baseline to the end of the study measured by the levels of serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT) and total bilirubin at all assessment points.

The secondary end points were:

- Change in icterus sign and symptom scores from baseline to end of treatment using a predefined 4-point scale.
- Change in Subjective Global Assessment (SGA) scores from baseline to end of treatment using a predefined 5-point scale.
- Change in Physician's Global Assessment (PGA) scores from baseline to end of treatment using a predefined 5-point scale.
- Change in general health symptoms, vital signs, hematology, renal function, serum lipids and urinalysis parameters from baseline to end of treatment.

After baseline assessment at Visit 1, 30 patients were administered two Beliv tablets per day for 56 days. They were evaluated at 4 assessment points: baseline (Visit 1, Day 0), follow-ups (Visits 2 and 3, Days 21 and 42, respectively) and final (Visit 4, Day 56) visits. Informed consent was obtained from all participants at Visit 1 (Day 0). The study was carried out according to the Declaration of Helsinki, Indian Council of Medical Research (ICMR) ethical guidelines for biomedical research and International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP).

At Visit 1 (Day 0), all subjects were assessed for baseline data, including physical examinations, vital signs, demographic data, medical histories, concomitant medications, efficacy and safety parameters.

After 3 weeks of treatment, all subjects underwent physical examination at follow-up visits and were assessed for vital signs, liver function test, icterus sign and symptoms, PGA and SGA scores, concomitant medications and adverse events. At the final follow-up visit, patients underwent tests for complete blood count (CBC), kidney function test (KFT), lipid profile and urine analysis.

Data were abstracted and presented as a number, percentage, mean and standard deviation (SD). All efficacy and safety variables were summarized using descriptive statistics. Data comparison between baseline and follow-up visits was performed using a paired *t*-test or one-way analysis of variance (ANOVA), as appropriate and data were expressed as mean, SD, 95% confidence interval (CI) and p-value. A p value of 0.05 was considered statistically significant.

RESULTS

A total of 30 subjects were enrolled in the study, which included 19 (63.33%) females and 11 (36.37%) males.

All of them completed the study; hence, the data of 30 subjects was analyzed for this study. The demographic information of the participants is summarized in Table 1.

Table 1. Summary of Demographic Data of the Subjects (n = 30)

Parameters	Range	Number (%)	Mean	SD
Age (year)	21-50	-	36.33	8.34
Male	-	11 (36.37)	-	-
Female	-	19 (63.33)	-	-
Height (cm)	146-180	-	164.10	8.62
Weight (kg)	50.10-86.50	-	65.35	8.58

Table 2. Comparison of Mean Change in Liver Function Parameters from Baseline to Different Follow-up Visits

Parameters	Visit (V)	Mean ± SD (n = 30)	Change from V1 (mean ± SD)	95% CI of Diff.	P value
SGOT (IU/L)	V1	124.20 ± 26.55	-	-	<0.0001***
	V2	92.03 ± 18.79	32.22 ± 15.17	20.33-44.10	
	V3	64.17 ± 8.99	60.08 ± 24.12	48.19-71.96	
	V4	32.69 ± 6.12	91.56 ± 26.38	79.68-103.4	
SGPT (IU/L)	V1	109.0 ± 20.79	-	-	<0.0001***
	V2	83.38 ± 11.46	25.60 ± 14.63	16.78-34.43	
	V3	58.21 ± 5.83	50.77 ± 19.75	41.95-59.60	
	V4	30.92 ± 7.16	78.06 ± 23.14	69.24-86.89	
Total bilirubin (mg/dL)	V1	1.06 ± 0.38	-	-	<0.0001***
	V2	0.79 ± 0.17	0.27 ± 0.27	0.10-0.445	
	V3	0.64 ± 0.14	0.42 ± 0.35	0.24-0.593	
	V4	0.55 ± 0.20	0.47 ± 0.50	0.302-0.647	

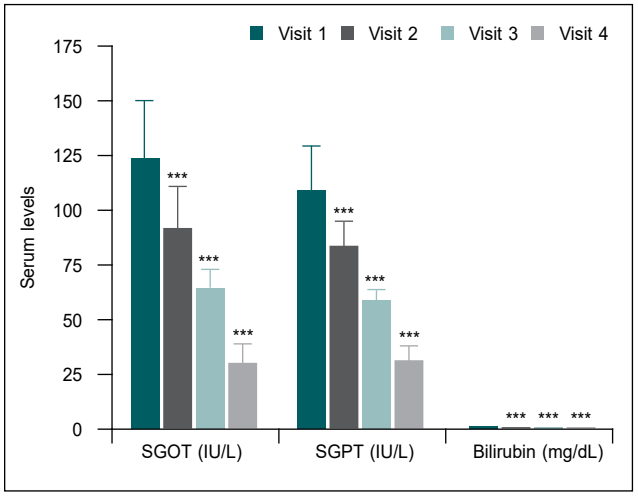

Figure 1. Comparison of mean change in liver function parameters at different visits.

Liver function parameters at baseline (V1) were compared with follow-up visits (V2, V3 and V4) using a one-way ANOVA test. Comparison: V1 vs. V2, V3 and V4. Significance level ***p < 0.001.

Efficacy Assessment

Assessment of liver function

Results showed a significant reduction in the serum levels of SGOT, SGPT and total bilirubin from baseline (V1) to 21 days (V2), 42 days (V3) and 56 days (V4). Changes were found to be statistically significant ($p < 0.0001$) compared to the baseline (Table 2 and Fig. 1).

Assessment of icterus symptoms

Icterus symptoms such as fatigue, loss of appetite, itching, nausea/vomiting were assessed on a 4-point scale at all assessment points. All icterus symptom scores were significantly ($p < 0.0001$) reduced at Days 21 (follow-up visit), 42 (follow-up visit) and 56 (final study visit) compared to baseline (Table 3 and Fig. 2). The total icterus symptom score was also significantly reduced from 5.17 ± 2.26 (baseline) to 2.6 ± 1.48, 1.37 ± 1.13 and 0.77 ± 0.73 at Days 21, 42 and 56, respectively.

Assessment of SGA and PGA

When compared to Day 21, both the SGA and PGA scores were significantly ($p < 0.0001$) lower on Days 42 (follow-up visit) and 56 (final study visit) (Table 4 and Fig. 3). The SGA score decreased significantly from 3.33 ± 1.16 (Day 21) to 2.33 ± 1.16 and 1.80 ± 0.76 at Days 42 and 56, respectively. The PGA score was also significantly reduced from 3.0 ± 1.02 (Day 21) to 2.07 ± 0.83 and 1.70 ± 0.79 at Days 42 and 56, respectively.

Assessment of other symptoms

Other liver disorder-related symptoms, such as fever, abdominal pain, flu-like symptoms, change in skin color, dark-colored urine and clay-colored stool, were also monitored at all assessment points during the treatment period. At baseline, some subjects experienced fever (4, 13.33%), abdominal pain (3, 10%), flu-like symptoms (2, 6.67%), change in skin color (2, 6.67%), dark-colored urine (3, 10%) and clay-colored stools (6, 20%) (Table 5). After 21 days of treatment, only 1 subject (3.33%) had a change in skin color, and 4 subjects (13.33%) had clay-colored stools.

However, none of the above-mentioned symptoms were observed after 42 and 56 days of treatment with Beliv.

Table 3. Comparison of Mean Change in Icterus Symptom Scores on a 4-Point Scale from Baseline to Different Follow-up Visits (n = 30)

Parameters	Visit (V)	Mean score (mean ± SD)	Change from V1 (mean ± SD)	95% CI of Diff.
Fatigue	V1	1.23 ± 0.77	-	-
	V2	0.77 ± 0.68	0.47 ± 0.57**	0.0709-0.862
	V3	0.50 ± 0.63	0.73 ± 0.78***	0.338-1.129
	V4	0.27 ± 0.45	0.97 ± 0.81***	0.571-1.362
Loss of appetite	V1	1.23 ± 0.94	-	-
	V2	0.67 ± 0.66	0.57 ± 0.63**	0.171-0.963
	V3	0.33 ± 0.48	0.90 ± 0.84***	0.504-1.296
	V4	0.13 ± 0.35	1.10 ± 0.96***	0.704-1.496
Itching	V1	0.87 ± 0.78	-	-
	V2	0.43 ± 0.50	0.43 ± 0.68*	0.093-0.773
	V3	0.27 ± 0.45	0.60 ± 0.77***	0.260-0.940
	V4	0.20 ± 0.41	0.67 ± 0.92***	0.327-1.007
Nausea/vomiting	V1	1.83 ± 1.05	-	-
	V2	0.73 ± 0.69	1.10 ± 0.96***	0.673-1.527
	V3	0.27 ± 0.45	1.57 ± 1.07***	1.139-1.994
	V4	0.17 ± 0.38	1.67 ± 1.15***	1.239-2.094
Total score	V1	5.17 ± 2.26	-	-
	V2	2.60 ± 1.48	2.57 ± 1.50***	1.904-3.830
	V3	1.37 ± 1.13	3.80 ± 2.11***	2.837-4.763
	V4	0.77 ± 0.73	4.40 ± 2.30***	3.437-5.363

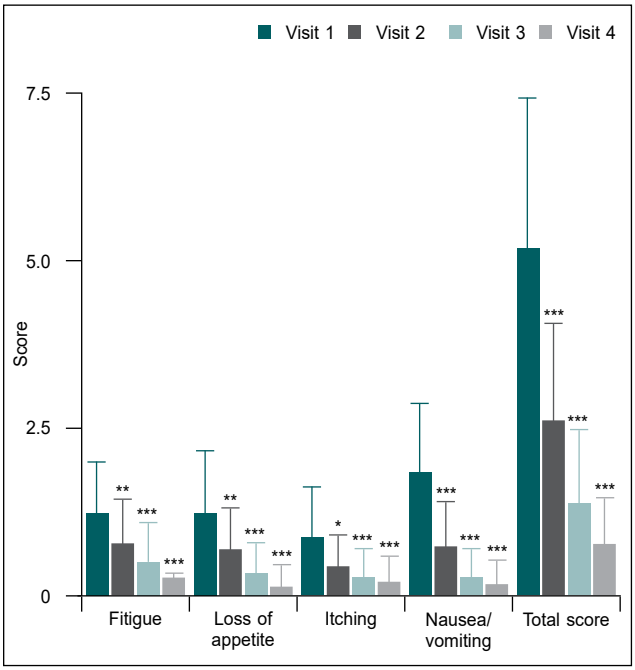

Figure 2. Comparison of mean change in icterus symptom scores from baseline (V1) to different follow-up visits (n = 30).

Icterus symptom scores at V1 were compared with follow-up visits (V2, V3 and V4) using one-way ANOVA. Comparison: V1 vs. V2, V3 and V4. Significance levels *p < 0.05, **p < 0.01 and ***p < 0.001.

Table 4. Comparison of Mean Change in SGA and PGA Scores from Day 21 to Days 42 and 56

Parameters	Visit (V)	Mean ± SD (n = 30)	Change from V1 (mean ± SD)	95% CI of Diff.	P value
SGA	V2	3.33 ± 1.16	-	-	<0.0001***
	V3	2.33 ± 1.16	0.93 ± 0.64	0.396-1.604	
	V4	1.80 ± 0.76	1.53 ± 0.82	0.929-2.137	
PGA	V2	3.0 ± 1.02	-	-	<0.0001***
	V3	2.07 ± 0.83	0.93 ± 0.64	0.419-1.447	
	V4	1.70 ± 0.79	1.30 ± 1.24	0.786-1.814	

Safety Assessment

Assessment of general health symptoms

No abnormalities were observed in the subjects' general appearance, eyes, ear, nose, throat, abdomen, heart, chest and ECG profile during all study visits.

