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Volume 23, No. 1, January-March 2022

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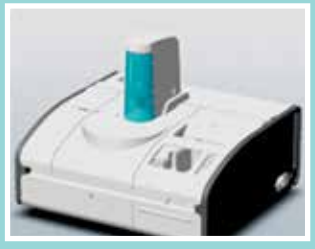

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The Asian Journal of
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Volume 23, No. 1, January-March 2022

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The Asian Journal of
DIABETOLOGY
Volume 23, No. 1, January-March 2022

Published, Printed and Edited by
Dr KK Aggarwal, on behalf of
IJCP Publications Ltd. and
Published at
39, Daryacha,
Hauz Khas Village, New Delhi - 110 016,
Phone: 011 26510097, E-mail: editorial@ijcp.com

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Asian Diabetes: Diversity in Unity

INTRODUCTION

India, Indonesia and Papua New Guinea, all Asia-Pacific nations, all share the motto "Unity in Diversity". Further afield, South Africa and the European Union subscribe to the same philosophy. Does Asian diabetes merit the same label?

The syndrome of diabetes mellitus covers a broad-spectrum of clinical conditions.[1] Though united by their degree of dysglycemia, they represent a wide variety of causative factors, clinical presentations, comorbid conditions, confounding issues, complications and consequences. Add to this, the diversity and dynamism of a continent as huge as Asia, and we have a situation tailor-made to create confusion and chaos.

ASIAN PHENOTYPES OF DIABETES

Diligent researchers and astute clinicians, however, have been able to connect the dots, to describe what are termed the "Asian phenotypes" of diabetes. These descriptions create a framework, which allows easier suspicion, screening and substantiation of the disease, as well as more efficient selection of interventions and supervision of therapy.

The clinical features that characterize the Asian diabetes phenotype include a low body mass index with increased visceral fat, associated metabolic and inflammatory dysfunction, along with insufficient beta cell response.[2] These have been reported from Eastern Asian as well as South Asian cohorts.[3,4] The relatively higher rate of childhood obesity, young-onset type 2 diabetes and gestational diabetes mellitus, along with greater risk of progression to renal disease and cancer has been noted.[2] Recent advances in technology have facilitated identification of clusters of diabetes, based upon age, insulin deficiency and insulin resistance.[5]

All these developments are welcome, as they contribute to the streamlining of diabetes care in our continent. Chan et al highlight the various challenges posed by the Asian diabetes epidemic, including biomedical and psychosocial realities. They also go on to explore multiple opportunities that this opens up, to ensure better health.[2]

FORGOTTEN PHENOTYPES

Much more, however, needs to be done to characterize the myriad forms of diabetes and its complications that are endemic to Asia. The World Health Organization (WHO) now lists "hybrid diabetes" in its classification of syndrome.[6] Such types of diabetes, variously known as type 1.5 diabetes, Flatbush diabetes and double diabetes are common in Asia. Pancreatic diabetes,

earlier known as fibrocalculous pancreatic diabetes, also occurs in certain geographical areas.[7] Malnutrition-related diabetes mellitus, which was recognized as a distinct entity till a few decades ago, has not disappeared entirely.[8]

Complications of diabetes, that owe their occurrence to suboptimal healthcare, are also reported from Asia. Examples include Mauriac syndrome and syndrome of limited joint mobility in type 1 diabetes,[9] as well as premature vascular complications in type 2 diabetes. Various challenges of diabetes are also unique to certain parts of Asia. Examples include the challenge in managing persons living with diabetes who wish to fast during religious occasions such as Ramadan, Buddhist Lent and Hindu or Jain festivals. Endemic forms of hypoglycemic encephalopathy such as litchi-associated encephalopathy, also exist in the continent.[10]

UNITED WE STAND

Modern diagnostics and therapeutics have enhanced our ability to manage diabetes.[11] These must be coupled, however, with an emphasis on public awareness and social marketing of the importance of diabetes care. These activities along with advocacy, will fuel a demand for diabetes care services. Policymakers, politicians, payers, pharmaceuticals and the physician fraternity will automatically step in to fill the gap and offer quality care.[12]

At the Asian Journal of Diabetology, we strive to ensure comprehensive coverage of advances and developments in diabetes care. We focus not only on the clinical aspects of diabetology, but on preventive and public health as well. Our discourse includes medical, as well as allied specialties and disciplines which contribute to diabetes management. We ensure that the diversity of our continent is heard, and that this leads to unity in terms of purpose. Through the pens of our authors, and the pages of our journal we hope to emerge as the voice of optimal diabetes management. With the Asian Journal of Diabetology, we aim to make Asia the Diabetes Care Capital of the world.

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The Tree of Karma

Life is destined to our deeds

we

Planted by genes

Cherish at womb like seeds

Play at lap

Touched by many

Life remains in cycle

Till touched by any

Human without humanity

Is just a machine

Lets play our roles

As we are destined

"Health happiness harmony and peace, together we care for diabetes" **Global Diabetes Forum**

Dr Raka Sheohare

The Expanding Role of Dapagliflozin Beyond the Glucose-lowering Effect

SANJAY KALRA*, AG UNNIKRISHNAN†, ARUNDHATI DASGUPTA‡, ATUL DHINGRA#, GANAPATHI BANTAVAL¥, MANASH P BARUAH£, MATHEW JOHN§, RAKESH SAHAY^, SAPTARSHI BHATTACHARYA¶, BHARATH HS||

ABSTRACT

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have varied metabolic effects beyond increasing glycosuria. This consensus review examines the role of dapagliflozin in health promotion, particularly its benefits in patients with and without type 2 diabetes mellitus (T2DM) and in cardiorenal rehabilitation post-coronavirus disease 2019 (COVID-19). Consensus recommendations were developed by subject experts in Endocrinology and Diabetology based on the online meeting held on 27 June 2020 to review the available evidence related to the role of SGLT2 inhibitors, with a focus on cardiovascular and renal metabolic therapy. Evidence suggests that dapagliflozin has a direct role in improving clinical outcomes in patients with chronic kidney disease (CKD) or heart failure (HF). These benefits of dapagliflozin were independent of reduction in blood pressure, glycemic control and weight, and also extend to patients without diabetes. The use of dapagliflozin in metabolic syndrome was endorsed by the majority of the experts; however, this would be off-label. It was opined that the role of dapagliflozin would currently be limited to treating T2DM with a focus on preventing HF or kidney disease progression. The need for conducting multidisciplinary academic meetings to have a balanced approach regarding the use of dapagliflozin among nondiabetic patients and the need for detailed evaluation of the role of SGLT2 inhibitors in vasculometabolic and cardiorenal rehabilitation post-COVID was also suggested.

Keywords: Dapagliflozin, heart failure, kidney disease, type 2 diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the most prevalent progressive, complex and metabolic disorder that is characterized by inconsistent insulin production and utilization. Estimates indicate that approximately 573 million people aged 20 to 79 years are living with diabetes globally, which may increase to 783 million by 2045. Currently, India has around 74.2 million individuals diagnosed with diabetes, which may increase to 124.9 million by 2045.[1] Current international guidelines consider sodium-glucose cotransporter 2 (SGLT2) inhibitors as an alternative to metformin plus either sulfonylurea or dipeptidyl peptidase-4 (DPP-4) inhibitors.[2,3] SGLT2 inhibitors can be used in patients with T2DM and atherosclerotic cardiovascular disease (ASCVD) or kidney disorder or indicators of high risk, or heart failure (HF).[3]

According to the 2016 management protocols of stable coronary artery disease (SCAD) in India, oral antidiabetic agents, including SGLT2 inhibitors should be considered for diabetes management.[4] The 2020 Research Society for the Study of Diabetes in India (RSSDI) guidelines recommend SGLT2 inhibitors for patients with HF, ASCVD, diabetic kidney disease (DKD) or those who require weight reduction.[5] The South Asian Federation of Endocrine Societies (SAFES) also endorsed the use of SGLT2 inhibitors for managing various comorbid conditions associated with T2DM.[6] Dapagliflozin, a selective SGLT2 inhibitor, is suggested to improve glycemic control along with diet and exercise in T2DM. It may be preferred in patients with

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chronic kidney disease (CKD) or HF with reduced ejection fraction (HFrEF), as it has favorable renal and cardiovascular (CV) effects.[7-9]

Prior studies have proven that most adults with diabetes in India have at least one comorbid condition.[10-12] In clinic-based studies, the prevalence of coronary artery disease among patients with diabetes was ~11% to 30%, while the prevalence in community-based studies was ~9% to 15%. CKD is also an inadequately addressed complication of T2DM affecting approximately 2 in every 5 patients. According to the Chennai Urban Rural Epidemiology Study (CURES), an urban population-based study of patients with diabetes in India, overall prevalence of nephropathy and microalbuminuria was 2.2% and 26.9%, respectively.[13]

Antidiabetic medications like metformin, originally indicated for the management of T2DM, have been prescribed for the management of polycystic ovarian syndrome. Liraglutide has the potential for being used as an antiobesity drug, while gliptins are being explored for their benefits beyond endocrinology.[14] Similarly, SGLT2 inhibitors, including dapagliflozin, have a role in several metabolic activities beyond glycosuria.[15] The chronic landscape of diabetes along with a high prevalence of concurrent chronic medical conditions necessitates multifaceted approach from both patients and healthcare providers. Considering the aforementioned literature views, this study aims to present expert opinions on the role of dapagliflozin beyond diabetes care.

METHODS

An advisory board comprising 9 regional endocrinologists/diabetes specialists from different parts of India was formed to review the role of SGLT2 inhibitors with a focus on CV and renal metabolic therapy. An online meeting of the advisory board was held on 27 June 2020 to arrive at conclusions regarding the benefits and drawbacks of SGLT2 inhibitors based on the existing knowledge and clinical experience. Recommendations were formulated based on the opinions and agreement of the majority post-discussion on the following:

- Role of dapagliflozin in health promotion
- Role of dapagliflozin in patients with and without T2DM
- Cardiorenal rehabilitation post-COVID.

