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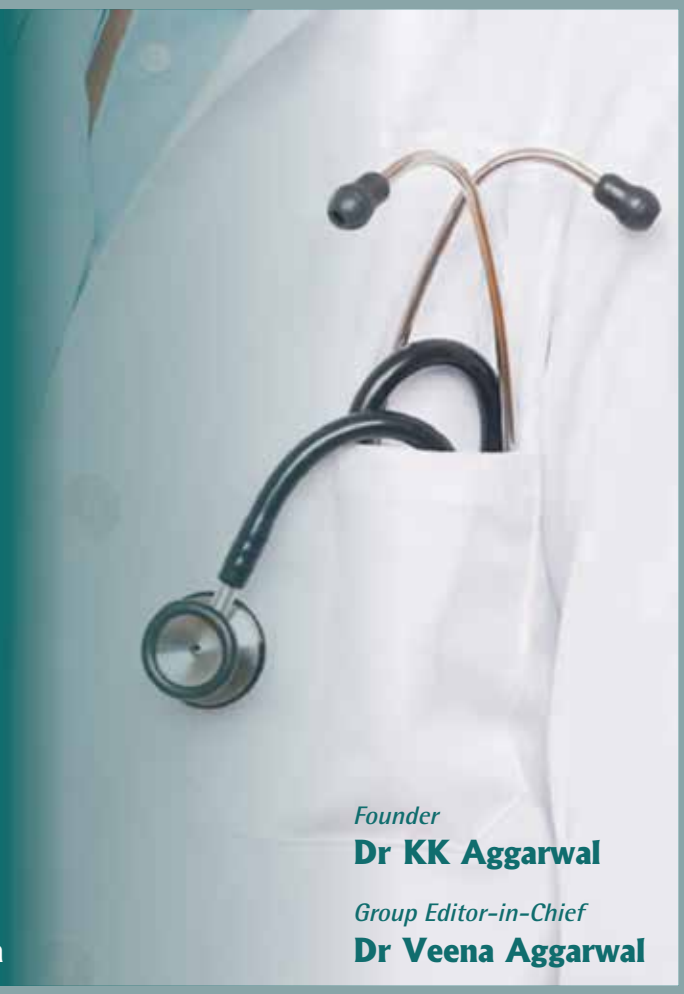

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Medicine Update

POST-HYSTERECTOMY PELVIC ORGAN PROLAPSE: A REVIEW

Total hysterectomy performed for benign gynecologic conditions is associated with a higher risk of pelvic organ prolapse, according to a study recently published in the journal *Maturitas*. On the other hand, subtotal and laparoscopic hysterectomy were not associated with an increased risk of pelvic organ prolapse.

This retrospective cohort study analyzed data from the Korean National Health Insurance Service database to evaluate the risk of pelvic organ prolapse after hysterectomy for benign conditions. For this, women who underwent benign hysterectomy between 2002 and 2011 were compared with those who did not have the procedure, but underwent national medical examinations during the same period. Each group had 16,492 participants with a median age of 47 years.

After a median follow-up period of 11.4 years, the incidence of new onset of pelvic organ prolapse, which was the main outcome measure of the study, was 0.5% in women who did not undergo hysterectomy and 0.6% in those who had had the hysterectomy. Overall, the hazard ratio (HR) for the occurrence of pelvic organ prolapse post-hysterectomy was 1.40 and it required the use of pessary or surgical intervention as a corrective procedure.

On subgroup analysis, the risk of pelvic organ prolapse was not elevated among women who underwent subtotal hysterectomy (HR 1.86) and laparoscopic surgery (HR 0.61). However, total hysterectomy was associated with an increased risk of organ prolapse with HR of 1.63.

These findings show that women who underwent hysterectomy for benign conditions had a higher likelihood of developing pelvic organ prolapse that was severe enough to require intervention suggesting hysterectomy as another risk factor for pelvic organ prolapse. The type of hysterectomy influenced the risk. These findings highlight the importance of surgical technique and procedure type in mitigating long-term risks such as pelvic organ prolapse. Also, women should be counseled preoperatively about the potential complications so that they can make informed decisions about the choice of surgery.

PREDICTIVE FACTORS FOR THE PROGRESSION OF ADENOMYOSIS

Presence and/or worsening of painful symptoms, such as severe dysmenorrhea, dyschezia, and chronic pelvic pain, as well as the presence of focal adenomyosis of the outer myometrium in women with adenomyosis increase the risk of disease progression, according to a study published in the *International Journal of Gynecology & Obstetrics*.

This prospective, observational, cohort study was undertaken at a tertiary referral center in Italy to assess the clinical progression of adenomyosis using ultrasound and clinical data over a period of 1 year. Patients diagnosed with adenomyosis via ultrasound from May 2022 to August 2022 were enrolled for the study. Demographic, clinical, and ultrasound data were

collected at baseline (T0). Data for these parameters was again gathered at 12 months (T1).