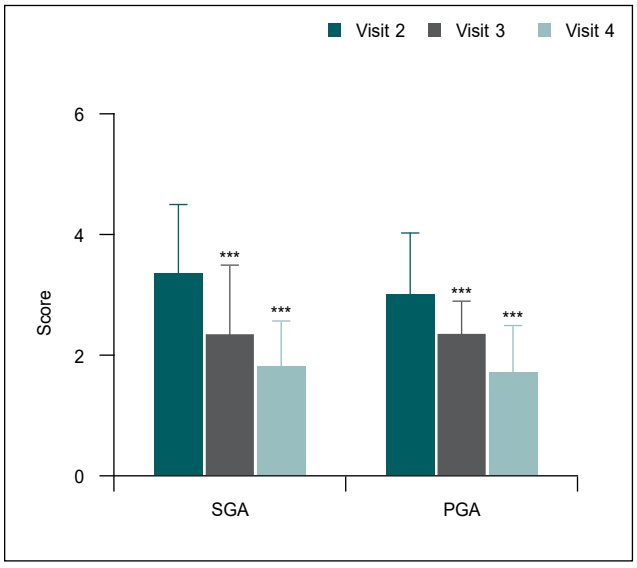

Figure 3. Comparison of mean change in SGA and PGA scores from Day 21 (V2) to Days 42 (V3) and 56 (V4) (n = 30).

SGA and PGA scores in V2 were compared with V3 and V4 using the one-way ANOVA test. Comparison: V2 vs. V3 and V4. Significance level ***p < 0.001.

Table 5. Other Signs/Symptoms of Liver Disorders among the Participants (n = 30)

Other signs/ symptoms	Visit 1 % (n)	Visit 2 % (n)	Visit 3 % (n)	Visit 4 % (n)
Fever	13.33 (4)	0	0	0
Abdominal pain	10 (3)	0	0	0
Flu-like symptoms	6.67 (2)	0	0	0
Change in skin color	6.67 (2)	3.33 (1)	0	0
Dark-colored urine	10 (3)	0	0	0
Clay-colored stool	20 (6)	13.33 (4)	0	0

Assessment of vital signs

All subjects' vital sign parameters, including heart rate, systolic and diastolic blood pressure, were measured at all assessment points. The baseline vital signs data were compared to the day obtained on Day 21, Day 42 and Day 56. No significant differences in vital signs were observed all through the treatment period (Table 6 and Fig. 4).

Assessment of complete blood profile

CBP was evaluated at the screening (V1) and end of the study (V4). There was no significant difference in the CBP parameters between screening and Day 56 data, and all values were within the normal range (Table 7 and Fig. 5).

Table 6. Comparison of Mean Change in Vital Signs from Baseline to Different Follow-up Visits

Parameters	Visit (V)	Mean ± SD (n = 30)	Change from V1 (mean ± SD)	95% CI of Diff.	P value
Heart rate (bpm)	V1	67.37 ± 6.37	-	-	0.459
	V2	65.53 ± 4.64	1.33 ± 5.42	-1.665 to 5.332	
	V3	66.47 ± 4.49	0.90 ± 4.16	-2.599 to 4.399	
	V4	67.30 ± 4.44	0.07 ± 5.56	-3.432 to 3.565	
SBP (mm/Hg)	V1	120.3 ± 7.18	-	-	0.877
	V2	121.0 ± 6.99	-0.67 ± 4.71	-5.482 to 4.149	
	V3	120.0 ± 6.74	0.33 ± 4.25	-4.482 to 5.149	
	V4	119.6 ± 6.87	0.77 ± 4.99	-4.049 to 5.582	
DBP (mm/Hg)	V1	79.20 ± 2.94	-	-	0.463
	V2	79.60 ± 2.85	-0.40 ± 2.27	-2.412 to 1.612	
	V3	78.77 ± 3.18	0.43 ± 3.37	-1.579 to 2.446	
	V4	79.90 ± 2.62	-0.70 ± 3.57	-2.712 to 1.312	

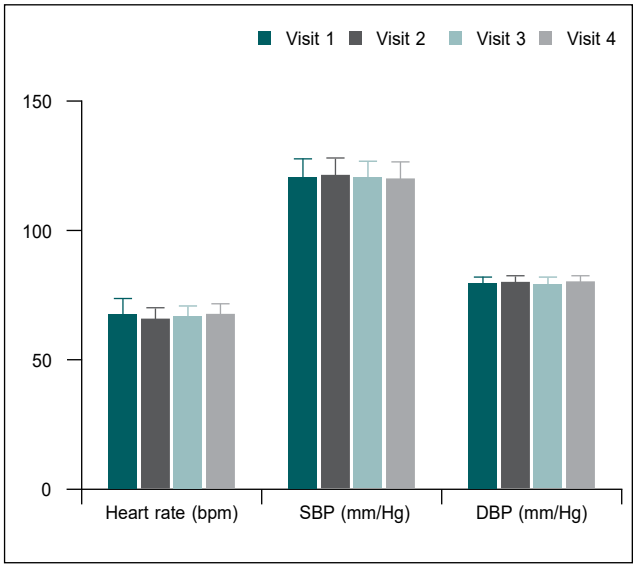

Figure 4. Comparison of mean change in vital signs from baseline to different follow-up visits (n = 30).

Vital signs data at baseline (V1) were compared to Days 21 (V2), 42 (V3) and 56 (V4) using the one-way ANOVA test. Comparison: V1 vs. V2, V3 and V4.

Table 7. Comparison of Mean Change in CBP Parameters from Screening to Day 56

Parameters	Visit (V1)	Mean ± SD (n = 30)	Change from V1 (mean ± SD)	95% CI of Diff.	P value
RBC (millions/cumm)	V1	5.28 ± 0.34	-0.06 ± 0.37	-0.200-0.0768	0.370
	V4	5.34 ± 0.47			
Hb (g/dL)	V1	13.53 ± 1.47	-0.13 ± 1.05	-0.526-0.260	0.495
	V4	13.67 ± 1.18			
WBC (10^9/L)	V1	7.37 ± 0.96	0.18 ± 0.71	-0.086-0.443	0.179
	V4	7.37 ± 0.51			
Neutrophils (%)	V1	51.21 ± 5.86	0.47 ± 4.21	-1.102-2.040	0.546
	V4	50.74 ± 4.23			
Lymphocytes (%)	V1	36.78 ± 5.71	-0.72 ± 4.25	-2.306-0.868	0.362
	V4	37.50 ± 3.92			
Monocytes (%)	V1	7.44 ± 1.02	0.14 ± 0.83	-0.172-0.446	0.373
	V4	7.31 ± 0.78			
Eosinophils (%)	V1	3.96 ± 1.06	0.07 ± 0.93	-0.275-0.422	0.70
	V4	3.89 ± 0.97			
Basophils (%)	V1	0.60 ± 0.20	0.04 ± 0.19	-0.030-0.110	0.26
	V4	0.56 ± 0.14			
Platelet count (x1000/cumm)	V1	336.7 ± 50.27	-0.37 ± 18.61	-7.315-6.582	0.91
	V4	337.1 ± 51.45			
ESR (mm 1st hour)	V1	21.33 ± 11.26	-0.47 ± 5.51	-2.525-1.592	0.646
	V4	21.80 ± 8.06			

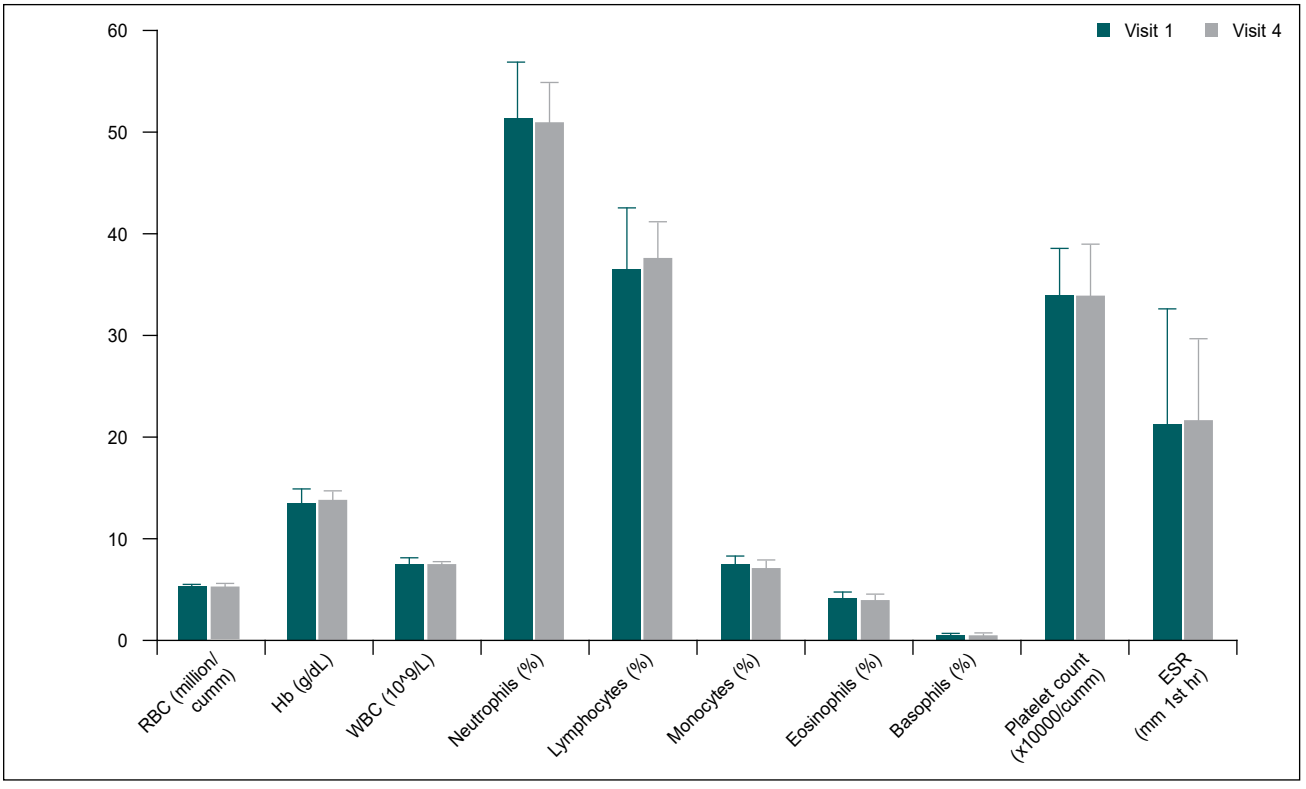

Figure 5. Comparison of mean change in CBP parameters from screening to Day 56 (n = 30).

CBP parameters at screening (V1) were compared to Day 56 (V4) using paired *t*-test. Comparison: V1 vs. V4.

Assessment of renal function

Serum levels of blood urea nitrogen (BUN) and creatinine were measured at baseline and Day 56 to assess renal function. The serum levels of BUN and creatinine were in the normal range at both assessment points, but the reduction in serum creatinine level at Day 56 was statistically significant ($p < 0.05$) (Table 8 and Fig. 6).