Based on the agreed statements, supporting data was extracted from multiple databases including PubMed/Medline, Embase, Cochrane and Google Scholar. The criteria for consensus were set to statements with ≥80% agreement among experts. The experts' statements on each of these topics were recorded and are presented in this article.

ROLE OF DAPAGLIFLOZIN IN HEALTH PROMOTION

Dapagliflozin, when added to conventional antidiabetic agents, is associated with improvement in hemoglobin A1c (HbA1c) by 0.50%, weight loss of 2 kg, systolic/diastolic blood pressure (SBP/DBP) by 4/2 mmHg, fasting plasma glucose (FPG) by 18 mg/dL and body mass index by 1.1%, over 6 to 13 months.[16,17] Growing evidence suggests that SGLT2 inhibitors have several benefits beyond glycemic control.[18] They have a myriad of metabolic and hemodynamic effects, such as increasing glucagon levels and hematocrit production, while promoting lipolysis, hepatic fatty acid oxidation and ketone production.[19-21] Further, SGLT2 inhibition can trigger a fasting-like physiological environment.[21] Inhibition of SGLT2 directly activates AMP-activated protein kinase (AMPK) and also causes inhibition of mammalian target of rapamycin (mTOR) in the kidneys with beneficial effects on autophagy, mitofusion, mitofission and endoplasmic reticulum stress.[20] Inhibition of SGLT2 also decreases the progression of diabetic nephropathy by activating AMPK in mesangial cells, which causes a decrease in inflammatory mediators.[22] Notably, SGLT2 inhibitors may also influence several physiological functions that can improve HF outcomes. The decreased glucose absorption by tubular cells improves the interstitial hypoxia and promotes erythropoiesis in patients with diabetes.

This leads to an increase in both hemoglobin and hematocrit and a decrease in the afferent renal neural activity. Subsequently, SGLT2 inhibition has effects on the downregulation of sympathetic activity and reduces the effect on preload and afterload of the heart.[23] By improving cardiac energy metabolism through an indirect increase in ketone oxidation, SGLT2 inhibition may provide an additional source of energy for the failing heart. Moreover, SGLT2 inhibition may increase glucose oxidation in the heart. These factors may improve the overall heart functioning.[24]

PLEIOTROPIC EFFECTS OF SGLT2 INHIBITORS

Weight Loss

Weight loss associated with dapagliflozin has been mainly attributed to reduction in visceral fat. A recent meta-analysis of randomized controlled trials (RCTs) reported that SGLT2 inhibitors, including dapagliflozin

(2.5-10 mg/d), as an add-on to metformin were associated with significant reduction in body weight vs. non-SGLT2 inhibitors at 52 weeks. Significant reduction was also noted in both visceral and subcutaneous adipose tissue, along with lean mass.[25] Similarly, reduction in weight by approximately 1.5 to 3 kg with dapagliflozin alone and up to 5 kg reduction in weight with dapagliflozin and sulfonylurea combination therapy was also reported.[26]

Blood Pressure Reduction

With the combined effects of osmotic diuresis, natriuresis and reduction in arterial stiffness, SGLT2 inhibitors may reduce blood pressure (BP) in patients with T2DM and diabetic nephropathy.[27-30] In a recent meta-analysis, the pooled estimate (22 RCTs on treatment with dapagliflozin) of the weighted mean difference of dapagliflozin on SBP and DBP was −2.59 mmHg (95% confidence interval [CI] −2.70 to −2.49) and −1.09 mmHg (95% CI −1.18 to −1.01), respectively.[28] Another study reported that dapagliflozin decreased SBP by 3.6 mmHg and DBP by 2.0 mmHg in patients with T2DM. Post-dapagliflozin treatment, treatment-naive patients with T2DM with inadequate glycemic control with diet and exercise had the highest reductions in SBP.[29]

Lipid Management

Dapagliflozin has been associated with an increase in total cholesterol by 2.5%, high-density lipoprotein cholesterol (HDL-C) by 3.3%, low-density lipoprotein cholesterol (LDL-C) by 3.9% and a reduction in triglyceride levels by 2.0%.[26] Dapagliflozin as an add-on to metformin and/or sulfonylurea significantly increased HDL-C and LDL-C vs. DPP-4 inhibitors (linagliptin, gemigliptin) add-on therapy.[31]

Outcomes in Cardiovascular and Renal Disease

In a pooled analysis of five trials (up to 52 weeks duration) including patients with T2DM and HF, dapagliflozin 10 mg monotherapy or add-on therapy produced a clinically meaningful reduction from baseline in HbA1c (placebo-adjusted mean change: 0.55%), weight (−2.7 kg) and SBP (−2.1 mmHg) over 52 weeks.[32] In a post hoc analysis of phase 2/3 clinical trials, dapagliflozin was found to reduce weight and BP with improvement in glycemic control among patients with T2DM and renal impairment.[33] Similarly, findings from RCTs support the benefits of dapagliflozin 10 mg in improving glycemic control and weight loss and lowering BP among patients with T2DM with mild or moderate renal insufficiency.[34,35]

ROLE OF DAPAGLIFLOZIN IN PATIENTS WITH AND WITHOUT T2DM

Several RCTs have determined the effects of dapagliflozin on CV and renal outcomes, which are discussed below.

The Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial evaluated the safety of dapagliflozin in over 17,000 patients with ASCVD or risk factors (including ~40% without cardiovascular disease [CVD]). Significant benefits were reported at median follow-up of 4.2 years. Treatment with dapagliflozin significantly reduced CV death or hospitalization for heart failure (HHF) compared to placebo (4.9% vs. 5.8%; hazard ratio [HR] 0.83; 95% CI, 0.73-0.95; p = 0.005). This finding was mainly driven by a reduction in HHF (HR 0.73; 95% CI, 0.61-0.88). Further, dapagliflozin was noninferior to placebo for major adverse cardiovascular events (MACE; p < 0.001 for noninferiority). The incidence of the composite of ≥40% decrease in estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73 m^2, new end-stage renal disease (ESRD), or death from renal or CV causes was also in favor of dapagliflozin versus placebo (HR 0.53 95% CI 0.43-0.66). Dapagliflozin did not increase the incidence of stroke, amputations or fractures compared to placebo. However, a higher rate of diabetic ketoacidosis (excess rate <1% per year) and genital infections compared to placebo were reported.[9]

The DECLARE-TIMI 58 study also analyzed (prespecified subgroup analysis) the clinical benefits of dapagliflozin in patients with T2DM and prior myocardial infarction (MI). Dapagliflozin significantly reduced MACE in patients with a prior history of MI (HR 0.84, 95% CI 0.72-0.99) vs. those without a prior history of MI (HR 1.00, 95% CI 0.88-1.13). However, HHF and CV death did not differ irrespective of prior MI status.[36] In another subgroup analysis, Kato et al assessed the outcomes of dapagliflozin according to baseline HF status. It defined HFrEF as ejection fraction <45%. Dapagliflozin greatly reduced CV death or HHF in patients with HFrEF (HR 0.62, 95% CI 0.45-0.86), but not in patients with HF without known reduced EF (HR 0.88, 95% CI 0.66-1.17 and HR 0.88, 95% CI 0.74-1.03, respectively). Dapagliflozin did not increase the incidence of diabetic ketoacidosis and amputation. The overall safety profile was comparable to placebo.[37] In a real-world study of patients who met DECLARE-TIMI 58 inclusion criteria (n = 28,408), 21% lower risk of CV mortality or HHF (HR 0.79, 95% CI 0.69-0.92) were noted with dapagliflozin therapy compared to

other glucose-lowering drugs (OGLDs) without any significant association with MACE (HR 0.90, 95% CI 0.79-1.03).[38]

The CVD-REAL study is the largest real-world comparative effectiveness study that evaluated a range of CV outcomes in patients with T2DM at high CV risk initiated on SGLT2 inhibitors vs. OGLDs. A total of 1,54,528 patients were grouped in each treatment group after propensity matching. Canagliflozin followed by dapagliflozin accounted for more drug exposure with 53% and 42%, respectively. Significant reduction of HHF (pooled HR, 0.61; 95% CI, 0.51-0.73; $p < 0.001$) and all-cause death (pooled HR, 0.49; 95% CI, 0.41-0.57; $p < 0.001$) were observed in the SGLT2 inhibitors group vs. the OGLDs group.[39] The CVD-REAL 2 study was conducted across 6 countries in the Middle East, Asia Pacific and North American regions. A total of 2,35,064 episodes of treatment were grouped in each treatment group after propensity matching (~27% had CVD). Of all SGLT inhibitors, dapagliflozin accounted for 75% of drug exposure time. The SGLT2 inhibitors were associated with a significant reduction in the risk of mortality (HR: 0.51, 95% CI 0.37-0.70; $p < 0.001$), HHF (HR 0.64; 95% CI 0.50-0.82; $p < 0.001$), mortality or HHF (HR 0.60, 95% CI 0.47-0.76; $p < 0.001$), stroke (HR 0.68; 95% CI 0.55-0.84; $p < 0.001$) and MI (HR 0.81; 95% CI 0.74-0.88; $p < 0.001$) compared to OGLDs.[40] The CVD-REAL 3 study conducted across five countries (Israel, Italy, Japan, Taiwan and the UK) included patients with measurements of eGFR within 3 months before and after initiation of SGLT2 inhibitor or OGLDs. After propensity matching, a total of 35,561 episodes of treatment were grouped in each of the treatment groups. In the SGLT2 inhibitor cohort, dapagliflozin and empagliflozin accounted for 58% and 34% of drug exposure time, respectively. The baseline mean HbA1c was 8.71%, and mean eGFR was 90.7 mL/min/1.73 m^2. The between-group difference in the rate of eGFR decline was 1.53 mL/min/1.73m^2 per year favoring SGLT2 inhibitors over OGLDs ($p < 0.0001$). The decline in eGFR across eGFR and HbA1c subgroups was similar and consistent, regardless of CVD or concomitant treatments with antihypertensives ($p < 0.0001$ in favor of SGLT2 inhibition in all subpopulations). Further, SGLT2 inhibitors were associated with a lower risk for ESRD alone compared to OGLDs (HR 0.33, 95% CI 0.16-0.68; $p = 0.0024$).[41]

The Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure (DAPA-HF) trial evaluated the safety and efficacy of dapagliflozin in patients with HF with reduced LVEF (defined as LVEF ≤40%) regardless of T2DM status (n = 4,744). The primary endpoint (a composite of death from CV causes or worsening HF) was significantly reduced in the dapagliflozin group vs. the placebo group (16.3% vs. 21.2%; HR 0.74; 95% CI 0.65-0.85; $p < 0.001$). Dapagliflozin was also associated with significant reduction in the individual components of the primary endpoints: worsening HF (10.0 vs. 13.7%; HR 0.70; 95% CI: 0.59-0.83) and CV mortality (9.6 vs. 11.5%; HR 0.82; 95% CI: 0.69-0.98; $p = 0.029$). These CV improvements were also seen in patients with diabetes (n = 215/1,075 in the dapagliflozin group and n = 271/1,064 in placebo group) as well as patients without diabetes (n = 171/1,298 and 231/1,307); with no difference between the groups (HR 0.75 (95% CI 0.63-0.90) in diabetes and HR 0.73 (95% CI 0.60-0.88) in no diabetes). The incidence of HHF or CV mortality in the dapagliflozin group was lower compared to the placebo group (16.1 vs. 20.9%; HR 0.75; 95% CI: 0.65-0.85; $p < 0.001$). The total first and recurrent events with dapagliflozin was 567 (340 HHF and 227 CV mortality) compared to 742 events with placebo (469 HHF and 273 CV mortality; HR 0.75; 95% CI: 0.65-0.88; $p < 0.001$). Further, the incidence of death from any cause was low with dapagliflozin vs. placebo (11.6 vs. 13.9%; HR 0.83; 95% CI: 0.71-0.97).[8] Physical function, symptom burden and quality of life in patients with HFrEF were also improved with dapagliflozin. The proportion of patients with ≥5-point improvement in the clinical summary of the Kansas City Cardiomyopathy Questionnaire (KCCQ) score was higher with dapagliflozin compared to placebo (58.3% vs. 50.9%; odds ratio [OR] 1.15, 95% CI: 1.08-1.23; $p < 0.001$), while significant deterioration was noted in a smaller proportion compared to placebo (25.3% vs. 32.9%; OR 0.84, 95% CI: 0.78-0.90; $p < 0.001$).[42] Hypoglycemia, volume depletion and renal dysfunction were the most frequent adverse events noted and were similar between the dapagliflozin and placebo arms.[8]

In an exploratory analysis of DAPA-HF patients without diabetes at baseline (n = 2,605), 6.0% of patients developed T2DM during the trial, of which 95.5% of patients had prediabetes at randomization (HbA1c 5.7-6.4%). The rate of new-onset diabetes was 4.9% with dapagliflozin compared to 7.1% with placebo, indicating a 32% reduction in risk with dapagliflozin.[43]

The DELIGHT trial was a prospective, double-blind, placebo-controlled randomized trial that assessed the effects of dapagliflozin alone or in combination with saxagliptin in patients with T2DM who were already on treatment with other glucose-lowering drugs and had moderate-to-severe CKD (n = 461). Dapagliflozin significantly reduced albuminuria by 21% (baseline

eGFR of ~50 mL/min/1.73 m^2 and a mean urine albumin-to-creatinine ratio [UACR] of ~27 mg/g) and by 38% with the combination of saxagliptin, 24 weeks post-treatment. The HbA1c reduction was three times higher with combination therapy compared to dapagliflozin monotherapy (58% vs. 16%). After adjusting for concomitant changes in HbA1c, SBP, eGFR and uric acid, dapagliflozin reduced albuminuria by 15% and by 31% with the combination therapy indicating that there was no influence of these covariates on the albuminuria-lowering effect. While minor hypoglycemia was more common with the dapagliflozin and saxagliptin combination, major hypoglycemia did not vary across the groups. Further, volume depletion and impaired kidney function related adverse events were common with the dapagliflozin and saxagliptin combination but did not differ between dapagliflozin alone and placebo groups.[44]

DAPA-CKD is a randomized double-blind trial that assessed the safety and efficacy of dapagliflozin in reducing renal events in CKD 2-4 stage patients (n = 4,304) The primary composite endpoint was the worsening of renal function, defined as a composite of an eGFR decline of at least 50%, onset of end-stage kidney disease, and death from a CV or renal cause. Overall, 197/2,152 primary endpoint events occurred with dapagliflozin, compared to 312/2,152 events with placebo (HR 0.61; 95% CI: 0.51-0.72; $p < 0.001$). The benefits of dapagliflozin were consistent regardless of T2DM status. Dapagliflozin also reduced worsening renal function or death due to kidney failure (HR 0.56; 95% CI: 0.45-0.68; $p < 0.001$); HHF or CV death (HR 0.71; 95% CI: 0.55-0.92; $p = 0.009$) and all-cause mortality (HR 0.69; 95% CI: 0.53-0.88; $p = 0.004$).[45]

Table 1 presents the expert opinions on the beneficial role of dapagliflozin concerning cardiac and renal outcomes.

Table 1. Expert Opinion

- There is emerging evidence about the role of dapagliflozin in prediabetes, especially in the space of cardiac and kidney disease, irrespective of diabetes status. In this context, the majority of the experts agreed to the use of dapagliflozin in patients with metabolic syndrome irrespective of diabetes status. However, it was highlighted that this treatment would be considered off-label. The experts opined that data on mechanistic aspects of dapagliflozin in CV and renal metabolic therapy would provide deeper insights into the role of dapagliflozin concerning cardiac and renal outcomes.
- With emerging data on HFrEF and data in CKD, it is evident that dapagliflozin is entering the nondiabetes arena. For now, the role of endocrinologists will largely remain in the space of T2DM with a focus on preventing HF and CKD. However, in nondiabetic patients, the experience of endocrinologists should be used, so that the product is utilized optimally by other specialists. Risk assessment tools are useful in identifying patients at risk of HF and for decision-making, in assigning specific treatment of diabetes control and prevention and or management of risk factors with SGLT inhibitors. The cardiac benefits can probably be attributed to the hematocrit mechanism. The experts suggested the need for publication and multidisciplinary academic meetings involving the endocrinologists and cardiologists' communities to have a balanced view of different specialists.

CARDIORENAL REHABILITATION POST-COVID

Since its outbreak in late 2019, there has been a rapid spread of the novel coronavirus disease (COVID-19) globally.[46] The healthcare system has been severely burdened by COVID-19, especially due to the absence of an approved therapeutic protocol.[47] Despite organ support, mortality is significantly high in patients receiving advanced respiratory support or dialysis or kidney transplant (65% and 78%, respectively). Further, a prospective observational study revealed that the involvement of cardiac complications and ongoing MI in patients post-COVID recovery was independent of severity and overall course of the acute illness, pre-existing conditions and the time from the original diagnosis.[48] Since SGLT2 inhibitors have shown cardio- and renal protection among diabetes and patients without diabetes, they may offer organ support in high-risk patients. The prospective beneficial mechanisms of SGLT2 include: 1) improving ventricular load by diuresis or natriuresis; 2) improving cardiac energy metabolism and 3) reducing the risk of kidney disease progression. Further preclinical data suggest benefits on the pulmonary system as well.[49] Expert opinion on role

Table 2. Expert Opinion

As known, survivors of severe acute respiratory syndrome (SARS) and other pandemics have several complications related to the cardiopulmonary, vasculometabolic and neuropsychiatric systems. In this context, there is a need for a publication on vasculometabolic and cardiorenal rehabilitation post-COVID, to evaluate the role of SGLT2 inhibitors.
Most complications related to post-respiratory infection are largely confined to the pulmonary system, and it would be interesting to know the role dapagliflozin/SGLT2 inhibitors play in preventing pulmonary complications. The ongoing DARE-19 (Dapagliflozin in Respiratory Failure in Patients With COVID-19) trial may provide valuable insights in this regard.[50]

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of dapagliflozin concerning cardiorenal rehabilitation post-COVID-19 is presented in Table 2.

CONCLUSION

In summary, there exist robust data supporting the beneficial role of dapagliflozin concerning cardiac and renal outcomes. Further, dapagliflozin was found to reduce HHF or CV death by 23% and reduce the risk of kidney disease progression by 45% independent of baseline ASCVD or history of HF.[51] Dapagliflozin substantially reduced the risk of ESRD or acute kidney injury, dialysis, transplantation or death due to kidney disease by ~30%. Renal protection was consistent across all eGFR and baseline albuminuria values.[52] Thus, the role of dapagliflozin in cardio- and nephroprotection potentially extends beyond T2DM patients.

Conflict of Interest: Bharath HS is an employee of AstraZeneca Pharma India Ltd.

Funding: This work was supported by AstraZeneca Pharma India Ltd.

Contribution Details

All authors have contributed equally towards the conception and design of the study, or acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content and for final approval of the version to be submitted.

Acknowledgment

The authors would like to thank AstraZeneca Pharma India Ltd for providing medical writing assistance in the development of this manuscript, in collaboration with BioQuest Solutions in accordance with GPP3 guidelines (http://www.ismpp.org/gpp3).