The study group was categorized into two groups based on the progression of adenomyosis at T1: the Progression Group with patients who experienced a significant increase in uterine volume, specifically >20% and the Stability/Regression Group with patients whose uterine volume either decreased or increased by 20% or less at T1. Both groups were similar in terms of baseline data.

In the study, the overall rate of adenomyosis progression, the primary study outcome, was 21.3%, with 47 out of 221 patients showing a significant increase in uterine volume (>20%) at T1. The rate was higher (30.7%) in hormonally untreated women, whereas it was lower (18.3%) in hormonally treated women.

The secondary study outcomes were clinical factors associated with the progression of adenomyosis. Presence of focal adenomyosis of the outer myometrium, moderate to severe dysmenorrhea, chronic pelvic pain, dyschezia, and worsening of chronic pelvic pain were associated with progression of adenomyosis.

This study has identified specific clinical symptoms and features that were linked to a greater likelihood of disease progression over time. Their presence in a patient with adenomyosis might help identify at-risk patients allowing more tailored follow-ups and individualized management strategies. Also, the rate of progression was lower among hormonally treated women suggesting that hormonal treatment may play a role in reducing the progression of adenomyosis.

■■■■

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Including Obesity in the Noncommunicable Disease Definition: The 4-1-4 Framework

It has been 70 years since the term 'noncommunicable disease' (NCD) was first used in medical literature[1]. The importance of noninfectious chronic diseases, however, was understood much earlier. The death of President Roosevelt, from an untimely stroke, was one factor which spurred investment in research on this topic[2]. The Framingham Heart Study, which later led to the concept of 'risk factors', was an outcome of this interest[3].

Over the past few decades, the scope and spectrum of NCD has changed and evolved. To bring clarity to an ever-expanding field, the World Health Organization (WHO) created a 4 × 4 framework, listing 4 major NCDs and 4 major risk factors[4]. This simple rubric facilitated a global movement on NCD prevention and management. While the diseases were chosen for their clinical and public health impact - diabetes, cardiovascular disease, cancer, and chronic respiratory diseases, the 4 risk factors (unhealthy diet, physical inactivity, tobacco, and alcohol) were listed as they are common to all the aforementioned disorders.

There has been criticism of the 4 × 4 framework, as it excludes many important diseases. There have also been calls to modify it to a 5 × 5 framework, with mental health and oral health claiming their place under the NCD sun[5]. It must be remembered, however, that the NCD campaign is a relatively recent one, and major changes to its taxonomy may confuse the intended audience rather than consolidate our efforts.

At the same time, innovation and improvement are an integral part of science, and we must continually strive to do better. In recent years, obesity has emerged as an opportunity for prevention of disease, and promotion of health. Obesity is recognized as a disease in itself, and is also a forerunner of all the conditions[6-8] listed in the 4 × 4 WHO NCD framework. It shares the same risk factors, and should respond to similar public health interventions as these diseases. The health economic impact of the obesity pandemic, and the financial savings that may accrue if we are able to arrest it, are significant[9].

It is logical, therefore, to call for a minor adjustment to the existing 4 × 4 framework. We suggest a reframing of this rubric, by adding obesity at the center (Fig. 1), and naming it the 4-1-4 framework. This seemingly simple change will have far-reaching beneficial effect on public as well as clinical health. Governments and

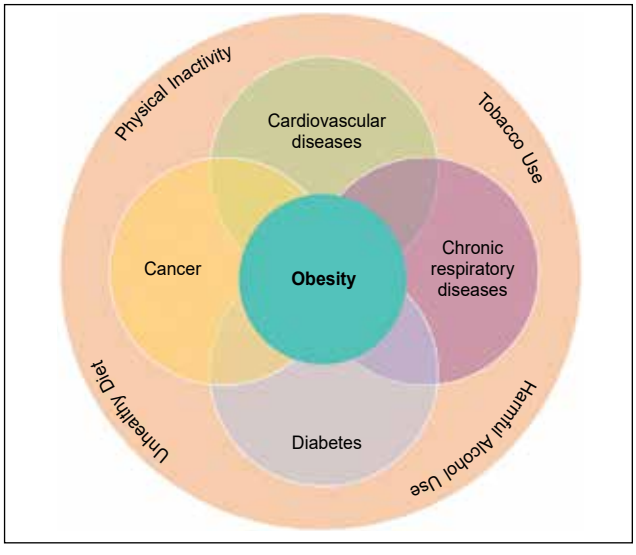

Figure 1.

other stakeholders will be able to focus efforts on the upstream opportunity of obesity, and prevent downstream disorders such as cardiometabolic disease and cancer, with a single intervention. Physicians and paramedical staff will be able to redouble their efforts to fight obesity and overweight, using a standard WHO reference point. Other stakeholders, such as insurance payers and non-governmental organizations will be able to support delivery of accessible and affordable obesity care. Most important of all, the public, which is perhaps the most important player, will realize the importance of overcoming obesity, and begin to act accordingly.