Assessment of Serum Lipids

Serum cholesterols, including total cholesterol, triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL) cholesterols, as well as the Chol:HDL ratio, were measured at baseline and Day 56. The serum levels of total cholesterol, TG, LDL, VLDL cholesterols, and the Chol:HDL ratio were reduced and HDL increased at Day 56 when compared to baseline (Table 9 and Fig. 7).

Table 8. Comparison of Mean Change in Renal Function Parameters from Baseline to Day 56

Parameters	Visit (V)	Mean ± SD (n = 30)	Change from V1 (mean ± SD)	95% CI of Diff.	P value
BUN (mg/dL)	V1	11.18 ± 3.65	0.45 ± 4.53	-1.236-2.143	0.587
	V4	10.73 ± 2.94			
Serum creatinine (mg/dL)	V1	0.94 ± 0.25	-0.13 ± 0.32	0.0116-0.250	0.033*
	V4	0.81 ± 0.17			

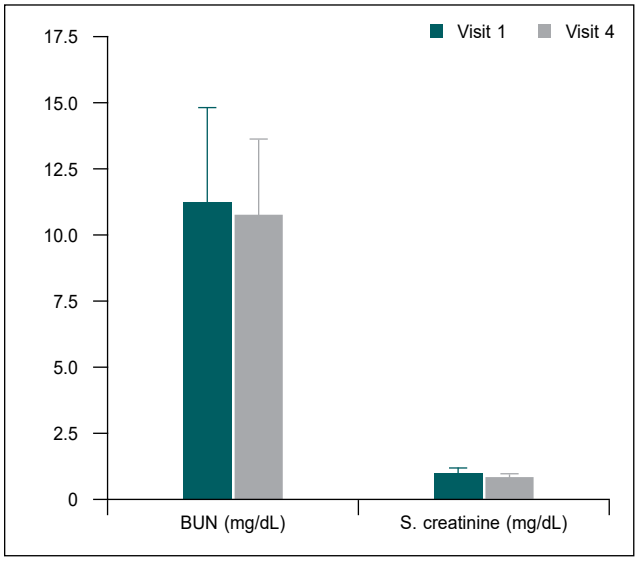

Figure 6. Comparison of mean change in renal function parameters from the baseline (V1) to the Day 56 (V4) (n = 30).

Renal function parameters at baseline (V1) were compared with Day 56 (V4) using the paired *t*-test. Comparison: V1 vs. V4. Significance level *$p < 0.05$.

Table 9. Comparison of Mean Change in Serum Lipids from Baseline to Day 56

Parameters	Visit (V)	Mean ± SD (n = 30)	Change from V1 (mean ± SD)	95% CI of Diff.	P value
Total cholesterol (mg/dL)	V1	164.3 ± 28.44	10.39 ± 13.25	5.443-15.34	0.0002***
	V4	153.9 ± 22.91			
TG (mg/dL)	V1	109.50 ± 30.21	10.95 ± 11.40	6.692-15.20	<0.0001***
	V4	98.55 ± 24.17			
HDL (mg/dL)	V1	67.09 ± 4.03	5.78 ± 10.97	1.681-9.873	0.0073**
	V4	70.45 ± 3.44			
LDL (mg/dL)	V1	94.10 ± 17.34	4.68 ± 19.22	-2.496-11.86	0.193
	V4	89.42 ± 11.14			
VLDL (mg/dL)	V1	28.46 ± 7.33	3.09 ± 8.86	-0.217-6.401	0.066
	V4	25.37 ± 4.38			
Chol:HDL ratio (mg/dL)	V1	2.46 ± 0.45	-0.075 ± 0.58	-0.290-0.141	0.484
	V4	2.19 ± 0.35			

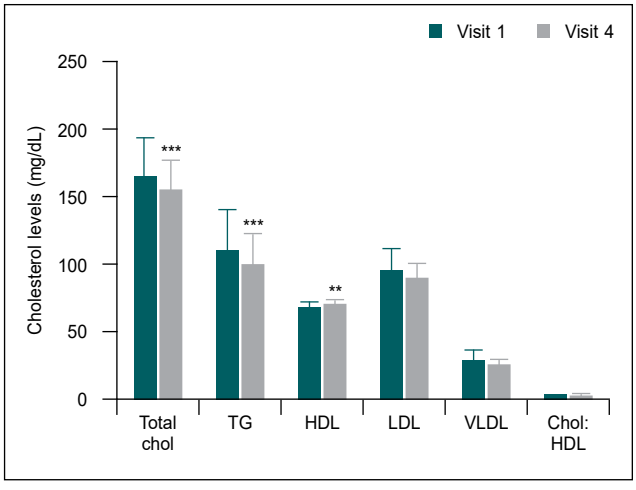

Figure 7. Comparison of mean change in serum lipids from the baseline to Day 56 (n = 30).

Serum lipid parameters at baseline (V1) were compared with Day 56 (V4) using the paired *t*-test. Comparison: V1 vs. V4. Significance levels **$p < 0.01$ and ***$p < 0.001$.

Despite the fact that all serum cholesterol levels were within the normal range, there was a statistically significant change in total cholesterol, TG and HDL levels from baseline.

Urinalysis

Urine analysis of all participants was performed at baseline and Day 56. Urinalysis parameters showed no significant difference between two evaluation points.

Adverse events

No adverse effects or serious adverse effects were observed during the study period. However, three participants at Visit 2, two participants at Visits 3 and 4 experienced mild abdominal discomfort; however, this effect was not related to Beliv treatment.

REVIEW OF LITERATURE

Beliv is a polyherbal formulation, which has been used to treat various liver disorders. It contains *T. cordifolia, P. kurroa, A. indica, E. alba, B. diffusa, A. paniculata, A. barbadensis* and *P. niruri*, which have been shown to be hepatoprotective in studies. These herbs also have anti-inflammatory, antimicrobial, antiviral, antiparasitic, antidiabetic, immunomodulator activity, antioxidant and antitumor properties, which are complementary to the hepatoprotective activity and are desirable in hepatic disorders.

The hepatoprotective property of *T. cordifolia,* commonly known as Giloy, was examined in an experimental study in hepatic damage caused by carbon tetrachloride (CCl_4). The liver enzymes (SGPT, SGOT, serum alkaline phosphatase [ALP]) and serum bilirubin returned to normal levels following administration of extract of *T. cordifolia*.[4] It also exhibited antifibrotic effect in liver injury models, which has been hypothesized to occur via activation of Kupffer cells, the liver macrophages.[5]

In another study of an animal model of lead-induced liver injury, the aqueous extracts of stem and leaves of *T. cordifolia* lowered the levels of transaminases and ALP and increased the antioxidant enzymes superoxide dismutase and catalase.[6]

Administration of hydroalcoholic extract of Kutki or *P. kurroa* for 4 weeks led to reversal of the fatty infiltration in a study of experimental nonalcoholic fatty liver disease (NAFLD). The liver fat content also reduced - 38.33 for 200 mg/kg and 29.44 for 400 mg/kg of *P. kurroa* compared to 130.07 mg/g of liver tissue in the high-fat diet group.[7] In a randomized placebo-controlled trial, patients with acute viral hepatitis (HBsAg negative) were treated with the root powder of *P. kurroa* in doses of 375 mg thrice a day for 2 weeks. A significant decrease in liver enzymes (SGPT 86 IU vs. 221 IU; SGOT 44 IU vs. 83 IU) and total serum bilirubin (4.15 mg/dL vs. 6.78 mg/dL) was seen compared to placebo. A rapid and marked improvement in symptoms of anorexia, nausea and malaise was also noted.[8] *P. kurroa* has been shown to reduce the ethanol-induced oxidative stress because of its antioxidant activity.[9]

The hepatoprotective activity of *A. indica*, commonly called Neem, has been demonstrated in a study of paracetamol-induced liver damage in rats and has been attributed to its antioxidant activity as evident by the increase in the levels of glutathione-dependent enzymes in the liver and activity of superoxide dismutase and catalase.[10,11] The leaf extract of *A. indica* ameliorated the hepatotoxicity induced by antitubercular drugs in rats.[12,13]

B. diffusa or punarnava has been widely used for its hepatoprotective property.[14] In a preclinical study, oral administration of an alcoholic extract of the whole plant improved the levels of serum ALT, TGs, cholesterol and total lipid in CCl_4-induced hepatotoxicity. Enhancement in normal bile flow was indicative of a strong choleretic activity.[15] It is also protective against paracetamol- and ethanol-induced hepatotoxicity.[16]

A. barbadensis or *Aloe vera* has been called the "miracle plant" because of its multitude of beneficial actions. It contains enzymes that aid digestion and functions of the liver such as detoxification.[17] Several animal model studies have suggested its hepatoprotective and antifibrotic effects.[18] In mice fed a high-fat and fructose diet, *A. vera* significantly reduced the levels of cholesterol and improved the activities of superoxide dismutase and catalase indicative of the antioxidant effects of *A. vera*.[19]

The antihepatotoxic, antilithic, anti-HIV and anti-hepatitis B properties of *P. niruri* have been explored in literature.[20] The aqueous extracts of the herb has been demonstrated to have radical scavenging activity including hepatoprotective activity. It also has protective effect against paracetamol-induced hepatotoxicity.[21] The efficacy of *P. niruri* in patients with mild to moderate alcoholic hepatitis was evaluated in a randomized, double-blind, parallel-arm placebo-controlled trial. After 4 weeks of treatment with *P. niruri*, an improvement in the total antioxidant levels was observed. It also increased the appetite. The liver function parameters showed an improvement, but this was not statistically significant.[22]

The extract of *E. alba* or Bhringraj was protective against CCl_4-induced acute liver damage and paracetamol-induced hepatotoxicity in animal studies.[23] Luteolin, wedelolactone and apigenin are the three major active phytoconstituents of the herb. These compounds have been shown to *in vitro* inhibit RNA-dependent RNA polymerase (RdRp) activity of hepatitis C virus (HCV) replicase; they also exhibited anti-HCV replication activity in cell culture systems thereby reducing the HCV RNA titer. These properties suggest *E. alba* as a potential complementary treatment of hepatitis C.[24] In animals with high-fat diet, *E. alba* reduced mononuclear infiltration, fat deposition and necrotic foci in the liver and also stimulated hepatocyte regeneration.[25]

Similar to the above-mentioned herbs, *A. paniculata* or Kalmegh was also protective against hepatotoxicity induced by CCl_4, paracetamol and ethanol. This hepatoprotective activity was exerted via andrographolide, its major antihepatotoxic component.[26] In patients with infective hepatitis, Kalmegh administered as a decoction improved the symptoms and liver biochemistry by reducing levels of serum bilirubin, ALP and the serum aminotransferases (SGOT and SGPT). This led to cure in 80% of the patients.[27] Its antiviral activity has been demonstrated in patients with acute viral hepatitis. A marked improvement in symptoms and liver enzymes was seen in patients receiving Kalmegh compared to the control group; 80.81% vs. 33.46%, respectively after 1 month, which was statistically significant.[28]

CONCLUSION

The results of the present clinical study demonstrated that the polyherbal formulation Beliv is highly effective for the treatment of liver disorders, as evidenced by the reduction in serum levels of SGOT, SGPT, total bilirubin, icterus symptoms and PGA and SGA scores. Furthermore, during the 56-day treatment period, no significant changes in vital signs, hematological profile, lipid profile, renal function or urinalysis parameters were observed. No treatment-related side effects were reported by any of the study participants suggesting that Beliv tablet is highly effective and safe for clinical use in humans for the treatment of liver disorders. All these effective actions are attributed to synergistic actions of its hepatoprotective ingredients.