Key Messages: Dapagliflozin, a SGLT-inhibitor, has been shown to improve HbA1c reduction in patients with major comorbidities associated with T2DM and is expected to become a preferred drug in T2DM. Recent studies have shown that dapagliflozin also significantly reduces cardiovascular events and delays kidney disease progression irrespective of diabetes. Dapagliflozin is emerging as a choice in these populations.

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REVIEW ARTICLE

Management of Diabetic End-stage Renal Disease: Role of Hemodialysis

H SUDARSHAN BALLAL

ABSTRACT

Diabetes mellitus is now the most common cause of end-stage renal disease (ESRD) all across the globe, including India. In view of the alarming rise in numbers, renal failure due to type 2 diabetes has been termed a "medical catastrophe of worldwide dimensions." When a patient develops uremic symptoms he needs renal replacement therapy. The renal replacement therapies available for all patients with ESRD are: hemodialysis, chronic ambulatory peritoneal dialysis (CAPD) and renal transplantation. Kidney transplantation is the best option for patients with diabetic ESRD. The 5-year survival of transplant patients of 75-85% is far superior to the 5-year survival rate of around 25% on dialysis.

Keywords: Diabetes mellitus, end-stage renal disease, renal replacement therapies, hemodialysis, CAPD, renal transplantation

Diabetes mellitus is now the most common cause of end-stage renal disease (ESRD) all across the globe, including India. It is estimated that 30-50% of patients being initiated on renal replacement therapy (RRT) have diabetes as the cause of their ESRD[1] and most of these patients have type 2 diabetes. In view of the alarming rise in numbers, renal failure due to type 2 diabetes has been termed a "medical catastrophe of worldwide dimensions".[2] This article will discuss the management of diabetic ESRD specifically related to type 2 diabetes.

RENAL REPLACEMENT THERAPY

When a patient's kidney function, as measured by the calculated glomerular filtration rate, has reached <10 mL/min (ESRD) or the patient develops uremic symptoms they need RRT.

The RRTs available for all patients with ESRD are:

- Hemodialysis
- Chronic ambulatory peritoneal dialysis (CAPD)
- Renal transplantation.

Though these modalities are available for all patients with ESRD, there are significant differences in the morbidity and mortality of any given modality between the diabetic and nondiabetic ESRD population. We will discuss some of these issues, specifically the modality of hemodialysis.

HEMODIALYSIS FOR DIABETIC ESRD

Although hemodialysis prevents death from uremia, the patient survival on hemodialysis is poor, especially for patients with diabetes, being approximately 20-25% at 5 years as compared to 40-50% for other causes of ESRD.[3] This is worse than many cancers. The survival of patients on maintenance hemodialysis in India seems dismal for both, diabetic and nondiabetic populations.[4]

The important contributors for mortality in the diabetic dialysis population are: Cardiovascular disease, adequacy of dialysis and nutritional status.

- **Cardiovascular disease (CVD):** CVD is the most common cause of death accounting for more than one-half of the cases.[5] The main reason for such a high mortality rate, which is of cardiovascular origin in the majority of cases is that the cardiovascular conditions of patients with diabetes are already severely impaired when they start RRT, as demonstrated by the high prevalence of coronary artery disease, stroke, peripheral occlusive disease and amputations. This also explains why patients who have diabetes and are on RRTs are at higher risk of developing *de novo* CVD, particularly ischemic heart disease, which not only is more frequent but also has a more aggressive course than in nondiabetic patients. In view of this, aggressive

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measures to manage CVD need to be adopted in all diabetic patients even before they reach the stage of dialysis.

- **Adequacy of dialysis:** Adequacy of dialysis, which also plays an important role in CVD and nutrition (MIA or malnutrition inflammation atherosclerosis syndrome), is also a contributor to the poor outcome and diabetics, in particular, seem to be more sensitive than nondiabetics to inadequate dialysis.[6] The increase in mortality of these patients largely disappears if there is an improvement in the nutritional status as reflected by an increase in serum albumin and creatinine.[7] This is a major problem in India where for various reasons like financial constraints, lack of access and availability of good dialysis units causes most patients to have inadequate dialysis.[8] Whenever possible, it is very essential to monitor the adequacy of dialysis by using biochemical measures like urea reduction rates, Kt/V and clinical well-being of patients and to take measures to improve the adequacy of dialysis.
- **Nutrition in dialysis:** Nutrition in dialysis patients is closely linked to inadequate dialysis, which leads to anorexia and poor calorie and protein intake. This is reflected by poor serum albumin and creatinine levels, which are indicators for mortality in dialysis patients. The problems of diabetic gastroparesis and diabetic enteropathy compound the nutritional problems.

The help of a good dietician and measures to treat diabetic gastroparesis and enteropathy by motility agents, frequent small foods and appropriate use of broad-spectrum antibiotics to treat bacterial infections in diabetic enteropathy are needed to maintain adequate nutrition. It is to be noted that cisapride is best avoided in this population because of the risk of fatal arrhythmias.[9]

DIET IN DIABETIC PATIENTS ON DIALYSIS

The general recommendation for diet in dialysis patients is given in Table 1. The iron requirement of dialysis patients varies and will need to be addressed on a patient to patient basis. In general, water-soluble vitamins are routinely prescribed and calcitriol may be needed in some patients.

Table 1. Daily Dietary Recommendations for Dialysis Patients versus Nonuremics[a]

Factor	Nonuremic	HD	PD
Protein (g/kg)	0.8	1.2	1.2-1.5
Calories (sedentary; kcal/kg)	30	30[b]	30-40[b,c]
Protein (%)	15-20	15	15
Carbohydrate (%)	55-60	55-60[d]	55-60[c,d]
Fat (%)	20-30	Balance	Balance
Cholesterol (mg)	300-400	300-400	300-400
Polyunsaturated/Saturated fat ratio	2.0:1.0	2.0:1.0	2.0:1.0
Crude fiber (g)	25	25	25
Sodium (1 g = 43 mEq)	2-6 g	2 g + 1 g/LUO	2-4 g + 1 g/LUO
Fluids (L)	Ad lib 1 L/LUO	1 L + 1 L/LUO	1.0-2.5 L + 1 L/LUO
Potassium (1 g = 25 mEq)	2-6 g	2 g + 1 g/LUO	4 g + 1 g/LUO
Calcium (g)	0.8-1.2	Diet +1.2	Diet + 1.2
Phosphorus (g)	1.0-1.8	0.6-1.2	0.6-1.2
Magnesium (g)	0.35	0.2-0.3	0.2-0.3

[a]All intakes calculated on the basis of normalized body weight (i.e., the average body weight of normal persons of the same age, height and sex as the patient).
[b]These levels of caloric intake are rarely attained in practice.
[c]Includes glucose absorbed from dialysis solutions.
[d]Carbohydrate intake should be decreased in patients with hypertriglyceridemia.
HD = Hemodialysis; PD = Peritoneal dialysis; LUO = Liters of urine output per day.

BLOOD SUGAR CONTROL IN DIABETIC DIALYSIS PATIENTS

There are certain special problems about blood sugar control in dialysis patients.

Altered Insulin Metabolism

In uremic patients (both diabetic and nondiabetic), insulin secretion by the β-cells of the pancreas is reduced and the responsiveness of peripheral tissues (e.g., muscle) to insulin is depressed. On the other hand, the rate of insulin catabolism (renal and extrarenal) is decreased, and therefore, the half-life of any insulin present in the circulation is prolonged.

All of these abnormalities are only partially corrected after institution of maintenance dialysis therapy.

Increased Sensitivity to Insulin

In diabetic dialysis patients treated with exogenous insulin, the importance of reduced insulin catabolism overrides the impact of insulin resistance; when exogenous insulin is administered, its effect may be intensified and prolonged. Thus, smaller than usual doses should be given.

Insulin Therapy

Tight control of sugar is sometimes difficult to achieve in diabetic dialysis patients. Nevertheless, good glucose control is worthwhile with split doses of insulin preferably. The "amount of insulin" per day required for patients receiving maintenance hemodialysis is usually small; optimum control of glycemia is achieved by administration of long-acting insulin at two separate times during the day (split dosing) and by supplementing with regular insulin for meals as needed. The proportions of long-acting and regular insulin, as well as the total insulin doses vary widely among different patients. Hypoglycemia is quite common in diabetic dialysis patients usually due to reduced insulin catabolism and reduced intake or food and/or poor absorption.

A fasting serum glucose of <140 mg/dL and a postprandial value <200 mg/dL is a reasonable goal to achieve.

Oral Hypoglycemic Agents

Lack of clinical studies on use of oral hypoglycemic agents (OHAs) in dialysis patients restricts the use of these agents.

Nevertheless, these agents are useful adjuncts in the treatment of diabetics and are used by many nephrologists. The safety of sulfonylureas depends on their mode of metabolism and their half-life. Use of short-acting agents primarily metabolized by the liver is, in general, safer in dialysis patients. Acetohexamide, chlorpropamide and tolazamide are excreted to a large extent in the urine. These drugs should not be used in dialysis patients because their half-lives will be greatly prolonged in the absence of renal function, possibly resulting in severe and prolonged hypoglycemia. The excretion of glyburide is 50% hepatic, and prolonged hypoglycemia has been reported using this drug in dialysis patients. Metabolism of glipizide, tolbutamide and gliclazide is almost completely hepatic. Consequently, the last three drugs should be considered if an OHA is desired. Many drugs frequently used in dialysis patients either antagonize (phenytoin, nicotinic acid, diuretics) or enhance (sulfonamides, salicylates, warfarin, ethanol) the hypoglycemic action of sulfonylureas.

Metformin, a biguanide, is associated with increased incidence of lactic acidosis in dialysis patients and should not be used. Acarbose inhibits α-glucosidase in the enteric mucosa and moderates postprandial hyperglycemia. It may prove to be a useful adjunct to other diabetic medications in diabetic patients. Troglitazone and other thiazolidinediones sensitize the target tissues to insulin and may be of help in obese, type 2 diabetics with insulin resistance. However, the use of this class of drugs may be associated with the risk of severe hepatotoxicity.