To have a healthier future, for ourselves, and for future generations, we must adopt the 4-1-4 framework. Obesity is an obstacle to health that we should not be oblivious to; at the same time obesity management is an opportunity, which we must not overlook.

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ORIGINAL RESEARCH

A Study to Estimate Spontaneous Bacterial Peritonitis in Chronic Liver Disease

SANDEEP AHARWAR*, RAJA GULFAM SHAIKH†

ABSTRACT

Introduction: Spontaneous bacterial peritonitis (SBP) is an infection of initially sterile ascitic fluid without a detectable, surgically treatable source of infection. We analyzed the prevalence, clinical and laboratory features of SBP in 100 patients of chronic liver disease to identify risk factors for incidence and mortality. **Material and methods:** One hundred patients (mean age 46 years, 92% males) with chronic liver disease and ascites were studied in our prospective study during the period from October 2013 to November 2014 in Gajra Raja Medical College, Gwalior, Madhya Pradesh. Diagnosis of SBP was based on: An ascitic fluid polymorphonuclear leukocyte (PMN) count ≥250/mm^3 *and* ascitic fluid culture positive for single microorganism *With* An absence of source of infection in abdomen. Clinical features of the patients were studied on the basis of history and clinical examination. Relevant blood studies were sent as soon as possible and results analyzed. **Results:** Overall prevalence of SBP was found to be 22% in our study. Symptoms significantly associated with increased incidence of SBP were icterus (p value 0.036), altered sensorium (p value 0.012) and abdominal tenderness (p value 0.003). Higher Child-Pugh grade (Grade C 18.4%) and increased Model for End-stage Liver Disease (MELD) (p value 0.0009) score were associated with higher risk of developing SBP. Also, increasing MELD score was associated with a higher mortality (p value 0.032). SBP +ve group was associated with an increased mortality (p value 0.01) as compared to SBP -ve group. Mortality in SBP was strongly associated with higher serum creatinine level (p value 0.0006). **Conclusion:** Icterus, altered sensorium, abdominal tenderness, and raised creatinine were associated with increased risk of SBP. Child-Pugh grade and MELD score were associated with increased risk of SBP in cirrhosis in the present study. MELD score was found to be significantly associated with mortality in SBP.

Keywords: Chronic liver disease, spontaneous bacterial peritonitis, cirrhosis

Cirrhosis of liver is one of the most common conditions affecting the liver chronically and causing a very high mortality and morbidity, leading to a great burden affecting both quality of life and longevity[1]. It predisposes the patient to a number of complications, one of the most common being ascites[2,3]. Ascites itself has a number of complications, like ascitic fluid infection, cardiorespiratory embarrassment and umbilical hernia. One of the form of ascitic fluid infection is spontaneous bacterial peritonitis (SBP). SBP is an infection of initially sterile ascitic fluid without identifiable, surgically treatable source of infection[4]. This severe complication of cirrhotic ascites was first described in the mid-1960s[5]. Along with hepatorenal syndrome, it is stated as most common life-threatening complication in cirrhosis[6]. Culture-negative neutrocytic ascites (CNNA) - ascites is sterile, bacterial infection is not demonstrable by culturing; only an increased number of polymorphonuclear leukocytes (PMNs) above the limit of 250 cells/mm^3 is revealed. Monomicrobial non-neutrocytic bacterascites (or only bacterascites) has rarely been described. In this disorder, positive bacterial cultivation is presented without increased leukocytes.

SBP and CNNA are identical, both from the clinical perspective as well as therapeutic approach. The consensus conference of the International Ascites Club[7] thus recommends not to differentiate between these two entities. Even in case of CNNA, SBP is talked about, and a raised number of neutrophils in ascites is enough for the diagnosis. A spontaneous infection complicating

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ascites may appear even in malignant ascites[8]; however, it is found most often in cirrhotic ascites.

SBP can present as a full blown syndrome with fever, hypotension, abdominal pain, abdominal tenderness, altered mentation or one or more of its components may be missing[6,9-11]. So, all cirrhotic patients must be screened for SBP with ascitic fluid analysis, PMN count and culture of ascitic fluid[12-15]. Patients must be treated aggressively with antibiotics as they have poor prognosis and high mortality if not treated early.

Present study was undertaken to identify SBP in chronic liver disease patients with ascites with focus on prevalence, presenting features and laboratory findings to identify risk factors for SBP in cirrhotic patients and risk factors for mortality in SBP patients.

MATERIAL AND METHODS

One hundred patients with chronic liver disease and ascites were studied during the period from October 2013 to November 2014. The results obtained were subjected to standard statistical methods for analysis and relevant conclusions were drawn from them. Results were expressed as mean (± standard deviation [SD]). Chi-square test was used wherever applicable. P value ≤0.05 was considered statistically significant.