Conflict of Interest

The author has no conflict of interest.

Disclosures

None.

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CASE REPORT

Milk-Alkali Syndrome: A Century Old Cause of Resurgence of Severe Hypercalcemia Due to Excessive Use of Calcium Supplements

UTSAV SAHU

ABSTRACT

The milk-alkali syndrome (MAS) is characterized by a triad of elevated calcium levels, metabolic alkalosis and acute kidney injury that commonly occurs due to the combined intake of large amounts of calcium and absorbable alkali. The syndrome can have an acute onset with the rapid development of hypercalcemia and, if left untreated, may result in acute renal failure and metastatic calcification. An increased number of cases of MAS have recently been reported. This is likely due to the common use of over the counter (OTC) preparations of calcium for preventing and treating osteoporosis in postmenopausal women. Herein, we report a case of severe hypercalcemia due to prolonged intake of calcium carbonate supplements in the absence of any alkali.

Keywords: Hypercalcemia, renal failure, alkalosis, calcium supplements

The milk-alkali syndrome (MAS) consists of the triad of hypercalcemia, metabolic alkalosis and varying degrees of renal failure associated with the ingestion of large amounts of calcium and absorbable alkali. This syndrome was discovered in the 1930s after treatment of peptic ulcer disease with milk and sodium bicarbonate had become common.[1] Once a classic cause of hypercalcemia, the MAS virtually disappeared with the advent of new therapies of peptic ulcer disease and, by 1985, was considered the cause of <1% of cases of hypercalcemia.[2]

Recently, however, an increased number of cases of MAS have been reported. This is likely due to the common use of over the counter (OTC) calcium preparations for preventing and treating osteoporosis in postmenopausal women. Calcium carbonate is also frequently prescribed to patients with chronic kidney disease to prevent secondary hyperparathyroidism. Various scholars have also suggested changing the syndrome's name to calcium-alkali syndrome due to the changing etiopathology.[3] MAS now accounts for more than 10% of the cases of hypercalcemia and is believed to be the third most common cause of in-hospital hypercalcemia, after hyperparathyroidism and malignant neoplasms.[4]

CASE REPORT

A 71-year-old normotensive, nondiabetic, euthyroid female, presented with confusion, irrelevant talks and urinary incontinence. Her blood pressure (BP) was 160/84 mmHg and random blood sugar (RBS) was 127 mg/dL. Routine blood investigations revealed, hemoglobin - 13.2 g/dL, urea - 103 mg/dL, creatinine - 4.2 mg/dL, total calcium - 14.9 mg/dL, phosphorous - 4.2 mg/dL, albumin - 3.9 g/dL, her arterial blood gas (ABG) showed metabolic alkalosis, with pH of 7.54. She gave history of taking analgesics for joint pains, and supplements of calcium carbonate for osteoporosis for last 20 years.

She was treated with saline diuresis and calcitonin for 2 days, and her symptoms and renal functions started improving. Other investigations revealed thyroid-stimulating hormone (TSH) of 6.2 mIU/mL, 25(OH)-vitamin-D of 40.4 ng/mL and normal serum protein electrophoresis. Despite high serum calcium levels, her parathyroid hormone (PTH) was not suppressed and intact PTH was found to be 46.1 pg/mL. But the ^{99m}TcSestaMIBI scan did not localize any parathyroid adenoma and positron emission tomography-computed tomography (PET-CT) ruled out possibility of any paraneoplastic syndrome.

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On the basis of metabolic alkalosis even in the setting of severe renal dysfunction, and excluding other causes of hypercalcemia, a diagnosis of MAS was made. On further questioning, the patient admitted to perhaps taking more calcium than she should have. But there was no history of any antacid intake. Within a week after admission, her renal functions improved significantly, her blood urea reduced to 50 mg/dL, creatinine to 1.8 mg/dL and total calcium came down to 8.5 mg/dL. The patient was discharged with clear instructions to avoid any calcium carbonate supplements.

DISCUSSION

Despite extensive clinical experience, scant data are available on the pathogenesis of MAS. Throughout the years, several contributing factors have been proposed, including loss of gastric juice, pre-existing renal disease, insufficient chloride intake, hemorrhage, anemia and impaired liver function. Ingestion of excessive quantities of calcium and absorbable alkali is a prerequisite for establishing the diagnosis. What constitutes "excessive" is unclear but generally indicates at least 4 to 5 g of calcium carbonate daily.[5]

For hypercalcemia to develop, calcium intake must be excessive, but inability to excrete the excess calcium is also an essential part of the process. Because the skeletal system does not have unlimited calcium buffer capacity, tight regulation of calcium absorption from the small intestine and excretion by the kidneys are paramount to maintain serum calcium levels. Individual variations in the buffering capacity of bone may also have a role in the susceptibility to development of hypercalcemia.

Increased intake of calcium results in decreased 25-hydroxylation of vitamin D by the kidneys, which leads to a marked decrease of fractional calcium absorption in the small intestine. In certain individuals, high urinary calcium excretion indicative of high intestinal absorption persists despite continuous calcium ingestion and suppressed 1,25-(OH) vitamin D levels. Under normal conditions, renal calcium excretion is a close reflection of calcium absorption. However, if large quantities of calcium are continuously ingested and the renal excretory capacity is blocked, hypercalcemia may be a predictable result. Failure to fully suppress calcitriol levels may contribute to development of MAS in a subset of individuals with high oral calcium intake.[6]

The PTH level should be suppressed by the high serum calcium level in patients with MAS. But in the setting of severe renal dysfunction, PTH level is raised. Renal dysfunction is also associated with metabolic acidosis. But in the setting of MAS, metabolic alkalosis is the essential feature. Differentiating MAS from other causes of hypercalcemia is important as treatment is supportive. Adequate hydration to correct hypovolemia, along with loop diuretics, like furosemide, to increase urinary calcium excretion may be sufficient to correct hypercalcemia. Bisphosphonates should generally be avoided in patients with MAS as they can cause prolonged hypocalcemia.[7]

CONCLUSION

The resurgence of MAS in the current era is a result of increased osteoporosis awareness and routine use of calcium carbonate supplements for prevention. The public needs to be educated about calcium supplementation and the potential adverse effects if the recommended dosage is exceeded. Daily elemental calcium intake of no more than 2 g is considered safe.[8] However, even doses lower than 2 g daily may result in MAS if additional predisposing factors are present.

The exact pathogenesis of MAS remains uncertain, but a unique interplay between hypercalcemia and alkalosis in the kidneys seems to lead to a self-reinforcing cycle, resulting in the clinical picture of MAS. Treatment is supportive and involves hydration and withdrawal of the offending agent. Physicians and the public need to be aware of the potential adverse effects of ingesting excessive amounts of calcium carbonate.

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BRIEF COMMUNICATION

The Traditional Indian Ocean Diet

SANJAY KALRA

ABSTRACT

Dietary advice forms the cornerstone in the management of cardiometabolic disease. Though various national and international guidelines suggest different macronutrient proportions, locally framed person-centric diet prescriptions are likely to have a better compliance. In this article, we propose an indigenous traditional Indian Ocean (TRIO) diet, which constitutes a similar pattern of the dietary practices followed by inhabitants of the Indian Ocean littoral region. The TRIO diet highlights on concepts of procurement, preparation, presentation, prioritization, preservation and partaking and may be a good alternative to the Mediterranean diet followed in western countries.

Keywords: Cardiometabolic disease, person-centric diet prescription, TRIO diet, littoral, Mediterranean diet

BACKGROUND

Metabolic and nutritional diseases are emerging as a major global health care challenge. Diabetes, obesity, hypertension and cardiovascular disease have attained pandemic status, and show no signs of abating.[1] As we try to address these diseases, the role of healthy nutrition is of paramount importance.[2] Though there are myriad definitions of healthy eating, the term 'Mediterranean diet' is often associated with health protection and promotion.

Current guidelines underscore the need for culturally relevant medical nutrition therapy prescriptions for the prevention and management of metabolic disease, including diabetes.[3] While multiple diet patterns are shown to have short-term benefits, the Mediterranean diet is suggested to be one of the most useful diets for long-term health. At the same time, it should be clarified that there is no single dietary plan, which is suited for all people.

THE MEDITERRANEAN DIET

In 2010, UNESCO, defined the Mediterranean diet as a set of skills, knowledges, rituals, symbols and traditions concerning crops, harvesting, fishing, animal husbandry, conservation, processing, cooking and particularly the sharing and consumption of food. Thus, it includes the production, processing and partaking of food.[4]

Modern medicine discovered the benefits of the Mediterranean diet when Ancel Keys conducted the Seven Countries Study in 1958, providing evidence of its cardiovascular advantages.[5,6] Balanced use of fiber-rich, antioxidant-rich, unsaturated fatty acid-rich foods, with a lower proportion of animal fats, characterize the Mediterranean diet. The rough proportion of nutrients is 55% to 60% carbohydrates (of which 80% are complex), 10% to 15% proteins (of which 60% are of animal origin) and 25% to 30% fat (mostly olive oil). Nutritionists and policy makers represent the diet as a Food Pyramid, which includes a variety of foods, in the right proportion, taken in moderation.[7]

From an Afro Asian perspective, one limitation of the Mediterranean diet, is its nomenclature. The name might imply that a foreign diet is better, and must supplant locally grown foodstuffs. An unwarranted emphasis on olive oil, which is not easily available and affordable, nor is it appropriate for the Afro Asian style of cooking, might lead to excessive and unnecessary expenditure on food.

THE TRADITIONAL INDIAN OCEAN (TRIO) DIET

In this communication, we attempt to conceptualize and define an Indian Ocean diet, as an authentic and appropriate, alternative to the Mediterranean diet.

The Indian Ocean diet is a diet that is inspired by, and incorporates, the dietary preferences and habits of the peoples who inhabit the littoral countries of the Indian Ocean. We propose the traditional Indian

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Ocean (TRIO) diet as a healthy option for the prevention and management of metabolic diseases.

We define the TRIO diet as the style and method of meal procurement, preparation, preservation, presentation and partaking, followed by the inhabitants of the Indian Ocean littoral region, which contributes to metabolic and overall health.

The Indian Ocean Littoral Region

The Indian Ocean, the third largest ocean in the world, touches the shores of Africa, the Middle East, South and South East Asia, as well as Australia. Though the inhabitants of this vast region represent a seemingly complex and diverse collection of people they are also united in many ways. Age-old trading and travel links have created a "fusion" of cultures, which has influenced cuisines as well.

In this communication, we define the Indian Ocean littoral region as including all the countries and islands which touch the Indian Ocean or are included in it. The authors represent the following countries: Australia, Bangladesh, Indonesia, India, Iran, Kenya, Malaysia, Maldives, Mauritius, Mozambique, Myanmar, Oman, Pakistan, Singapore, South Africa, Sri Lanka, Tanzania, Ghana, Thailand and the United Arab Emirates.

Cooking and dining are a family affair, and sometimes, even a community affair. The sense of sharing (Ubuntu in South Africa) extends to presenting food and preparing food in joint family kitchens.