In general, insulin use is preferable in diabetic dialysis patients but judicious use of appropriate OHAs can be done.

Specific problems of hemodialysis in diabetic patients:

- Difficulty in creating and maintaining a vascular access because of severe peripheral vascular disease (PVD) in older diabetic patients.
- Inability to tolerate volume shifts giving rise to hypotension during hemodialysis because of autonomic neuropathy and CVD.
- Risk of infection.
- Progression of diabetic retinopathy.

In view of all these problems, meticulous planning and appropriate management should start in the predialysis period well before dialysis is anticipated and would involve a special diabetic team consisting of an Ophthalmologist, Vascular Surgeon, Podiatrist, Endocrinologist, Cardiologist, Neurologist and Dietician to help the nephrology team in keeping the patient as fit as possible even before they reach dialysis.

TIMING OF DIALYSIS IN DIABETIC ESRD

In general, most nondiabetic patients are initiated on dialysis when the creatinine clearance is <10 mL/min.

In diabetic patients, dialysis may have to be initiated at creatinine clearance even >15 mL/min.[9] The reasons for this being:

- Renal functions deteriorate rapidly in this group
- Hypertension is very difficult to control with severe renal failure
- Most patients have CVD with volume overload
- Uremic symptoms may manifest earlier than non-diabetic patients.

In spite of these recommendations, dialysis is usually started as an emergency in most Indian patients because of uremia, pulmonary edema or severe hyperkalemia because of poor awareness, financial constraints and lack of facilities for dialysis.[4,8]

ROLE OF CAPD

CAPD is another modality of treatment in diabetic ESRD. Though it has its advantages and disadvantages, the following factors decide the modality of dialysis:

- Comorbid conditions
- Family and home support
- Financial support
- CVD and PVD leading to poor vascular access for dialysis
- Hemodynamic stability
- Availability of hemodialysis centers.

CAPD is 30-50% more expensive than hemodialysis in India and is generally used for patients who do not have access to hemodialysis, have severe chronic heart failure (CHF), hemodynamic instability, poor vascular access and are not candidates for transplantation. The patient and the family should be motivated and have adequate financial support. Table 2 gives the comparison between the two modalities of dialysis.

Table 2. Dialysis Modalities for Diabetics

Modality	Advantages	Disadvantages
Hemodialysis	Very efficient	Risky for patients with advanced cardiac disease
	Frequent medical follow-up (in center)	Multiple arteriovenous access surgeries often required; risk of severe hand ischemia
	No protein loss to dialysate	High incidence of hypotension during dialysis session
		Predialysis hyperkalemia
		Prone to hypoglycemia
CAPD	Good cardiovascular tolerance	Peritonitis, exit site and tunnel infection risks similar to those in nondiabetic dialysis patients
	No need for arteriovenous access	Protein loss to dialysate
	Good control of serum potassium	Increased intra-abdominal pressure effects (hernias, fluid leaks, etc.)
	Good glucose control, particularly with use of intraperitoneal insulin; less severe hypoglycemia	Schedule not convenient for helper if one is required (e.g., for a patient with physical disability like blindness, stroke, etc.)
CCPD	Good cardiovascular tolerance	Protein loss to dialysate
	No need for arteriovenous access	
	Good control of serum potassium	
	Good glucose control with use of intraperitoneal insulin	Very very expensive
	Good for patients with disability	
	Peritonitis risk slightly less than for CAPD	

CAPD = Continuous ambulatory peritoneal dialysis; CCPD = Continuous cycling peritoneal dialysis.

SURVIVAL ON HEMODIALYSIS AND PERITONEAL DIALYSIS

There have been conflicting data about the survival of patients on CAPD compared to hemodialysis. Initial data from Michigan suggested an advantage for CAPD.[10] However, most studies after adjustment for comorbid condition, have not found a statistically significant survival difference between the two modalities.[11]

TRANSPLANTATION

Kidney transplantation is the best option for patients with diabetic ESRD. The 5-year survival of transplant patients of 75-85%, though less than that of nondiabetic ESRD, is still far superior to the 5-year survival rate of around 25% on dialysis.[3,12] Though in general healthier patients go on to transplant and sicker patients remain on dialysis the survival rates are better, even when these are factored in. Transplantation is also associated with a better quality-of-life and high degree of rehabilitation.

The pre- and post-transplant care of diabetic patients is generally similar to that of nondiabetics. However, in view of the high prevalence of CVD in this population, meticulous attention has to be paid to screen these patients for CVD prior to the transplantation.[13]

RECOMMENDATIONS FOR TREATMENT OF DIABETIC ESRD PATIENTS

Kidney transplant remains the best option of RRT for patients with diabetic ESRD in all suitable candidates. Recommendations for those not suitable for transplantation-

CAPD is recommended for patients with:

- Poor vascular access because of PVD
- Severe CVD with hemodynamic instability during hemodialysis
- Nonavailability of hemodialysis centers
- Good family and financial support
- Motivated patients.

Hemodialysis is the treatment for all the rest which is the treatment available for the vast majority of patients with diabetic ESRD in India who are not candidates for transplantation. In view of the multiple associated comorbid conditions, a multidisciplinary approach is needed to prevent and manage the complications of vascular diseases, malnutrition and retinopathy in diabetic dialysis patients.

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DIABÉTIX

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CASE REPORT

Cocktail Inferno – Multiple Sclerosis with Type 2 Diabetes Mellitus in a Patient with Lepromatous Leprosy

SONIA JAIN*, PRIYANKA DATE†, NEERAJ DODKE‡

ABSTRACT

Co-occurrence of multiple sclerosis with type 2 diabetes mellitus with lepromatous leprosy is rare. We hereby report a case of multiple sclerosis with type 2 diabetes mellitus with lepromatous leprosy in a middle-aged female. She was clinically diagnosed as having multiple sclerosis with type 2 diabetes mellitus and presented with fever, ENL and neuritis. Her MRI reports were normal but she had a positive slit-skin smear and skin biopsy as lepromatous leprosy. Proceeding with this diagnosis, she was treated with baclofen for spastic bladder, antibiotics for urinary tract infection, oral hypoglycemic agents and oral steroids with multibacillary treatment for leprosy with type 2 reactions. She responded well and currently is being followed-up.

Keywords: Multiple sclerosis, leprosy, diabetes mellitus, demyelinating neuropathy

Multiple sclerosis is a disorder with heterogeneous clinical and pathologic features reflecting various pathways to tissue injury.[1] Inflammation, demyelination and axonal degeneration are the key pathologic mechanisms, which lead to clinical manifestations.[2,3] However, the cause of multiple sclerosis remains unknown.[4,5] The most widely accepted theory suggests that it begins as an inflammatory immune-mediated disorder characterized by autoreactive lymphocytes.[1,6] Later, the disease is dominated by microglial activation and chronic neurodegeneration.[2]

Leprosy (Hansen's disease) is an infectious disease caused by *Mycobacterium leprae* that involves the skin and peripheral nerves. Early diagnosis and a full course of treatment are critical for preventing lifelong neuropathy and disability.[7] Although the infection is highly responsive to treatment, leprosy became an important global health concern due to deformities and disabilities of the eyes, hands and feet secondary to neuropathy which are often irreversible and require lifelong care and rehabilitation. Therefore, early diagnosis and management are necessary to minimize the likelihood of these disabilities.[8]

Type 2 diabetes mellitus is characterized by hyperglycemia, insulin resistance and relative impairment in insulin secretion. It is a common disorder with a prevalence that rises markedly with increasing degrees of obesity.[9]

The prevalence of type 2 diabetes has risen alarmingly in the past decade,[10] in large part linked to the trends in obesity and sedentary lifestyle.[11]

CASE REPORT

A 55-year-old female was brought by her relatives to the skin department. She had flexor spasms, difficulty in walking, spastic bladder with an indwelling catheter since last 4 years and was diagnosed to have multiple sclerosis. She had multiple admissions for fever and urinary tract infection and was on oral hypoglycemic agents on regular basis. She presented with fever, multiple red-colored raised lesions (Erythema nodosum leprosum or ENL) all over the body (Fig. 1), with weakness, tingling and numbness over both

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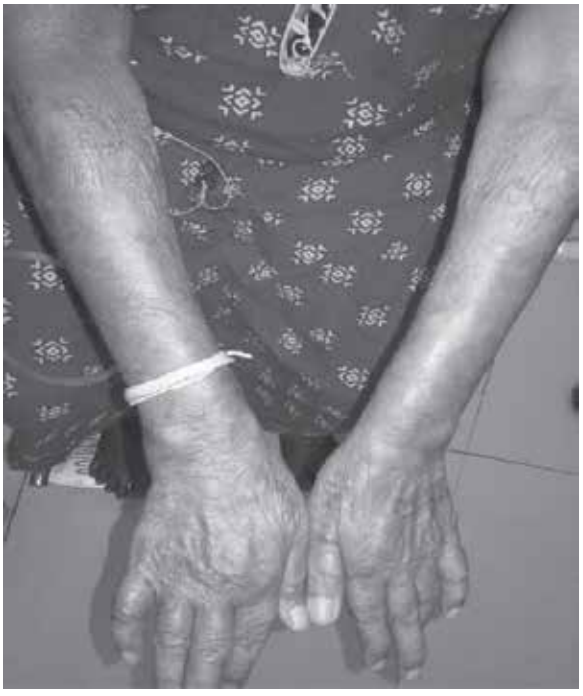

Figure 1. Multiple red-colored raised lesions (ENL) over body.