Inclusion Criteria

- All the cases of chronic liver disease with ascites on the basis of clinical, laboratory and radiological features suggestive of chronic liver disease.

Exclusion Criteria

- Patients found to have a secondary cause of peritonitis like ruptured liver abscess, perinephric abscess, etc.
- Patients found to have more than one organism in ascitic fluid culture.
- Patients who had an antibiotic treatment within last 10 days.
- Patients having a history of recent paracentesis within 10 days.

Diagnosis of SBP

Diagnosis of SBP was based on:

An ascitic fluid PMN count ≥250/mm^3
And
Ascitic fluid culture positive for single microorganism
With
An absence of source of infection in abdomen.

All patients underwent paracentesis within 24 hours of admission. About 30 mL of ascitic fluid was aspirated with aseptic precautions; 10 mL of fluid was sent to laboratory in sterile condition for conventional culture; 10 mL of ascitic fluid was utilized for biochemical and cytological examination.

Clinical features of the patients were studied on the basis of history and clinical examination. Relevant blood studies were sent as soon as possible and results analyzed.

RESULTS

Most of the patients studied were males (n = 92; Table 1).

Age of the patients studied ranged from 22 to 85 years, with the most number of patients in the age group of 40 to 49 years (n = 41); mean age of the patients studied was 46.81 ± 13.18 years (Table 2).

Among 100 patients of chronic liver disease studied, 22 patients showed >250 PMN/mm^3 of ascitic fluid (Table 3). Of these 22 patients, half of them (n = 11) showed ascitic fluid culture positive for single microorganism. Including its variants, overall prevalence of SBP was found to be 22%.

This makes up the prevalence of classical SBP to be 11% and the prevalence of CNNA to be 11% as well. None of the patients who had ascitic fluid PMN count <250/mm^3 showed positive ascitic fluid culture, so there

Table 1. Gender Distribution of Patients Studied

Sex	No. of cases	Percentage (%)
Female	8	8.0
Male	92	92.0
Total	**100**	**100.0**

Table 2. Age Distribution of Patients Studied

Age in years	No. of cases	Percentage (%)
20-29	6	6.0
30-39	18	18.0
40-49	41	41.0
50-59	15	15.0
60-69	9	9.0
70-79	9	9.0
>80	2	2.0
Total	**100**	**100.0**

Table 3. Prevalence of Spontaneous Bacterial Peritonitis

Total no. of patients (100)	Ascitic PMN count >250/mm^3		Ascitic PMN count <250/mm^3		Polymicrobial bacterascites
	Culture positive	Culture negative	Culture positive	Culture negative	
	SBP	CNNA	Bacterascites	Ascites	
100	11	11	0	78	0

was no patient with monomicrobial non-neutrocytic bacterascites. None of the patients showed ascitic fluid culture positive for more than one microorganism, so no patient of polymicrobial bacterascites was seen.

All of the patients (Table 4) who were positive for SBP (n = 11) belonged to either alcohol related (n = 9) or hepatitis B related (n = 2) chronic liver disease.

Most of the patients (Table 5) were having icterus (n = 62), of which 10 were positive for SBP; 30 patients had pedal edema, of which 2 were positive for SBP; 19 had fever, of which 4 were having SBP; 15 had abdominal tenderness, of which 5 were positive for SBP; 10 patients had flapping tremors, of which 2 were positive for SBP.

Coming to the mode of presentation, most of the patients presented with increased abdominal distension (n = 72), of which 6 were positive for SBP, followed by abdominal pain in 34 patients, of which 5 were positive for SBP. Nineteen patients presented with fever, of which 4 were positive for SBP; altered sensorium was evident in 18 patients, of which 5 were positive for SBP. Sixteen presented with gastrointestinal (GI) bleeding, of which 2 were positive for SBP; vomiting was evident in 10 patients, of which only 1 patient was positive for SBP and reduced urine output presented in 6 patients, of which 2 were positive for SBP (Table 6).

Icterus (p value 0.036), altered sensorium (p value 0.012) and abdominal tenderness (p value 0.003) were found to be significantly associated with SBP +ve group as compared to those in SBP -ve group.

Abdominal pain (p = 0.39), increased abdominal distension (p = 0.17), vomiting (p = 0.91), fever (p = 0.13), reduced urine output (p = 0.074), GI bleeding (p = 0.81), pedal edema (p = 0.365) and flapping tremors (p = 0.338) were not found to be of significant value.

Seventeen of the total 100 patients belonged to Child-Pugh Grade A (Table 7), out of which none of the patients had SBP. Thirty-four patients belonged to Child-Pugh Grade B, of which 2 patients were positive for SBP making 5.9% of the patients in Grade B. Most of the patients, i.e., 49, belonged to Grade C, of which 9 patients

Table 4. Etiology in Correlation with SBP

Etiology of CLD	Total No. of cases	Positive cases (SBP)	% positivity
Alcoholic liver disease	79	9	11.4
HBsAg positive	14	2	14.2
HCV related	2	0	0.0
NASH	4	0	0.0
NCPF	1	0	0.0
Total	**100**	**11**	**11**

CLD = Chronic liver disease; HBsAg = Hepatitis B surface antigen; HCV = Hepatitis C virus; NASH = Nonalcoholic steatohepatitis; NCPF = Noncirrhotic portal fibrosis.