Most traditional Indian Ocean littoral cuisines are based upon locally available whole grains (rice, wheat, maize), eaten in various forms. In recent years, the proportion of whole grain consumption, as opposed to refined grain intake, has reduced. This is especially true in island states, which import their cereal requirements.[8]

The cereal is usually consumed with dishes that are made of vegetables, legumes and lentils. Coastal cuisines have a strong presence of fish, seafood and fish products. Meat is an integral part of Indian Ocean littoral states, but is not a major contributor to caloric intake in most cuisines.

Beverages such as water, lemonade, hibiscus juice, kokum juice, coconut water, soup, tea and coffee are a prominent part of the Indian Ocean diet. This is a necessity, due to hot weather that prevails throughout much of the year in the region.

Various means of cooking are used across the region, including boiling, steaming, sautéing, baking and frying. In most settings, economy of fuel and economy are in the interest of parsimony. A wide range of cooking oils is used, as per availability. Coconut oil and palm oil, which are clubbed as 'tropical oils' are used in the eastern Indian Ocean littoral region, while mustard oil, peanut (groundnut) oil and clarified butter (ghee) are used elsewhere.[7]

Mustard oil is a liquid oil that is low in saturated fat and is popular in South Asia. Australia, New Zealand and the European Union (27 countries) have established upper limits for tolerable intake of mustard oil. In contrast mustard oil is one of the most popular cooking oils in Asia, particularly in India where it is recommended as a heart-healthy oil by the Lipid Association of India (LAI). However, the US Food and Drug Administration (FDA) has banned the use of mustard oil for cooking.[9] Fruits are ubiquitous in Indian Ocean diet. Locally available, seasonal fruits are preferred. Some parts of the region, such as the Middle East and South Asia, exhibit a preference for rich (and tasty) desserts.

THE TRADITIONAL INDIAN OCEAN AND MEDITERRANEAN DIET

In most ways, the Indian Ocean diet that we describe is similar to the Mediterranean diet. Reliance on whole grains, vegetables, legumes and fruits is common to both systems. Use of fish is noted in coastal Indian Ocean communities as well as the Mediterranean. Nuts and olive oil, important features of Mediterranean diet, are represented by groundnuts and other cooking oils in the Indian Ocean. Less focus on use of red meat, processed meat and refined cereals is common in both traditional cuisines. Similarly, the concept of an Indian Ocean diet, can be used to create an overarching model that can be customized as per local needs and requirements.

THE HEALTHY TRAY

We suggest the healthy thali (tray) rubric, rather than the pyramid or plate, to represent the Indian Ocean diet.

The healthy tray provides a conceptually practical person-friendly means of representing the food and drink that should be consumed, to the regional population, in order to ensure healthy nutrition and accomplish healthy outcomes. It represents a wholesome and comprehensive method of representing an optimal diet in a person-friendly manner. The healthy tray goes beyond mere nutrition by including culinary science and art in education. The concepts of plating and presentation, along with portion size meal sequencing, can be demonstrated through the tray model.

THE WAY FORWARD

The concept that we share has the potential to become a useful tool for sharing and teaching healthy nutrition. The advantage is its relevance to a vast swathe of the world's population, and the sense of empowerment as well as responsibility that it brings to them. This will hopefully invite more interest, discussion and debate, as well as research in order to achieve this potential. In many countries, the local food is a blend of different cultures. For instance, people from Mauritius enjoy eating locally adapted Chinese cuisine as much as they enjoy Indian cuisine. Blending brings cultural enrichment of existing traditions. However, as much as we are keen to respect our traditions or any associated influences from other cultures, it is our duty to educate our patients on what could be deleterious to their health. For e.g., we may still respect the plating of a particular dish, whilst decreasing the proportion of carbohydrates. Quantity is often overlooked and this issue should be addressed as well. Also, we may still address our food eating behaviors while enjoying the same food without it being harmful to our health. For instance, some studies are advocating for meal sequencing for better metabolic benefits.[10,11]

Table. Components of the TRIO Diet

Procurement/sourcing of food
• Locally grown and available
• Seasonal items
• Fresh food
• Seafood/fish
Preparation
• Local styles of cooking
• Economy in fuel
• Economy in cooking oil
• Addition of locally grown spices
Presentation
• Communal plates
• Moderate/small-sized utensils
Prioritization in meal sequencing and proportions
• Low calorie beverages - water, soups as fillers
• Consumption of protein before carbohydrate
• Reducing the quantum of carbohydrate intake
• Whole fruits as dessert
Preservation
• Preservation of grains, for 6-12 months
• Pickling
• Sun drying
Partaking
• Family meals
• Sharing food with guests/visitors

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China Develops its First mRNA COVID Vaccine

China has approved its indigenously developed mRNA COVID-19 vaccine, according to the CSPC Pharmaceutical Group Ltd increasing its arsenal against future outbreaks. According to the company, the vaccine had significantly lower adverse effects in elderly subjects compared to an adult group. In December last year, China had lifted its zero COVID restrictions and reopened its borders. Since then, the cases have declined… (*Source: Medscape, March 23, 2023*).

Canada Removes COVID Test Requirement for Travelers from China

Canada has joined the list of countries that have removed mandatory COVID testing requirements for travelers from China, Hong Kong and Macao. According to the Health Ministry, this step was taken in view of the improving COVID situation in China… (*Source: Reuters, March 17, 2023*).

LETTER TO EDITOR

Importance of Logistics in Health Care in Myanmar

SARTHAK BAGGA

Health care logistics is a critical component of any health care system, ensuring the timely and efficient delivery of medical supplies and life-saving medications to those in need.[1] In Myanmar, a Southeast Asian country with a population of over 54 million, logistics plays a vital role to ensure that the health care needs of the people are met, particularly in the remote areas where over 80% of the population resides.

One of the primary challenges facing health care in Myanmar is poor infrastructure. Many of the road networks are poorly developed and some of the remote areas can only be accessed on foot or via boat. In such cases, delivering essential medicines, supplies and equipments along with providing quality health care services can be a daunting task. This leads to suboptimal utilization of modern medical services.[2] Standardized logistics plays a critical role in overcoming these challenges and bridging this gap by providing efficient and reliable transportation systems to deliver services to these underdeveloped areas and minimizing the disparity of access between urban and rural communities, with rural communities being severely underserved.

Another significant challenge is the shortage of trained health care workers and medical professionals. Myanmar has a high prevalence of infectious diseases such as tuberculosis (TB), malaria and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), which require timely diagnosis and treatment. However, due to the shortage of trained health care workers and medical professionals, especially in rural areas, this creates a bottleneck in providing effective services.[3] Health care logistics can help in addressing this challenge by providing a reliable supply chain for essential medicines and medical supplies, enabling health care workers to provide quality care to those patients.

Constantly changing government regulations have been a hurdle for the industry. It has become a tedious task for existing companies to predict which products will be approved for import. This has made it challenging to plan for future needs, resulting in shortages of critical products and price increases for available products. Resolving issues of this magnitude require a team of experienced logistics support who are able to communicate effectively with the regulators and make visible changes for their company.

In conclusion, health care logistics plays a huge role in Myanmar, mostly in ensuring access to health care services for people in the underdeveloped areas. A standardized logistics system can help to bridge the health care access gap and improve the overall health outcomes of the entire population. As Myanmar continues to develop its health care system,[4] it is crucial for the government and other relevant stakeholders to invest in health care logistics to improve the overall health care system in the country.

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Can Drugs be Supplied by the Registered Practitioner to his Patient?

The registered medical practitioner is entitled to supply the drugs to his patients which have been prescribed by him but the same are with certain conditions of exemptions as mentioned in Item No. 5 of the Schedule K of the Drugs and Cosmetics Rules, 1945. However, the registered medical practitioner is not entitled to exploit his patients or keep an open shop or sell across the counter or engage in the import, manufacture, distribution or sale of drugs.

The import, manufacture, distribution and sale of drugs and cosmetics in India is being regulated by Drugs and Cosmetics Act, 1940 and Drugs and Cosmetics Rules, 1945. Chapter IV of the Drugs and Cosmetics Act, 1940 deals with the manufacture, sale and distribution of drugs and cosmetics thereby laying down certain conditions for the same.

According to Rule 123 of the Drugs and Cosmetics Rules, 1945, the drugs specified in Schedule K of the Rules, 1945 are exempted from the provisions of Chapter IV of the Act and the rules made thereunder to the extent and subject to the conditions specified in that Schedule.

According to Item No. 5 of the Schedule K of the Drugs and Cosmetics Rules, 1945, Drugs supplied by a registered medical practitioner to his own patient or any drug specified in Schedule C supplied by a registered medical practitioner at the request of another such practitioner if it is specially prepared with reference to the condition and for the use of an individual patient provided the registered medical practitioner is not (a) keeping an open shop or (b) selling across the counter or (c) engaged in the importation, manufacture, distribution or sale of drugs in the provision of Chapter IV of the Act and the rules thereunder.

However, there are certain conditions mentioned in Item No. 5 of the Schedule K of the Drugs and Cosmetics Rules, 1945 which need to be followed:

- The drugs shall be purchased only from a dealer or a manufacturer licensed under these rules and records of such purchases showing the names and quantities of such drugs together with their batch numbers and the names and addresses of the manufacturers shall be maintained. Such records shall be open to inspection by an Inspector appointed under the Act, who may, if necessary, make enquiries about purchases of the drugs and may also take samples for test.
- In the case of medicine containing a substance specified in Schedule G, H or X the following additional conditions shall be complied with:
  - The medicine shall be labeled with the name and address of the registered medical practitioner by whom it is supplied.
  - If the medicine is for external application, it shall be labeled with the words "For external use only" or if it is for internal use with the dose.
  - The name of the medicine or ingredients of the preparation and the quantities thereof, the dose prescribed, the name of the patient and the date of supply and the name of the person who gave the prescription shall be entered at the time of supply in register to be maintained for the purpose.
  - The entry in the register shall be given a number and that number shall be entered on the label of the container.
  - The register and the prescription if any on which the medicines are issued shall be preserved for not less than 2 years from the date of the last entry in the register or the date of the prescription as the case may be.
- The drug will be stored under proper storage conditions as directed on the label.
- No drug shall be supplied or dispensed after the date of expiration of potency recorded on its container, label or wrapper or in violation of any statement or direction recorded on such container, label or wrapper.

Further, according to Clause 6.3 of the Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations, 2002, a physician should not run an open shop for sale of medicine for dispensing prescriptions prescribed by doctors other than himself or for sale of medical or surgical appliances. It is not unethical for a physician to prescribe or supply drugs, remedies or appliances as long as there is no exploitation of the patient. Drugs prescribed by a physician or brought from the market for a patient should explicitly state the proprietary formulae as well as generic name of the drug.