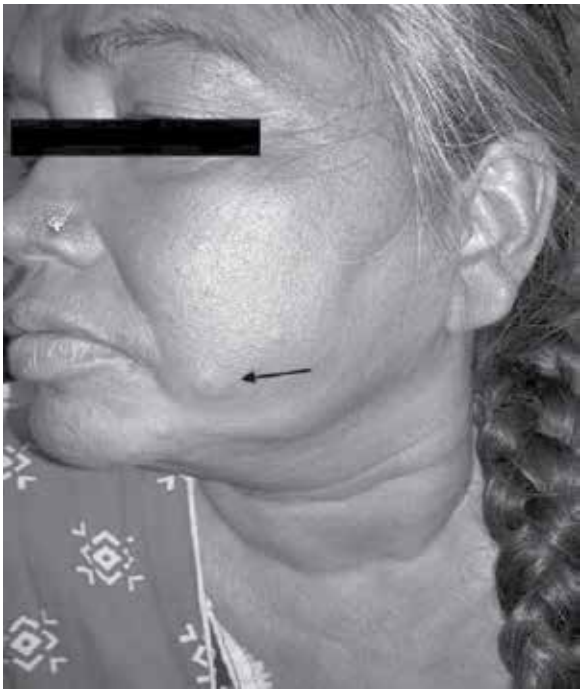

Figure 2. ENL present over face adjacent to angle of mouth (*arrow*).

upper and lower limbs. ENL were also present over her face adjacent to the angle of mouth (Fig. 2). Xerosis and ichthyosis characteristic of leprosy was visible over bilateral upper limbs (Fig. 3). There was no history of photosensitivity or any drug intake or application of any local irritant prior to the initial lesion.

Her detailed central nervous system evaluation revealed upper motor neuron type of paraparesis, sensorimotor with proximal as well as distal muscle involvement with urge incontinence suggestive of spastic type of neurogenic bladder. Her mental functions were intact with no cranial nerve involvement. Cardiovascular system, respiratory system and per abdominal evaluation was within normal limits.

Her routine blood biochemistry was normal except for low hemoglobin levels (5.9%), raised white blood cell (WBC) counts (15,800) and raised random blood sugar (RBS) levels (157 mg/dL). Urine analysis revealed urinary tract infection for which she was treated with antibiotics. Bladder care was given. She was treated with baclofen. Skin examination revealed positive slit-skin smear for acid-fast bacilli with bacteriological index of 3.5 and skin biopsy consistent with lepromatous leprosy. She was put on oral steroids for type 2 lepra reaction and multibacillary anti-leprosy treatment for leprosy. Appropriate oral hypoglycemic agents were continued as she was reluctant with insulin administration. Brain imaging was normal. She responded well and her

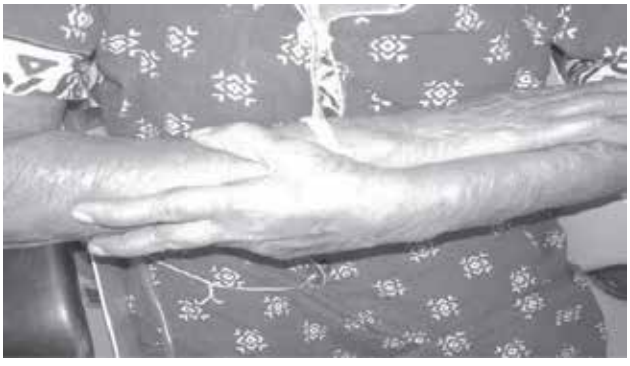

Figure 3. Xerosis and icthyosis visible over bilateral upper limbs.

flexor spasms decreased. A psychiatric consultation was sought for her depression due to chronic illness and was started on antidepressants.

DISCUSSION

Dominant or recessive genetic mutations give rise to a number of inherited neuropathies. The basic pathology happens to be in the Schwann cells, the myelinating unit of the neuron leading to defective myelination, alteration of the axonal cytoskeleton and disruption of the axonal transport.[12] Genes involved in the axonal transport are the chief site of mutation in the majority of inherited neuropathies leading to the atrophy of the axons and directly correlate with the clinical features in the inherited neuropathies.[12]

Diabetes mellitus is characterized by a number of sensorimotor and mixed neuropathies. The pathologic hallmark of neuropathies occurring in long-term diabetics involves the advanced glycation end products, persistent oxidative stress, polyol pathway flux and protein kinase C activation, ultimately contributing to microvascular disease and nerve dysfunction.[13]

Common symptoms of multiple sclerosis include sensory abnormalities including pain, motor symptoms due to involvement of the pyramidal tracts, visual disturbances, ataxia and Lhermitte sign. The pattern of abnormalities can vary from subtle limb weakness or sensory symptoms like Uhthoff phenomenon to more severe sensorimotor noncompressive myelopathies like acute transverse myelitis. Retrobulbar neuritis and optic neuritis have been the common causes of transient visual disturbances in multiple sclerosis. The onset is often polysymptomatic. Neuropathy is an early feature in Hansen's disease, as earliest diagnostic lesions are characterized by hypoesthesia.[14] Though early sensory loss is a common finding in leprosy, in some cases, patients can present with pain, which is often late in the course of the disease.[15,16]

In the tuberculoid spectrum of the Ridley-Jopling classification, neuropathy occurs in the proximity of the skin lesions, as against neuropathy in lepromatous disease, which is more generalized. Common nerves include the ulnar, median nerves (claw hand), the common peroneal nerve (foot drop), the posterior tibial nerve (claw toes and plantar insensitivity), the facial nerve (lagophthalmos), the radial cutaneous nerve, and the great auricular nerve. Subclinical neuropathy is found more commonly, as against it was previously believed in leprosy.

These results may have implications for the design of ErbB2 RTK-based therapies for both leprosy nerve damage and other demyelinating neurodegenerative diseases.[17]

Here we report this case as to the best of our knowledge, leprosy with multiple sclerosis has not been reported in literature.

CONCLUSION

Multiple sclerosis, Hansen's disease and diabetes mellitus are multisystem diseases with distinct etiologies affecting the sensory as well as motor nerve fibers. It is considerably rare to find a demyelinating, infectious and autoimmune disease of the nerves to coexist in the same patient. All these conditions can be managed simultaneously and successfully.

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BRIEF COMMUNICATION

Diabetes Therapy by the Ear via this Health Promoting Attitude Called Salutogenesis

UTSAV SAHU

ABSTRACT

Diabetes is a major public health problem that is approaching epidemic proportions globally. Despite the best efforts by healthcare providers, persons with diabetes and the community at large, remain unsatisfied with the approach to diabetes management. This brief communication utilizes Antonovsky's concept of salutogenesis, to suggest a person friendly and community friendly framework for diabetes care. Salutogenesis is used as a means of studying the biopsychosocial domains of diabetes, and as a guiding principle for health-related communication. Adoption of a salutogenic approach to diabetes care should help improve outcomes and satisfaction with healthcare.

Keywords: Diabetes, biopsychosocial communication, health promoting attitude, patient-centered care

Salutogenesis is derived from two Latin words, "salus" meaning health and "genesis" meaning origin. The concept of salutogenesis was proposed by Aaron Antonovsky, an Israeli medical sociologist, nearly 40 years back.[1] The salutogenic theory uses a positive thought process to describe health, focusing on factors that support well-being, rather than those that cause disease (pathogenesis). It's an approach which focuses on factors that support human health and wellness rather than diseases and their complications. It's an umbrella term which encompasses gratitude, empathy, humor optimism and positivity, wellness and mindfulness, attachment and emotional intelligence.

Chronic disease is characterized by a strong psychosocial component, in addition to biomedical dysfunction. As lifestyle is an important contributor to chronic disease pathophysiology, lifestyle modification becomes an integral strategy of management. This requires multiple and significant changes, which can create a lot of discomfort and distress. Asking them to leave sweets and all their favorite food items, and then asking them to get out of their comfort zone, and go for walks and exercise daily, may lead to impaired adjustment to the chronic disorder. In diseases such as diabetes, this has been termed as "diabetes distress".[2] Diabetes distress is when a person feels frustrated, defeated or overwhelmed by diabetes. Diabetes is not limited to quantitative variables such as glucose, weight, blood pressure or lipids. The diabetes care provider also tries to assess emotional and social domains of health.

Disease cannot be managed until it is screened for, diagnosed and monitored. However, diagnosis and management can occur together in clinical medicine. The concept of therapeutic patient education suggests that patient interaction and education have a direct therapeutic effect as well. Another term for this diagno-therapeutic strategy is "diabetes therapy by the ear", delivered with "words of comfort".[3] Half the patient's pain, agony and suffering should get better with the comforting words from their doctor. If we give time to the patient, if we just listen to them, they feel heard and they start getting better.

The medical interview serves several functions. It is used to collect information to assist in diagnosis (the "history" of the present illness), to understand patient values, to assess and communicate prognosis, to establish a therapeutic relationship, and to reach agreement with the patient about further diagnostic procedures and therapeutic options. It also serves as an opportunity to influence patient behavior, such as in motivational discussions about smoking cessation or medication adherence.[4] To help improve adherence in the long-term, physicians should counsel about the importance of taking medicine and reinforce it by using the teach back method.[5] Though delivered to the best of our ability, we are sometimes unable to explain the rationale of our interventions, thus creating lack of confidence and distrust. A 3I strategy (interaction,

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information, involvement) has been proposed to bridge the patient-provider gap in communication.[6] The clinician's role does not end with diagnosis and treatment. The importance of the empathic clinician in helping patients and their families bear the burden of serious illness and death cannot be overemphasized. "To cure sometimes, to relieve often and to comfort always" is a French saying as apt today as it was five centuries ago—as is Francis Peabody's admonition: The secret of the care of the patient is in caring for the patient.[7] Training to improve mindfulness and enhance patient-centered communication increases patient satisfaction and may also improve clinician satisfaction.