Table 5. Clinical Signs in Correlation with SBP

Signs	No. of cases (n = 100)	Positive for SBP (n = 11)	Percentage (%)
Icterus	62	10	16.1
Fever	19	4	21.1
Abdominal tenderness	15	5	33.3
Flapping tremors	10	2	20.0
Pedal edema	30	2	6.7

Table 6. Mode of Presentation in Correlation with SBP

Mode of presentation	Total No. of cases (n = 100)	Positive for SBP (n = 11)	Percentage (%)
Abdominal pain	34	5	14.7
Increased abdominal distension	72	6	8.3
Fever	19	4	21.1
Vomiting	10	1	10.0
Altered sensorium	18	5	27.8
GI bleeding	16	2	12.5
Reduced urine output	6	2	33.3

had SBP, making 18.4% of the patients in Grade C. So, a higher Child-Pugh grade was found to be associated with higher percentage of patients having SBP.

Mean value of MELD (Model for End-stage Liver Disease) score (Table 8) in patients who were SBP +ve was 24.4 with a SD of 6.99 as compared to 16.6 in SBP -ve group with SD of 7.16 with a p value of 0.0009, suggesting that increasing MELD score is associated with a higher risk of developing SBP.

Comparing mean laboratory investigations (Table 9) between SBP +ve and SBP -ve groups, mean total bilirubin (p value 0.002) and INR (p < 0.001) were only significantly associated with SBP +ve group.

From among 100 patients selected, total 4 patients expired. Of SBP -ve group (n = 89), 2 patients expired while in SBP +ve group also, 2 patients expired (Table 10). P value came out to be 0.010 signifying

Table 7. Child-Pugh Classification and SBP

Child-Pugh grade	Total cases	SBP +ve	SBP -ve	% positivity
A	17	0	17	0.0
B	34	2	32	5.9
C	49	9	40	18.4
Total	**100**	**11**	**89**	**11.0**

Table 8. MELD Score in Correlation with SBP

	No. of patients	Mean MELD	SD
SBP -ve	89	16.6	7.16
SBP +ve	11	24.4	6.99

Unpaired *t*-test, p value 0.0009.

Table 9. Comparison of Mean Investigations for SBP +ve and -ve Groups

Investigations	SBP +ve		SBP -ve		P value
	Mean	SD	Mean	SD	
Hemoglobin (g/dL)	8.4	2.2	8.3	2.5	0.9
WBC count (/mm^3)	7215.4	3723.8	5763.6	2136.0	0.2
Total bilirubin	**3.1**	**3.8**	**7.4**	**6.8**	**0.002**
SGOT (IU/L)	73.7	63.4	95.6	53.0	0.274
SGPT (IU/L)	53.5	37.3	79.4	76.6	0.06
SAP (IU/L)	83.5	69.7	81.6	55.2	93
INR	**1.5**	**0.4**	**2.0**	**0.4**	**<0.001**
Blood urea (mg %)	46.6	39.2	53.8	26.3	0.55
S. creatinine (mg %)	2.3	6.2	1.6	0.6	0.69
S. protein (T) (g/dL)	3.8	0.6	3.9	0.5	0.79
S. albumin (g/dL)	2.3	0.7	1.9	0.7	0.11
Ascitic fluid total protein (g/dL)	1.9	0.4	1.9	0.4	0.68
Ascitic fluid albumin (g/dL)	0.5	0.1	0.4	0.2	0.55

Unpaired *t*-test

Table 10. Correlation of SBP with Mortality

	SBP +ve	SBP -ve
Survived	9	87
Expired	2	2
Total	**11**	**89**

Table 11. Laboratory Features as Mortality Predictors in SBP

Lab investigations	SBP +ve expired (2)		SBP +ve survived (9)		P value
	Mean	± SD	Mean	± SD	
Hemoglobin (g/dL)	9.1	2.3	8.2	2.6	0.68
WBC count (/mm^3)	4350.0	919.2	6077.8	2233.1	0.14
Total bilirubin (mg %)	6.4	1.7	7.7	7.6	0.65
SGOT (IU/L)	97.5	2.1	95.2	59.2	0.91
SGPT (IU/L)	59.0	24.0	83.9	84.4	0.46
SAP (IU/L)	105.5	6.4	76.3	60.3	0.19
INR	2.0	0.2	2.0	0.5	0.97
Blood urea (mg %)	55.5	17.7	53.4	28.7	0.87
S. creatinine (mg %)	2.3	0.6	1.4	0.5	0.0006
Ascitic fluid total protein (g/dL)	2.1	0.6	1.9	0.3	0.71

Unpaired *t*-test

Table 12. MELD Score in Correlation with Mortality in SBP

SBP +ve and outcome	N	Mean MELD score	SD
Expired	2	30.50	2.121
Survived	9	23.11	7.008

Unpaired *t*-test, p = 0.032.

that SBP +ve group was associated with an increased mortality as compared to SBP -ve group.