HCFI Dr KK Aggarwal Research Fund

Round Table Environment Expert Zoom Meeting on "E-waste (Management) Rules, 2022 – Implementation Effective from 1st April, 2023"

March 19, 2023 (Sunday, 12 noon-1 pm)

- E-waste refers to all items of electronic and electrical equipment and its parts that have been discarded as waste without intending to reuse them.
- India is the third largest generator of e-waste in the world after China and the United States.
- In India, management of e-waste is carried out under the E-waste (Management) Rules, 2016 and the amendments thereof.
- The E-waste (Management) Rules, 2022 were notified by the Ministry of Environment, Forest and Climate Change, Govt. of India on 2nd November, 2022. These rules will replace the existing 2016 rules and their implementation will be effective from 1st April, 2023.
- The new rules will launch a new Extended Producer Responsibility (EPR) regime for e-waste recycling where the producer of a specific category of waste is responsible for the treatment and safe disposal.
- The new rules are applicable to every manufacturer, refurbisher, dismantler and recycler. All of them are now required to register on the online portal developed by the Central Pollution Control Board (CPCB). Authorization has been replaced by registration.
- No business shall be carried out with any business, which is not registered.
- Under the EPR regime, 106 electrical and electronic equipment (EEE) have been included.
- The new rules provide an annual e-waste recycling targets to the producers. The target may be made stable for 2 years starting from 60% for the year 2023-24, 70% for 2025-26 and 80% for 2027-28 and 2028-29 and onwards.
- Solar photovoltaic (PV) modules/panels/cells have been added in the new rules.
- The quantity recycled will be calculated based on end products to avoid any false claims.
- The new rules have provisions for generation and transaction of EPR certificate, environment compensation and verification and audit and constitution of a Steering Committee to oversee their overall implementation. The new rules provide for reduction of hazardous substances in manufacturing of EEE.
- Every producer of EEE and their components must ensure that their products do not contain mercury, lead and other hazardous material beyond the prescribed limit.
- The rules provide for recognition and registration, skill development, monitoring and ensuring safety and health of workers involved in dismantling and recycling of e-waste.
- The manufacturers have to collect the e-waste generated during the manufacture of any EEE and ensure its recycling or disposal. They are required to file annual and quarterly returns in the laid down form on the portal on or before the end of the month succeeding the quarter or year, as the case may be, to which the return relates.
- The producers are responsible for obtaining and implementing EPR targets. The producers having the EPR plan under the provisions of the 2016 rules will migrate under the new rules as per the provisions laid down by the CPCB.
- The produces also have the responsibility to create awareness through media, publications, advertisements or by any other means of communication. They also have to file annual and quarterly returns in the laid down form on the portal.
- The refurbisher has to collect e-waste generated during the process of refurbishing and hand over the waste to the registered recycler and upload the information on the portal. They have to ensure that the refurbished equipment will be as per the Compulsory Registration Scheme of the Ministry of Electronics and Information Technology and the standards prescribed by the Bureau of Indian Standards framed for the purpose. They also have to file annual and quarterly returns.
- The bulk consumer must ensure that the e-waste generated by them is handed over only to the registered producer, refurbisher or recycler.
- The recyclers have to ensure that the facility and recycling processes are in accordance with the

standards or guidelines laid down by the CPCB. They also have to ensure that the material not recycled in their facility is sent to the respective registered recyclers and that the residue generated during the recycling process is disposed of in an authorized treatment storage disposal facility.

- The recyclers have to maintain a record of the e-waste collected, dismantled, recycled and sent to the registered recycler on the portal. They have to file annual and quarterly returns and accept annual EEE or components (not listed in Schedule 1) for recycling provided that they do not contain any radioactive material. This information is to be uploading on the portal. They have to account for and upload information about any non-recyclable e-waste or any quantity which is not recycled and disposed of. They can take the help of dismantlers; however, the responsibility lies with the recycler.
- The CPCB coordinates with the State Pollution Control Boards (SPCBs). It has to prepare and issue guidelines and standard operating procedures (SOPs) for collection, storage, transportation, segregation, refurbishment, dismantling, recycling and disposal of e-waste under these rules. The CPCB can also conduct random checks to determine compliance to the rules.
- Responsibilities of CPCB also include documentation and compilation of data on e-waste, action against violation of the rules, conducting training programs to develop capacity, conduct awareness programs on e-waste management, integrate all stakeholders with the centralized digital system and submit annual report to the Ministry.
- The CPCB is also required to interact with the IT Ministry for reducing hazardous substances and enforce provisions regarding reduction in the use of hazardous substances in the manufacture of EEE.
- The SPCB have to maintain an inventory of the e-waste, monitor compliance of EPR as directed by the CPCB. They can conduct random inspection of recycler and refurbisher and monitor utilization of recycling capacity.
- The urban local bodies have to ensure that the e-waste, which is mixed with the municipal solid waste is properly segregated, collected and is sent to the registered recycler or refurbisher. They have to set up e-waste collection, segregation and disposal system and conduct training sessions to develop capacities of the urban and rural local bodies.
- The world's largest and innovative industry is the electronic industry, which is increasing day by day across the year because of its requirement. Hence, every year the volume of e-waste being generated is also increasing. Apart from the construction sector, the sector that generates the most waste is that of electronics, which directly or indirectly affects the health of each individual if not handled properly.
- E-waste is not found discarded on the roads. It either goes to the dump ground or to the illegal processing place.
- Today, around 2 billion metric tonnes per annum of e-waste is estimated to be generated by India. It is crucial to know where this is waste going and how it is collected. The biggest challenge is the collection of e-waste and its disposal. There is no efficient system of collection, storage. There are only refurbishing or dismantling centers; India does not have any refinement centers.
- If properly accounted, it will generate a lot of employment, might generate some kind of revenue.
- Most e-waste has important elements, which can be mined, especially cadmium, lithium and lead, which can be of further use as raw material for battery manufacturers for electric vehicles.
- In India, recycling of e-waste is left almost entirely to the informal sector, which is not there in the present rules. This could be due to its illegality.
- An e-waste recycling or refining center for recovery of precious metals from e-waste is being set up in Hyderabad in collaboration with a US company with support of government of Telangana.
- The states of Maharashtra, Tamil Nadu, Andhra Pradesh and Uttar Pradesh are the largest producers of e-waste. The top cities generating e-waste are Ahmedabad, Bangalore, Chennai and Delhi.
- The toxins present in e-waste, which affect health are lead, cadmium, beryllium, lead oxides, bromine, etc.
- There is lot of child labor involved in this. Legislation needs to improve on these aspects.
- Audit in terms of collection, transportation and dismantling needs improvement. Responsibilities need to be fixed. Incentives are needed.
- These rules have to reach schools, colleges, offices and other institutions, etc. as they too are e-waste generators.
- Participation and awareness are required.

- Expanding the definition of e-waste and electronic items specifying the recycling target with proper implementation mechanism clearly specifying the penalties for violation of Rule 2022 will assist in better implementation of the collection, processing and recycling of e-waste.
- The rules touch upon two aspects, but do not clearly state the requirement for ensuring the recovery tangent.
- The new notification does away with Producer Responsibility Organizations (PROs) and dismantlers and vests all the responsibility of recycling on authorized recyclers. PROs acted as an intermediary between producers of electronic goods and formal recyclers by bidding for contracts from producers and arranging for certified and authorized recycling.
- Many producers in Delhi have not set up collection centers. And formal companies also fail to provide doorstep collection to consumers when the quantum of e-waste is not enough to meet their overhead expenses or transport. Consumers are unaware about the existence of any such service.
- E-waste *per se* is not like the municipal solid waste or hazardous waste. It is a low volume and high-cost waste.
- We copy western ideas for e-waste management because it is governed under Basel Convention. They do not have formal/informal sector for newspaper buying or selling but we have this.
- We have to see that the manufacturer has obligation to take his product back but at a reasonable cost. The manufacturer has to be regulated; they introduce models with new features making the old equipment useless.
- There has to be different thinking; more thought needs to be given to the consumers.
- Many residential societies in Gurugram have started segregated disposal of e-waste and handing over their e-waste to authorized recyclers.

Participants: Dr Anil Kumar, Dr Dipankar Saha, Mr Sanjeev Kumar, Mr Neeraj Tyagi, Mr RN Jindal, Mr Rajeev Sharma, Mr Lovekesh Chandra, Ms Ruchika Sethi Takkar, Dr S Sharma

Coronavirus Updates

COVID-19 may stop being a public health emergency of international concern this year

COVID-19 may be over as a public health emergency of international concern this year. Dr Tedros Ghebreyesus, WHO Director General expressed this hope at a media briefing last week. On 30th January 2020, the WHO declared COVID-19 as a public health emergency of international concern and a pandemic was declared on 11th March the same year. "We are certainly in a much better position now than we have been at any time during the pandemic," he further said… (*Source: WHO, March 17, 2023*).

India COVID situation: Rising COVID cases

In 22nd March, 1300 new infections were recorded taking the number of active infections in the country to 7605, according to data from the Health Ministry. Nearly 90,000 tests were carried out yesterday. The recovery rate is 98.79%. The positivity rate is 1.46% (daily) and 1.08% (weekly). With 7530 doses given in last 24 hours, so far a total of 220.65 crore vaccine doses, which includes 95.20 crore second doses and 22.86 crore precaution doses have been administered... (*Source: Press Information Bureau, March 23, 2023*).

Over 300 samples of XBB1.16 found in India

The XBB.1.16 variant of coronavirus has been suggested to be behind the recent increase in the number of new infections in the country. Three hundred forty-nine samples have tested positive for this new strain. Maharashtra has 105 cases, Telangana 93 cases, Karnataka 61 and Gujarat 54 cases. First detected in January in two cases. The number increased to 140 in February and then rose to 207 earlier this month… (*Source: Times of India, March 23, 2023*).

Predeparture COVID test not mandatory now for Chinese travelers to England

Chinese travelers to England will no longer need to provide a negative predeparture COVID test from April 5. Recently, testing of travelers from mainland China on arrival has also ended. These measures had been instituted in January this year in view of the surge in cases in China… (*Source: Reuters, March 17, 2023*).

With inputs from Dr Monica Vasudev

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Diabetes India 2022: 12th World Congress of DiabetesIndia

NONSTEROIDAL MRAs: A NEW HOPE FOR IMPROVED CARDIORENAL OUTCOMES IN PATIENTS WITH CKD AND T2D

Dr Shashank Joshi, Mumbai

- Chronic kidney disease (CKD) progression in type 2 diabetes (T2D) is driven by the combined effects of metabolic, hemodynamic, inflammatory and fibrotic factors. Inflammation and fibrosis are potential treatment targets to address the residual risk in CKD and T2D.
- Mineralocorticoid receptor (MR) overactivation is a major driver of kidney damage.
- MR overactivation, which contributes to inflammation and fibrosis, is a potential treatment target to slow CKD progression.
- Finerenone, a novel, nonsteroidal, selective mineralocorticoid receptor antagonist (MRA), blocks MR overactivation and reduces albuminuria.
- Finerenone is different from available steroidal MRAs. Finerenone is hypothesized to slow CKD progression and prevent cardiovascular (CV) events by directly targeting inflammation and fibrosis.
- FIDELIO-DKD and FIGARO-DKD results indicate that finerenone is an effective investigational treatment option for CV and kidney protection in patients with CKD stage 1-4 and T2D.

GEN 2.0 BASAL INSULIN: LEVERAGING TIME-IN-RANGE TO IMPROVE PATIENT OUTCOMES

Dr Jothydev Kesavadev, Thiruvananthapuram

- Time-in-range (TIR) and glucose variability (GV) have emerged integral in diabetes management.
- In range is the first randomized clinical trial comparing TIR and GV of the two second-generation basal insulin, in adults with type 1 diabetes mellitus (T1DM). The trial met the primary end point of noninferiority of U300 glargine vs. U100 degludec with respect to TIR. The GV, hypoglycemic episodes and safety were also comparable.
- We need to adopt better, newer therapies so as to prevent microvascular complications in diabetes.

CARDIORENAL METABOLIC DISORDER, IS THE PANACEA AVAILABLE NOW?