As clinicians, we should always keep a health promoting attitude and add scoops of salutogenesis during the conversation with our patients to motivate them to strive for good health and well-being.

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Medicolegal Insights

Can the Consent be Taken a Few Days Before the Procedure?

Recall of informed consent is not affected by the timing of obtaining informed consent before any procedure.

Evidence: Sixty patients scheduled for colonoscopy or esophagogastroduodenoscopy were enrolled in a prospective, randomized study. Each patient received informed consent 24-72 hours or immediately before the procedure, and follow-up occurred 1-3 days post procedure. There was no statistically significant difference in recall of informed consent or the individual elements of informed consent (indication, risks, benefits, alternatives) between the two groups. The study concluded that recall of informed consent is similar whether consent is obtained immediately or several days before endoscopic procedures.

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What are the Duties of a Doctor in Respect of Signing Professional Certificates, Reports and Other Documents?

Regulation 7.7 elaborates on the issue of signing professional certificates, reports and other documents.

It states as follows: "Registered medical practitioners are in certain cases bound by law to give, or may from time to time be called upon or requested to give certificates, notification, reports and other documents of similar character signed by them in their professional capacity for subsequent use in the courts or for administrative purposes, etc. Such documents, among others, include the ones given at Appendix 4.

Any registered practitioner who is shown to have signed or given under his name and authority any such certificate, notification, report or document of a similar character which is untrue, misleading or improper, is liable to have his name deleted from the Register."

Can Deviation from Medical Practice be Termed Medical Negligence?

In Jacob Mathew v. State of Punjab SC/0457/2005:(2005) 6 SCC 1, the Supreme Court of India has observed: "Deviation from normal practice is not necessarily evidence of negligence. To establish liability on that basis, it must be shown:

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

What are the Violations in Advertising in Indian Penal Code?

Sec. 292(2) (d) of Indian Penal Code, 1860, makes it a punishable offence to publish, distribute, sell, hire or circulate any obscene advertisement.

Section 292 in The Indian Penal Code

[260][292. Sale, etc., of obscene books, etc.—[261]]

(1) For the purposes of Sub-section (2), a book, pamphlet, paper, writing, drawing, painting, representation, figure or any other object, shall be deemed to be obscene if it is lascivious or appeals to the prurient interest or if its effect, or (where it comprises two or more distinct items) the effect of any one of its items, is, if taken as a whole, such as to tend to deprave and corrupt person, who are likely, having regard to all relevant circumstances, to read, see or hear the matter contained or embodied in it.

[262][(2)] Whoever—

(a) sells, lets to hire, distributes, publicly exhibits or in any manner puts into circulation, or for purposes of sale, hire, distribution, public exhibition or circulation, makes, produces or has in his possession any obscene book, pamphlet paper, drawing, painting, representation or figure or any other obscene object whatsoever, or

(b) imports, exports or conveys any obscene object for any of the purposes aforesaid, or knowing or having reason to believe that such object will be sold, let to hire, distributed or publicly exhibited or in any manner put into circulation, or

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(d) advertises or makes known by any means whatsoever that any person is engaged or is ready to engage in any act which is an offence under this section, or that any such obscene object can be procured from or through any person, or

(e) offers or attempts to do any act which is an offence under this section, shall be punished [263][on first conviction with imprisonment of either description for a term which may extend to 2 years, and with fine which may extend to two thousand rupees, and, in the event of a second or subsequent conviction, with imprisonment of either description for a term which may extend to 5 years, and also with fine which may extend to five thousand rupees].

Can a Patient Seek Redressal for Grievances Regarding Treatment Received?

Yes, patient who is the sufferer from the negligent act of the doctors can seek remedy under various laws:

1. **Compensatory action -** Complaint against doctors, staff or hospital whether private or government hospitals who committed negligence seeking monetary compensation before:
   i. Civil Court under law of Torts or Law of Contract,
   ii. High Court under the Constitutional Law, or
   iii. Consumer Courts under Consumer Protection Act.
2. **Punitive action -** Criminal complaint under Indian Penal Code against the doctor.
3. **Disciplinary action -** Complaint seeking disciplinary action against the medical practitioner or the hospitals as the case may be, before statutory bodies governing the medical practitioners such as Medical Council of India or State Medical Council.
4. **Recommendatory action -** Complaint before the National/State Human Rights Commission seeking compensation.

Does a Decision Taken in Good Faith Amount to Negligence?

A decision taken in good faith is not a crime. Defenses are available to the doctors under Indian Penal Code (IPC) sections 88, 92 and 93.

- **Section 88.** Act not unintended to cause death, done by consent in good faith for person's benefit: Nothing, which is not intended to cause death, is an offence by reason of any harm which it may cause, or be intended by the doer to cause, or be known by the doer to be likely to cause, to any person for whose benefit it is done in good faith, and who has given a consent, whether express or implied, to suffer that harm, or to take the risk of that harm.
- The illustration along with this section is: "A, a surgeon, knowing that a particular operation is likely to cause the death of Z, who suffers under a painful complaint, but not intending to cause Z's death and intending in good faith, Z's benefit, performs that operation on Z, with Z's consent. A has committed no offence."
- **Section 92.** Act done in good faith for benefit of a person without consent: Nothing is an offence by reason of any harm which it may cause to a person for whose benefit it is done in good faith, even without that person's consent, if the circumstances are such that it is impossible for that person to signify consent, or if that person is incapable of giving consent, and has no guardian or other person in lawful charge of him from whom it is possible to obtain consent in time for the thing to be done with benefit.
- The illustration along with this section is: Z is thrown from his horse, and is insensible. A, a surgeon, finds that Z requires to be trepanned. A, not intending Z's death, but in good faith, for Z's benefit, performs the trepan before Z recovers his power of judging for himself. A has committed no offence. A, a surgeon, sees a child suffer an accident which is likely to prove fatal unless an operation be immediately performed. There is no time to apply to the child's guardian. A, performs the operation in spite of the entreaties of the child, intending, in good faith, the child's benefit. A committed no offence.
- **Section 93.** Communication made in good faith. No communication made in good faith is an offence by reason of any harm to the person to whom it is made, if it is made for the benefit of that person. Illustration A, a surgeon, in good faith, communicates to a patient his opinion that he cannot live. The patient dies in consequence of the shock. A has committed no offence, though he knew it to be likely that the communication might cause the patient's death.

A Specialist Gives an Opinion to a Physician on Phone Regarding a Patient (not seen by him). Is he/she Liable for any Mishap?

No legal liability will fall upon the doctor for giving an opinion on phone for cases not seen by him as there is

no contract between him and the patient. For negligence to be proved there has to be a duty, breach of that duty and resultant damage. In this case, there will no breach of duty. But, if the specialist has charged a fee for his opinion from the patient (patient can sue) or from the physician (patient and doctor both can sue), then he/she is liable. If the fee has been paid by the referring physician, it will be deemed to be paid by the patient.

Is There a Difference Between Active Euthanasia and Passive Euthanasia?

Yes. Active euthanasia and passive euthanasia differ from each other.

Active euthanasia means where death is caused by the administration of a lethal injection or drugs. Active euthanasia also includes physician-assisted suicide, where the injection or drugs are supplied by the physician, but the act of administration is undertaken by the patient himself. Active euthanasia is not permissible in most countries. The jurisdictions in which it is permissible are Canada, the Netherlands, Switzerland and the States of Colorado, Vermont, Montana, California, Oregon and Washington DC in the United States of America.

Passive euthanasia is when medical practitioners do not provide life-sustaining treatment (i.e., treatment necessary to keep a patient alive) or remove patients from life-sustaining treatment. This could include disconnecting life support machines or feeding tubes or not carrying out life-saving operations or providing life extending drugs. In such cases, the omission by the medical practitioner is not treated as the cause of death; instead, the patient is understood to have died because of his underlying condition.

In the matter titled as **"Common Cause versus Union of India, 2018 (5) SCC 1" the Hon'ble Constitution Bench of 4 Judges of the Supreme Court of India,** has held that:

"(v) There is an inherent difference between active euthanasia and passive euthanasia as the former entails a positive affirmative act, while the latter relates to withdrawal of life support measures or withholding of medical treatment meant for artificially prolonging life.

(vi) In active euthanasia, a specific overt act is done to end the patient's life whereas in passive euthanasia, something is not done which is necessary for preserving a patients life. It is due to this difference that most of the countries across the world have legalized passive euthanasia either by legislation or by judicial interpretation with certain conditions and safeguards."

Can a Patient Seek Redressal for Grievances Regarding Treatment Received?

Yes. The National Board for Accreditation of Healthcare (NABH) Patient Charter has provisions for this.

5. Right to redress

- Patient has the right to justice by lodging a complaint through an authority dedicated for this purpose by the health care provider organization or with government health authorities.
- The patient has the right to a fair and prompt hearing of his/her concern.
- The patient in addition has the right to appeal to a higher authority in the health care provider organization and insist in writing on the outcome of the complaint.

The Patient was not Getting Cured. Can this be Termed as Medical Negligence?

No doctor can give 100% guarantee about the treatment or surgery. The only assurance which a doctor can give or can be understood to have given by implication is that he is possessed of the requisite skill in that branch of profession which he is practicing and while undertaking the performance of the task entrusted to him he would be exercising his skill with reasonable competence.

The Hon'ble Apex Court in various judgments has duly held that no guarantee is given by any doctor or surgeon that the patient would be cured.