On comparing biochemical findings (Table 11), mortality in SBP was strongly associated with higher serum creatinine level in patients who were SBP +ve (p value 0.0006).

The other biochemical parameters, i.e., hemoglobin, white blood cell (WBC) count, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum alkaline phosphatase (SAP), serum bilirubin, international normalized ratio (INR), blood urea, and ascitic fluid total protein, were not found to be significantly different between survived and expired group.

Higher MELD score was found to be significantly associated with mortality group (n = 2), as compared to survived group (n = 9).

Thus, it can be said that higher MELD score is associated with increased mortality in SBP +ve patients as shown in Table 12.

DISCUSSION

The present study was conducted in 100 patients of chronic liver disease; 22 had ascitic fluid PMN count >250/mm^3 and 11 patients had ascitic fluid culture for single organism. So, prevalence of classical SBP was 11% and overall prevalence was 22%. Other studies have reported variable prevalence rate (24-30%)[16-21]. In studies done by Piroth et al[16] and Muhammad et al[17], prevalence of SBP was found to be 30%. In an Indian study by Agarwal et al[18], the prevalence of SBP was 34.14%, while in the study by Gill et al[19], the prevalence was 24%. In a study by Obstein et al[20], prevalence was 26%. In a study by Andreu et al[21], prevalence of SBP was found to be 25.45%.

In the present study, most of the patients of chronic liver disease had alcoholic liver disease (79%) followed by viral hepatitis B related (14%), HCV related (2%), nonalcoholic steatohepatitis (4%), noncirrhotic portal fibrosis (1%). In the study done by Campillo et al[22], out of 200 patients, 175 had alcoholic liver disease, 16 were hepatitis C related, 6 hepatitis B related, 1 case was of

hemochromatosis and 1 was cryptogenic cirrhosis. In an Indian study by Mohan and Venkataraman[23], alcoholism was seen in 55.5% and the cause was hepatitis B related in 21.8%.

SBP should be suspected when a patient with cirrhosis deteriorates, particularly with encephalopathy and/or jaundice. Patients with variceal bleeding or previous SBP are at particular risk. Clinical signs and symptoms such as fever and abdominal pain and systemic leukocytosis may be noted. In our study, icterus (p value 0.036), altered sensorium (p value 0.012) and abdominal tenderness (p value 0.003) were found to be significantly associated with SBP +ve group as compared to those in SBP -ve group.

Fever (p = 0.13), abdominal pain (p = 0.39), increased abdominal distension (p = 0.17), vomiting (p = 0.91), reduced urine output (p = 0.074), GI bleeding (p = 0.81), pedal edema (p = 0.365) and flapping tremors (p = 0.338) were not found to be of significant value.

Peripheral leukocytosis was found to be a strong indicator for presence of ascitic fluid infection. But these are also nonspecific markers for the presence of ascitic fluid infection and have not been of any statistical significance (p value 0.2) according to this study. Raised bilirubin levels (p value 0.002), and increased INR (p < 0.001) were only seen in most patients of SBP. Ascitic fluid protein levels did not significantly differ between SBP and non-SBP groups of patients and low ascitic protein was not associated with higher incidence of SBP in our study.

Advanced liver disease/Child-Pugh Class C had the highest incidence of spontaneous ascitic fluid infection among patients with cirrhosis. In the present study, 9 patients of 11 patients found to have SBP were present in Child-Pugh score Grade C while only 2 belong to Grade B, suggesting that 18.4% of Grade C patients had SBP while only 5.9% of Grade B had SBP. No patients of Grade A had SBP. In the study done by Campillo et al[22], Child-Pugh score was associated with higher incidence of SBP and mortality in SBP (0.0011). In the study by Puri et al[24], 95% of the patients who developed SBP belonged to Child-Pugh Grade C. In the study done by Agarwal et al[18], 12 of the 14 patients, i.e., 85.71% with SBP belonged to Class C and 2 (14.28%) patients were in Class B Child-Pugh score.

In the present study, mean MELD score of patients with SBP +ve was 24.4 ± 6.99 as compared to 16.6 ± 7.16 for those with SBP -ve, with p value of 0.0009, suggesting that increasing MELD score is associated with a higher risk of developing SBP. In the study by Obstein et al[20], mean MELD score for SBP +ve was 24 and without SBP was 18 (p = 0.0003). They concluded that MELD score is independently associated with a greater risk of SBP. In the study by Gill et al[19], mean MELD score for SBP +ve group was 19 ± 2.42 and 15 ± 3.93 for SBP -ve group.