Dr Mangesh Tiwaskar, Mumbai

"It should be the function of medicine to have people die young as late as possible." —Ernest L Wynder

- Diabetes treatment for cardiovascular disease (CVD) reduction is categorized in two arms, i.e., sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor (GLP-1R) antagonists with hemodynamic effect and anti-atherogenic effect mechanism of action, respectively.
- SGLT2 inhibitors improve ventricular loading conditions (diuresis, natriuresis, etc.), myocardial energetics, TGF, IGH, etc. by modulating sympathetic nervous system (SNS) activity.
- GLP-1R on the other hand has anti-inflammatory effects, reduces oxidative stress, inhibits renin-angiotensin-aldosterone system (RAAS), increases natriuresis, etc.
- SGLT2 inhibitors and GLP-1R provide complete CV renal protection combined and are a challenge.

SGLT2 INHIBITOR IS 2ND ADD-ON FOR EVERYONE

Dr Piyush Desai, Surat

- Over the last 5 years, several landmark trials such as EMPA-REG, CANVAS, CREDENCE, DAPA-HF and KDIGO have shown the multidimensional action of SGLT2 inhibitors in diabetes therapy and reducing the risk of CV renal outcomes.
- Based on this evidence, American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) guidelines have been changed and recommend early prescription of SGLT2 inhibitors for patients with a high risk of ASCVD, CKD, HF, etc.
- According to AACE guidelines, SGLT2 inhibitors can be used in combination with metformin, if the entry-level HbA1c is high.
- SGLT2 inhibitor is a cost-effective drug that when reduces weight and the risk of hypoglycemia along with controlling several other risk factors.

News and Views

Predictors of Chronic Diseases in Pregnant Women

The association of hypertensive disorders of pregnancy with risk of future cardiovascular disease (CVD) is well-established. Similarly, gestational diabetes is also a risk factor for diabetes later in life. A team of Japanese researchers conducted a cross-sectional study between April 2017 and November 2020 at a tertiary hospital to examine if gestational glycosuria, proteinuria and borderline hypertension also had a similar correlation with these chronic diseases. For this, they evaluated three parameters: glycosuria, proteinuria and systolic BP (<130, 130-139 and ≥140 mmHg) during pregnancy in 312 women. Questionnaires were used to find out the self-reported incidences of hypertension, diabetes and kidney disease after 35.8 years of childbirth.

Results published in the *Journal of Obstetrics and Gynaecology Research* show that women with glycosuria were 3 times more at risk of diabetes mellitus with adjusted odds ratio (aOR) of 3.62. Women with proteinuria were 4 times more likely to develop kidney disease with aOR of 4.07. Systolic BP ≥140 mmHg was significantly associated with risk of hypertension with aOR of 4.26. However, the association between systolic BP 130-139 mmHg and hypertension was nonsignificant (aOR 1.72).

These findings demonstrate a positive association between gestational glycosuria, proteinuria and raised BP with development of chronic diseases such as diabetes, hypertension in older age. Routine screening of these simple parameters during pregnancy can identify at-risk women for timely implementation of preventive actions.

Reference

1. Hosoya S, et al. Gestational glycosuria, proteinuria, and borderline hypertension in pregnancy are predictors for the later onset of maternal chronic disease. J Obstet Gynaecol Res. 2023;49(2):641-8.

Spinal Cord Stimulation could Benefit Patients with Diabetic Neuropathy

Among 37 million diabetic Americans, 25% of them have a painful disease, diabetic neuropathy, which results in nerve loss and usually affects the hands and feet, and can cause discomfort and numbness. This study included 216 participants with painful diabetic neuropathy symptoms unresponsive to treatment for at least a year.

After 6 months, the participants reported an average pain reduction of 76%, compared to a 2% rise in discomfort for those who did not.

Two years later, participants reported 80% improvement in their motor skills, sensitivity and reflexes, and 66% still exhibited progress. Eight people who suffered illnesses by their devices experienced three recoveries, while the other five required device removal owing to infection. Also, participants reported an 80% improvement in their average level of discomfort, and 66% said that their motor function, sensitivity and reflexes had improved. With acceptable safety, high-frequency stimulation reduces pain more effectively than low-frequency stimulation.

Three percent of people had their implants removed due to infection, but none had the gadgets removed due to the device's effectiveness. Additionally, the results show that high-frequency stimulation appears to be more effective at reducing pain than low-frequency stimulation.

This study reveals that high-frequency stimulation offers dependable long-term pain alleviation. Further improvements in motor function, sensation, and reflexes show that this therapy may have disease-modifying potential. More studies were required to confirm the understanding of this spinal cord stimulation therapy for treating diabetic neuropathy. (*Source: https://www.hindustantimes.com/lifestyle/health/diabetic-neuropathy-patients-can-benefit-from-spinal-cord-stimulation-study-101678097408374.html*)

Vitamin D Consumption Might Help Prevent Dementia

Researchers in Canada and the UK investigated the link between dementia and vitamin D intake.

More than 12,388 members of the US National Alzheimer's Coordinating Center, with a mean age of 71 and no dementia at the time of enrollment, participated in the study published in *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*.

The percentage of the group that used vitamin D supplements, 37% (4,637), was found to be dementia-free for a lifespan. During 10 years, 2,696 persons from

the overall sample developed dementia; of these, 2,017 (or 75% of them) had no exposure to vitamin D at any point during their visits before being diagnosed with dementia, while 679 (or 25% of them) had baseline exposure.

Although vitamin D was effective in all groups, the team discovered that females experienced effects that were noticeably bigger than those in males. Impacts were more pronounced in those with normal cognition compared to individuals who reported minor cognitive impairment.

The APOEe4 gene increases the chance of developing Alzheimer's dementia. According to scientists, those with the APOEe4 gene had improved intestinal absorption of vitamin D, which might lessen the effects of vitamin D supplementation. Also, it was observed that vitamin D effects were noticeably stronger in those who did not contain the APOEe4 gene than in noncarriers. To verify this theory, no blood samples were taken.

Previous studies have also revealed that vitamin D may assist in protecting the brain from tau buildup, another protein linked to the onset of dementia, and helps remove amyloid from the brain, which builds up in Alzheimer's disease.

Thus the current study concluded that vitamin D intake might help prevent dementia. (*Source: https://theprint.in/health/study-shows-taking-vitamin-d-might-help-prevent-dementia/1420995/*)

CDC Reveals Lasting Effects of COVID Virus on Nearly Every Organ

An updated Center for Disease Control and Prevention (CDC) guidance for certifying deaths due to coronavirus disease has revealed that emerging evidence suggests that COVID virus can have long-lasting effects on almost every organ and organ system of the body weeks, months and possibly years after infection.

Clinical symptoms and COVID-19 consequences in the acute phase, including death, have been recorded in varied degrees. However, those who survive the acute stage of the illness may still experience long-term consequences, often known as "long COVID".

According to the updated CDC recommendations, documented severe post-COVID disorders now include complications of cardiovascular, neurological, pulmonary, endocrine, hematological, renal and gastrointestinal systems along with death. Recent studies from the University of Waterloo in Canada suggest that long COVID has also been linked to lower brain oxygen levels, decreased performance on cognitive tests, and increased psychiatric symptoms like depression and anxiety.

Pre-existing chronic illnesses, particularly those that cause a reduction in lung capacities, such as chronic obstructive pulmonary disease (COPD) or asthma, might occasionally make it more challenging to recover from COVID. The CDC advice stated that while these medical conditions do not directly cause COVID-19, they can raise the risk of acquiring a respiratory infection and dying from it.

A most recent assessment of 200 COVID-19 studies, published in the journal *Nature Reviews Microbiology*, estimated that at least 65 million people have long COVID. The US-based researchers state that 10% of the more than 651 million COVID-19 instances reported globally have Long COVID. (*Source: https://www.tribuneindia.com/news/health/covid-virus-can-have-lasting-effects-on-nearly-every-organ-for-years-cdc-485714*)

Go Slow on that Cup of Coffee If You have Severe Hypertension

Drinking 2 or more cups of coffee everyday doubles the risk of death due to heart disease among those who are severely hypertensive, according to a study published in the *Journal of the American Heart Association*.[1]

A total of 18,609 people from the Japan Collaborative Cohort Study for Evaluation of Cancer Risk were included in this study. They were enrolled between 1988 and 1990 and their ages at the time of recruitment ranged from 40 to 79 years. The study objective was to examine the impact of self-reported coffee and green tea intake on mortality due to heart disease among participants with severe hypertension. Depending on the BP, the participants were categorized into four groups: optimal and normal BP, high-normal BP, Grade 1 hypertension and Grade 2-3 hypertension.

The participants were followed up for a median duration of 18.9 years; during this period, 842 CVD deaths occurred. Coffee drinkers who had Grade 2-3 hypertension were at a higher risk of cardiac-related mortality. Compared to those who did not drink coffee, the risk increased twofold among those who drank ≥2 cups of coffee daily with hazard ratio (HR) of 2.05. The HR for <1 cup/day was 0.98. No such association was observed among participants with optimal and normal, high-normal BP and Grade 1 hypertension. In contrast, consumption of green tea did not increase the risk of CVD in any BP category.

This study shows that drinking too much coffee every day increases the risk of death due to CVD particularly among those who are severely hypertensive. However, intake of green tea did not increase the risk of cardiovascular mortality.

Reference

1. Teramoto M, et al. Coffee and green tea consumption and cardiovascular disease mortality among people with and without hypertension. J Am Heart Assoc. 2023;12(2):e026477.

Moderate to Severe Proteinuria and Risk of Adverse Pregnancy Outcomes

Women with proteinuria during pregnancy, ranging from 1,000 to 3,500 mg/day of protein in urine, are at risk of adverse perinatal outcomes, according to a study published in the *Journal of Obstetrics and Gynaecology*.[1]

To investigate the association between proteinuria and adverse pregnancy outcomes, researchers recruited 142 pregnant women who had proteinuria during their pregnancy. Data was collected between January 2018 and December 2020. Based on the 24-hour proteinuria, 76 women were categorized as having mild proteinuria (300-1,000 mg/day), 39 had moderate proteinuria with 1,000-3,500 mg/day of protein in the urine, while 27 women had severe proteinuria of more than 3,500 mg/day.

Retrospective analysis of data revealed that women with severe proteinuria were more likely to have fetal growth restriction versus women who had mild proteinuria. Their newborns were also more likely to require intensive care and treatment in the neonatal intensive care unit (NICU).

Compared to mild and moderate proteinuria groups, women in the severe proteinuria group had higher odds of giving birth to preterm and low birth weight infants or neonatal asphyxia. The odds ratio (OR) for adverse perinatal outcomes was 97.2 for moderate proteinuria and 34 for severe proteinuria.

Pregnant women should be closely monitored for proteinuria during pregnancy. This will enable early detection of renal dysfunction. Categorizing the degree of 24-hour proteinuria is predictive of adverse pregnancy outcomes as shown in this study. Timely intervention can improve maternal and fetal outcomes.

Reference

1. Hu M, et al. Association between proteinuria and adverse pregnancy outcomes: a retrospective cohort study. J Obstet Gynaecol. 2023;43(1):2126299.

A Steady Rise in TB and Leprosy Cases Seen with Decreasing COVID-19 Cases

The economic survey stated that although COVID-19 cases have been decreasing, diseases like tuberculosis (TB) and leprosy cases are steadily increasing in Maharashtra. According to the report's public health statistics, there were 750 suspected TB cases per lakh people in 2021-2022, and the cure rate was 84%. The corresponding numbers for 2022-2023 were 1,552 and 85% (up to December 2022; same for current and succeeding cases). The report stated that eradicating TB cost Rs. 88.2 crore in 2021-2022 and Rs 75.8 crore in 2022-2023. The survey reported that the leprosy cases were 14,520 and 11,607 in 2021-2022, respectively, with a prevalence rate of 0.89 per 10,000 people. There were 15,945 newly reported cases of leprosy and 16,090 active cases during 2022-2023.