- In the matter titled as **"P. B. Desai versus State of Maharashtra, AIR 2014 SC 795,"** the Hon'ble Apex Court has held that:

"39. It is not necessary for us to divulge this theoretical approach to the doctor-patient relationship, as that may be based on model foundation. Fact remains that when a physician agrees to attend a patient, there is an unwritten contract between the two. The patient entrusts himself to the doctor and that doctor agrees to do his best, at all times, for the patient. Such doctor-patient contract is almost always an implied contract, except when written informed consent is obtained. While a doctor cannot be forced to treat any person, he/she has certain responsibilities for those whom he/she accepts as patients. Some of these responsibilities may be recapitulated, in brief:

(a) to continue to treat, except under certain circumstances when doctor can abandon his patient;

(b) to take reasonable care of his patient;

(c) to exhibit reasonable skill: The degree of skill a doctor undertakes is the average degree of skill possessed

by his professional brethren of the same standing as himself. The best form of treatment may differ when different choices are available. There is an implied contract between the doctor and patient where the patient is told, in effect, "Medicine is not an exact science. I shall use my experience and best judgment and you take the risk that I may be wrong. I guarantee nothing."

(d) Not to undertake any procedure beyond his control: This depends on his qualifications, special training and experience. The doctor must always ensure that he is reasonably skilled before undertaking any special procedure/treating a complicated case.

(e) Professional secrets: A doctor is under a moral and legal obligation not to divulge the information/ knowledge which he comes to learn in confidence from his patient and such a communication is privileged communication."

- In the matter **"Malay Kumar Ganguly vs. Sukumar Mukherjee & Ors. AIR 2010 SC 1162,"** the Hon'ble Supreme Court of India has held that:

  "INDIVIDUAL LIABILITY OF THE DOCTORS There cannot be, however, by any doubt or dispute that for establishing medical negligence or deficiency in service, the courts would determine the following:

  (i) No guarantee is given by any doctor or surgeon that the patient would be cured.

  (ii) The doctor, however, must undertake a fair, reasonable and competent degree of skill, which may not be the highest skill.

  (iii) Adoption of one of the modes of treatment, if there are many, and treating the patient with due care and caution would not constitute any negligence.

  (iv) Failure to act in accordance with the standard, reasonable, competent medical means at the time would not constitute a negligence. However, a medical practitioner must exercise the reasonable degree of care and skill and knowledge which he possesses. Failure to use due skill in diagnosis with the result that wrong treatment is given would be negligence.

  (v) In a complicated case, the court would be slow in contributing negligence on the part of the doctor, if he is performing his duties to the best of his ability.

  Bearing in mind the aforementioned principles, the individual liability of the doctors and hospital must be judged."

- In the landmark judgment of **"Jacob Mathew Petitioner v. State of Punjab & Anr. 2005 (3) CPR 70 (SC),"** the Hon'ble Supreme Court has held that:

  "Para 28: No sensible professional would intentionally commit an act or omission which would result in loss or injury to the patient as the professional reputation of the person is at stake. A single failure may cost him dear in his career. Even in civil jurisdiction, the rule of res ipsa loquitur is not of universal application and has to be applied with extreme care and caution to the cases of professional negligence and in particular that of the doctors. Else it would be counterproductive. Simply because a patient has not favorably responded to a treatment given by a physician or a surgery has failed, the doctor cannot be held liable per se by applying the doctrine of res ipsa loquitur."

- In the matter titled as **"Martin F. D'Souza versus Mohd. Ishfaq, 2009(3) SCC 1,"** the Hon'ble Supreme Court has held that:

  "Para 124: "It must be remembered that sometimes despite their best efforts the treatment of a doctor fails. For instance, sometimes despite the best effort of a surgeon, the patient dies. That does not mean that the doctor or the surgeon must be held to be guilty of medical negligence, unless there is some strong evidence to suggest that he is."

- In the matter titled as **"Lok Nayak Hospital versus Prema, RFA No. 56/2006,"** the Hon'ble High Court of Delhi vide judgment dated 06.08.2018 has held that:

  "8. Firstly, it is to be noted that the only allegation of negligence alleged by the respondent/plaintiff against the appellant/defendant is that the tubectomy/ sterilization operation failed. ***Since medically there is never a 100% chance of success in sterilization operations, the mere fact that the operation was not successful, that by itself cannot be a reason to hold the appellant/defendant and its doctors guilty of negligence.*** *This aspect is no longer res integra and is so held by a Division Bench of this Court in the case of Smt. Madhubala Vs. Govt. of NCT of Delhi, 118 (2005) DLT 515 (DB)."*

■■■■

What are Satvik Offerings in Vedic Literature?

- **Food offerings:** Panchashasha (grains of five types – brown rice, mung or whole green gram, til or sesame, mashkalai (white urad dal) or any variety of whole black leguminous seed, jowar or millet).
- **Panchagobbo:** Five items obtained from cow (milk, ghee or clarified butter, curd, cow dung and gomutra), curd, honey, brown sugar, three big noibiddos, one small noibiddo, three bowls of madhupakka (a mixture of honey, curd, ghee and brown sugar for oblation), bhoger drobbadi (items for the feast), aaratir drobbadi mahasnan oil, dantokashtho, sugar cane juice, an earthen bowl of atop (a type of rice), til oil (sesame oil).
- **Water offerings:** Ushnodok (lukewarm water), coconut water, sarboushodhi, mahaoushodhi, water from oceans, rain water, spring water, water containing lotus pollen.
- **Three aashonanguriuk** (finger ring made of kusha).
- **Puja Items:** Sindur (vermillion), panchabarner guri (powders of five different colors – turmeric, rice, kusum flowers or red abir, rice chaff or coconut fiber burnt for the dark color, bel patra or powdered wood apple leaves), panchapallab (leaves of five trees – mango, pakur or a species of fig, banyan, betel and Joggodumur or fig), pancharatna (five types of gems – gold, diamond, sapphire, ruby and pearl), panchakoshay (bark of five trees – jaam, shimul, berela, kool, bokul powdered in equal portions and mixed with water), green coconut with stalk, three aashonanguriuk (finger ring made of kusha).
- **Panchamrit:** A mixture of honey, milk, curd, ghee and brown sugar.

■■■■

Lighter Side of Medicine

HUMOR

A NICE BOY?

One night a teenage girl brought her boyfriend home to meet her parents, and they were appalled by his appearance: leather jacket, motorcycle boots, tattoos and pierced nose.

Later, the parents pulled their daughter aside and confessed their concern. "Dear," said the mother diplomatically, "he doesn't seem very nice."

"Oh please, Mom," replied the daughter, "if he wasn't nice, why would he be doing 500 hours of community service?"

TELL HIM I CAN'T SEE HIM

The nurse came in and said, "Doctor, there is a man here who thinks he's invisible."

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

COMPUTER POWER

A man dragged himself home and dropped his chair.

His wife was standing there with a cool drink and a comforting word.

"You look tired," she said. "It must have been a hard day. What happened to make you so exhausted?"

"It was terrible," the man said, "The computer broke down and all of us had to do our own thinking."

HOW DO YOU START A FLOOD?

A doctor had bought a villa on the French Riviera. He met an old lawyer friend whom he hadn't seen in years.

The lawyer had also bought a nearby villa. They discussed how they came to live at the Riviera. The lawyer said that the office complex he had bought caught fire, and he retired there with the fire insurance proceeds.

The doctor said that he had bought real estate in Mississippi. But the river overflowed, and he came to the Riviera with the flood insurance proceeds. He said that it was amazing how both of them ended up there in similar ways.

The lawyer looked puzzled and asked, "How do you start a flood?"

IDENTITY

A little girl, when asked her name, would reply, "I'm Mr Sugarbrown's daughter."

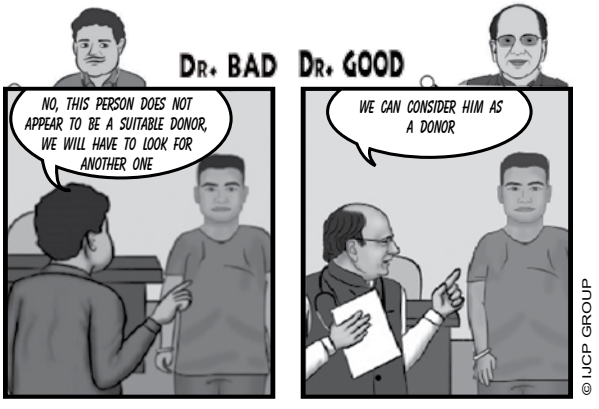
Her mother told her that must say, "I'm Jane Sugarbrown."

The Vicar spoke to her in Sunday School and said, "Aren't you Mr Sugarbrown's daughter?"

She replied, "I thought I was, but her mother says she's not."

Dr. Good and Dr. Bad

SITUATION: A patient who had to get corneal transplantation done told the doctor that he was getting a donor who had insulin-dependent diabetes mellitus and medical complications resulting from the disease



LESSON: Although corneas from donors with insulin-dependent diabetes mellitus and medical complications resulting from the disease have lower mean values of endothelial cell density in contrast to other donors, a retrospective review has suggested that corneas of these people are equally likely to be included in the donor pool for corneal transplantation

Cornea. 2017;36(5):561-6.

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

Books

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

Articles in Books

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- Perfect Health Mela, an innovative health awareness concept was used for the first time in the world in 1993. Government of India earmarked the event by releasing a commemorative postal stamp of Rs. 6.50.
- Perfect Health Parade on the lines of Republic Day Parade on April 7, 2000 (World Health Day) from Vijay Chowk to Red Fort. Flagged off by Smt. Sheila Dikshit, the Chief Minister of Delhi.
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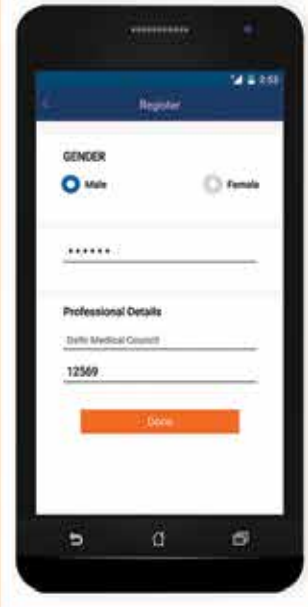

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