Overall mortality in present study was 4% with SBP +ve group associated with an increased mortality as compared to SBP -ve group (p value 0.01). In the present study, we found serum creatinine as strong predictor for mortality in patients of SBP with chronic liver disease. In a study by Llovet et al[25], mortality was 17%. Factors associated with increased mortality were presence of upper GI bleeding at admission and PMN count in ascitic fluid. In another study by Rawat and Bhatnagar[26], mortality was 39%. Factors related were jaundice, hepatic encephalopathy, total leukocyte count, total bilirubin, hyponatremia, serum albumin, INR, blood urea and serum creatinine. Musskopf et al[27], in 2012, reported mortality of 40%. Factors associated with increased mortality were total bilirubin, serum creatinine and MELD score.

CONCLUSION

A large number of patients suffering from chronic liver disease with ascites were found to be suffering from SBP or its variant (22% in present study). This complication predisposes an individual to additional mortality risk.

Clinical features such as icterus, abdominal tenderness and altered sensorium were found to be associated with a higher risk of SBP. But none of the other clinical features was consistently associated with SBP in all the patients. None of the clinical features in expired group was found to be significantly associated with mortality in SBP. Higher serum creatinine was found to be associated significantly with expired group.

Child-Pugh grade and MELD score were associated with increased risk of SBP in chronic liver disease patients in the present study.

MELD score was found to be significantly associated with mortality in SBP.

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■■■■

REVIEW ARTICLE

Lipoprotein(a) – A Potential Cardiovascular Risk Factor and Therapeutic Approaches

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ABSTRACT

Lipoprotein(a), also called as Lp(a), has been shown to be an independent, causal, genetic risk factor for cardiovascular disease and aortic stenosis by genetic and numerous epidemiological studies. High Lp(a) level is an important risk factor for coronary heart disease, cerebrovascular disease, atherosclerosis, thrombosis, and stroke. The physiological functions, the mechanism and sites of Lp(a) catabolism, and pathophysiological details are not well-understood though several mechanisms of Lp(a) participation in atherogenesis have been proposed. The goal of therapy is to bring down elevated Lp(a) levels to below 50 mg/dL. Both statins and estrogens are not used for therapy of elevated Lp(a) levels. Niacin and aspirin are two relatively safe, easily available and inexpensive drugs, which significantly reduce raised Lp(a) levels. A variety of other medications that are in various stages of development are dealt with including miscellaneous agents whose role has not been clinically verified.

Keywords: Lipoprotein(a), atherogenesis, therapeutic approaches

Lipoprotein(a) [also called as Lp(a) or LPA] is a lipoprotein subclass. Lipoprotein is an independent, causal, genetic risk factor for cardiovascular disease (CVD)[1]. Genetic studies and numerous epidemiological studies have also identified Lp(a) as a risk factor for atherosclerotic diseases such as coronary heart disease (CHD) and stroke[2-5]. Lp(a) was discovered in 1963 by Kare Berg[6]. Interestingly, Lp(a) is present only in humans, apes, and old world monkeys.

STRUCTURE

The chemical structure of Lp(a) consists of a low-density lipoprotein (LDL)-like particle and the specific apolipoprotein (a) [apo(a)], which is covalently bound to the apoB-100 of the LDL-like particle via one disulfide bridge[7,8]. Thus, Lp(a) is composed of apoB-100 and apo(a). Lp(a) is a spherical macromolecular complex with a diameter of approximately 25 nm, and density ranging from 1.05 g/mL to 1.12 g/mL[7]. Its concentrations are not significantly affected by dietary or environmental effects. Lp(a) plasma concentrations are highly heritable and mainly controlled by the apo(a) gene (LPA) located on chromosome 6 q 26-27. Probably, LPA gene may be responsible for 91% of the variation in Lp(a) concentration; of these 69% are due to the number of kringle IV (KIV) type 2 repetitions. Lp(a) plasma concentration ranges from <1 mg to >1,000 mg/dL. It is worth mentioning that individuals without Lp(a) or with very low Lp(a) levels seem to be healthy.

Apo(a) proteins vary in size due to a size polymorphism (KIV-2 VNTR), which is caused by a variable number of so called KIV repeats in the LPA gene. This size variation at the gene level is expressed on the protein level as well, resulting in apo(a) proteins with 10 to >50 KIV repeats[8,9]. These variable apo(a) sizes are known as apo(a) isoforms. Generally, there is inverse correlation between the size of the apo(a) isoforms and the Lp(a) plasma concentration[10]. As smaller apo(a) isoforms can be generated more quickly per unit time, hence small isoforms are associated with higher plasma Lp(a) levels. Age and sex have little influence on Lp(a) levels, though racial factor has an important influence on Lp(a) levels. The half-life of Lp(a) in the circulation is about 3 to 4 days. There are 6 different alleles for Lp(a). The protein apo(a) is highly homologous (similar) to

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plasminogen, one of the proteins of the fibrinolytic system, though apo(a) has important differences compared with plasminogen.