The National TB Program (NTP) was introduced in 1962 and revitalized by the GoI in 1993 and became the Revised National TB Control Program (RNTCP). To control and eradicate TB in India by 2025, the RNTCP has published the "National Strategic Plan for Tuberculosis 2017-2025" (NSP). TB eradication has been incorporated into the four strategic pillars of: detect-treat-prevent-build, claims the NSP. The directly observed treatment short (DOTS) course is one RNTCP approach.

The National Leprosy Eradication Project intends to eradicate leprosy (prevalence of less than 1 case per 10,000 people in all districts), increase disability prevention and medical rehab for those with the disease, and lessen the stigma associated with it. Last week, the Chief Minister, Eknath Shinde, suggested forming a committee by the state government comprising of senior officials and people running NGOs like Prakash Amte and Vikas Amte to decide on a rehabilitation strategy and explore options to find employment for leprosy patients. (*Source: https://health.economictimes.indiatimes.com/news/industry/tb-leprosy-on-the-rise-with-waning-of-covid-19/98505461*)

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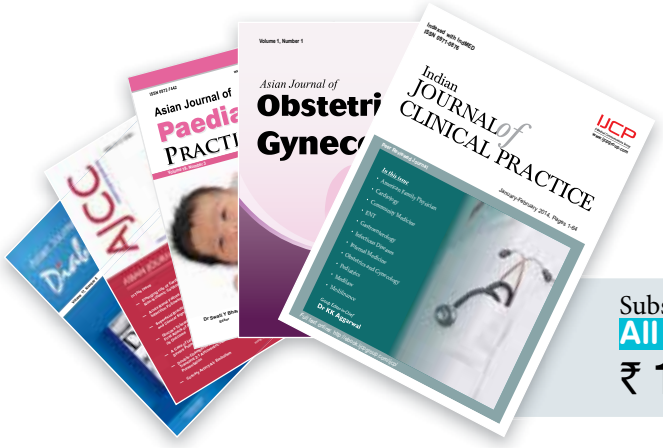

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Lighter Side of Medicine

INSPIRATIONAL STORY

DO WE REALLY LOVE?

A story is told about a soldier who was finally coming home after having fought in Vietnam. He called his parents from San Francisco.

"Mom and Dad, I'm coming home, but I've a favor to ask. I have a friend I'd like to bring home with me." "Sure," they replied, "we'd love to meet him".

"There's something you should know," the son continued, "he was hurt pretty badly in the fighting. He stepped on a land mine and lost an arm and a leg. He has nowhere else to go, and I want him to come live with us."

"I'm sorry to hear that, son. May be we can help him find somewhere to live." "No, Mom and Dad, I want him to live with us."

"Son," said the father, "you don't know what you`re asking. Someone with such a handicap would be a terrible burden on us. We have our own lives to live, and we can't let something like this interfere with our lives. I think you should just come home and forget about this guy. He'll find a way to live on his own."

At that point, the son hung up the phone. The parents heard nothing more from him. A few days later, however, they received a call from the San Francisco police. Their son had died after falling from a building, they were told. The police believed it was suicide. The grief-stricken parents flew to San Francisco and were taken to the city Morgue to identify the body of their son. They recognized him, but to their horror they also discovered something they didn't know, their son had only one arm and one leg. The parents in this story are like many of us. We find it easy to love those who are good looking or fun to have around, but we don't like people who inconvenience us or make us feel uncomfortable. We would rather stay away from people who aren't as healthy, beautiful or smart as we are.

Thankfully, there's someone who won't treat us that way. Someone who loves us with an unconditional love that welcomes us into the forever family, regardless of how messed up we are.

Tonight, before you tuck yourself in for the night, say a little prayer that God will give you the strength you need to accept people as they are, and to help us all be more understanding of those who are different from us!!!

There's a miracle called Friendship that dwells in the heart, you don't know how it happens, or when it gets started.

But you know the special lift. It always brings, And you realize that Friendship, Is God`s most precious gift!

Friends are a very rare jewel, indeed. They make you smile and encourage you to succeed. They lend an ear, they share a word of praise, and they always want to open their hearts to us. Show your friends how much you care...

HUMOR

VALIANT STUDENT AND A FEARSOME DOG!

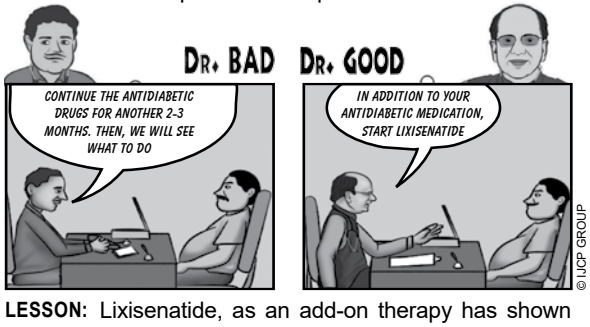
Deciding to take a day off from his important job, a young hot-shot broker went back to visit some of his professors at his old school. Entering the school, he saw a dog attacking a small child. He quickly jumped on the dog and strangled it.

The next day, the local paper reported the story with the headline "Valiant Student Saves Boy from Fearsome Dog."

The broker called the editor of the paper and strongly suggested that a correction be issued pointing out that he was no longer a student, but a successful Wall Street Broker. The following day, the paper issued a correction, with a headline that read, "Pompous Stock Broker Kills School Mascot."

Dr. Good and Dr. Bad

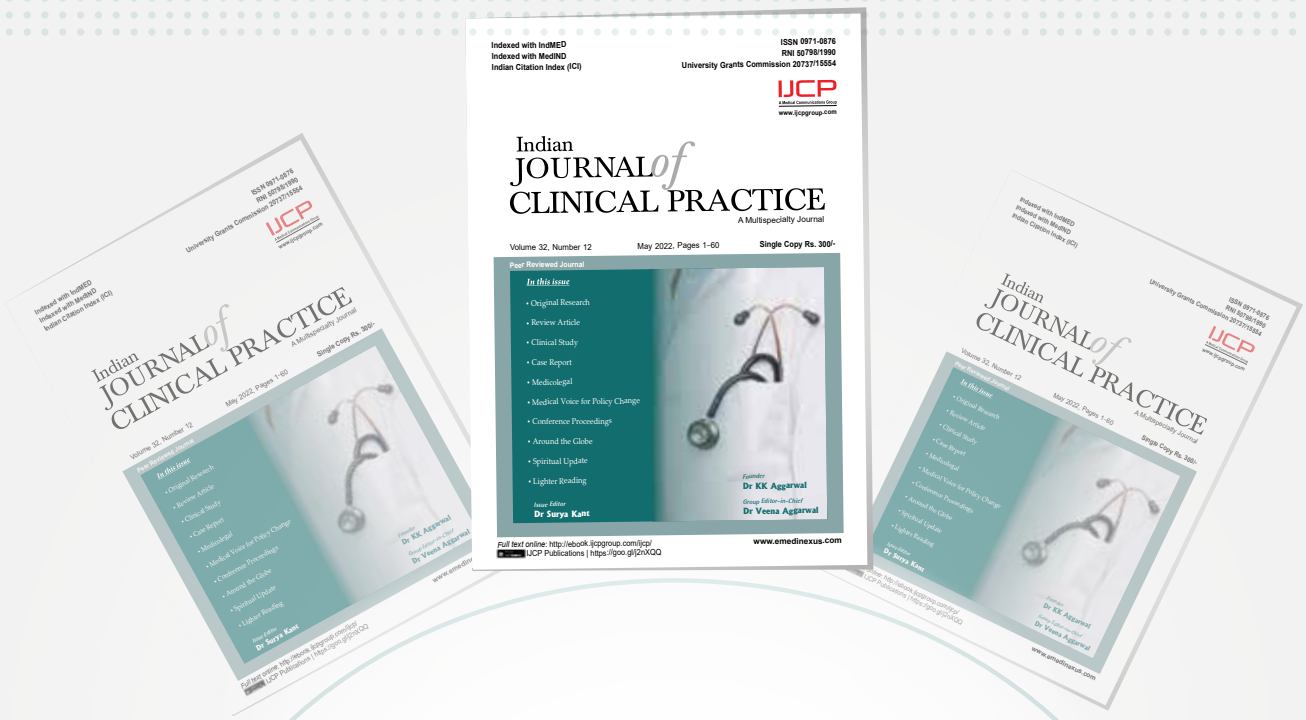
SITUATION: A 48-year-old male was at an advanced stage of T2DM and had poor residual β-cell function.



LESSON: Lixisenatide, as an add-on therapy has shown high potential in improving HbA1c, FPG and PPG, irrespective of β-cell function. Therefore, it appears to be a suitable option for reducing hyperglycemia, even in those with advanced stages of disease and poor residual β-cell function.

Diabetes Metab Res Rev. 2017;33(6):e2897.

IJCP GROUP



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Books

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

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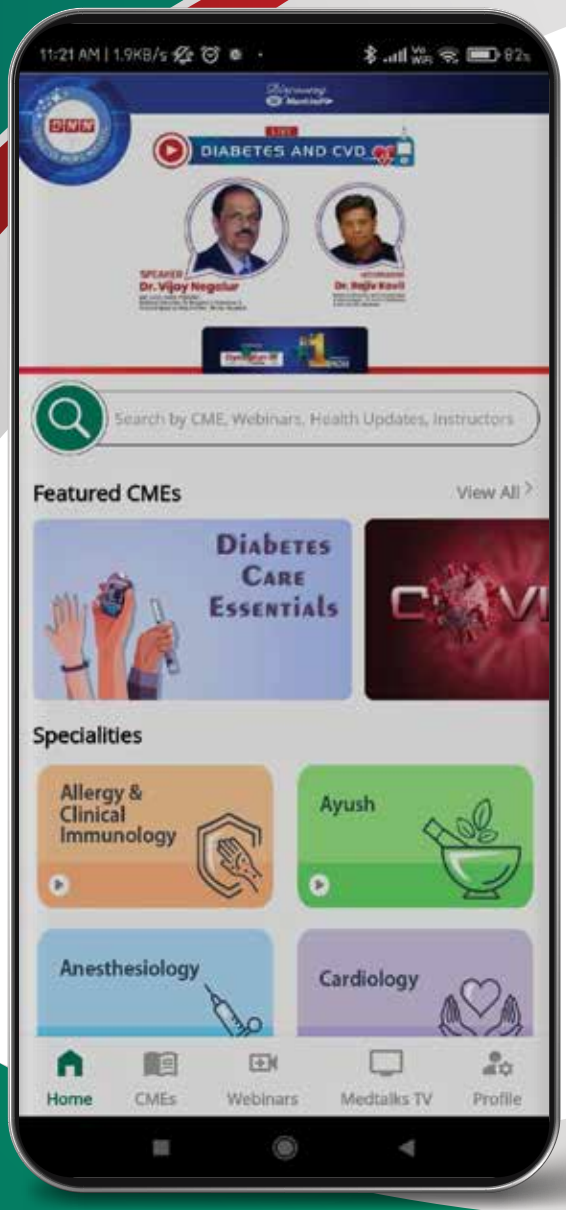

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