SYNTHESIS AND METABOLISM

The synthesis and metabolism of Lp(a) have not been completely clarified and are totally independent from LDL synthesis and metabolism in spite of structural similarities between Lp(a) and LDL. Lp(a) is synthesized in the liver. Apo(a) is expressed by liver cells (hepatocytes). There is no coordination between the synthetic pathways of apo(a) and of apoB-100, as there is no coordination between synthesis of Lp(a) and of plasminogen, its structural analog[7]. Further, Lp(a) levels are not related to lipoprotein lipase activity.

The mechanism and sites of Lp(a) catabolism are also not well-defined. Moreover, the way cellular uptake occurs is also not well-established[7]. Uptake via LDL receptor is not a major pathway of Lp(a) metabolism[11] and the role of LDL receptor or isoforms size in that process is limited since only a small fraction of Lp(a) binds to hepatoma cells via LDL receptors. Probably, kidneys may play a role in Lp(a) clearance from plasma[12]. Other receptors, such as asialoglycoprotein receptors, megalin receptors and macrophage scavenger receptors may be involved in Lp(a) uptake[13].

METHODOLOGY TO DETERMINE LP(a)

Lp(a) is commonly estimated by determining the apo(a) concentration by using monoclonal anti-apo(a) antibodies. It may be mentioned, there are difficulties in standardizing the methodology to determine Lp(a) for accurate comparison between different studies. Presently, there are a variety of methods for determining Lp(a). A standardized reference material accepted by the World Health Organization (WHO) Expert Committee on Biological Standardization and the International Federation of Clinical Chemistry and Laboratory Medicine has been notified towards standardizing results. Moreover, a test with simple quantitative results may not provide a complete assessment of risk. Therefore, these assays must be validated with reference standard.

Lipoprotein(a) – Lp(a):

- Desirable: <14 mg/dL
- Borderline risk: 14-30 mg/dL
- High risk: 31-50 mg/dL
- Very high risk: >50 mg/dL.

Lp(a) Concentration and Populations

The racial factor has an important influence on Lp(a) levels. There is two- to threefold higher Lp(a) plasma concentration in populations of African descent compared to Asian, Oceanic or European populations[14], but these levels are not related to coronary artery disease (CAD) in Africans.

Physiological Function

The physiological function of Lp(a)/apo(a) is still unknown. The data till date did not show a physiological function for Lp(a) in lipid transportation or metabolism regulation[7]. Its role within the coagulation system seems plausible owing to high similarity between apo(a) and plasminogen[8]. Apo(a) has potent lysine binding domains similar to those on plasminogen and binds to damaged endothelial cells and exposed or injured subendothelial matrix proteins, delivers cholesterol for cell membrane growth. The other functions may be related to recruitment of inflammatory cells through interaction with Mac-1 integrin, angiogenesis, wound healing, innate immunity, and infection.

Pathophysiology

There are 4 major categories of lipid abnormalities in human beings[1]: a) A raised LDL cholesterol, b) a low high-density lipoprotein (HDL) cholesterol, c) elevated triglycerides, and d) elevated Lp(a). Of these, LDL cholesterol, HDL cholesterol and triglyceride levels are modulated by diet. In contrast, Lp(a) plasma levels are mediated largely by the LPA gene locus present on chromosome 6 q 22-23 and is minimally affected by diet[15].

Presently, Lp(a) remains conceptually only a 'pathogenic lipoprotein.' Lp(a) level >50 mg/dL is typically considered to be elevated for clinical biomarkers. Transient increases in Lp(a) levels are noted in the presence of inflammatory processes or tissue damages, such as those occurring with other acute phase proteins (haptoglobin, α_1-antitrypsin, and C-reactive protein)[15]. This can be seen with an episode of acute myocardial infarction, wherein Lp(a) levels are considerably increased in first 24 hours, returning to base values in approximately 30 days. Lp(a) levels are also increased in chronic inflammatory disease, such as rheumatoid arthritis, systemic lupus erythematosus, and acquired immune deficiency syndrome and following heart transplantation, pulmonary arterial hypertension, and chronic renal failure[16]. In contrast, liver diseases and abusive use of steroid hormones decrease Lp(a) levels[16]. The relationship between Lp(a) and diabetes has not

been well-defined. Contrary views have been expressed in type 1 diabetes mellitus. Similarly, conflicting results have been reported for type 2 diabetes as well.

Lp(a) concentrations have a hereditary character, tending to remain constant throughout the life and are not altered by environmental factors. Elevated Lp(a) level is a risk factor for CHD, CVD, atherosclerosis, thrombosis and stroke, though, association between Lp(a) levels and stroke is not as strong as that between Lp(a) and CVD[2].

Several mechanisms have been proposed for Lp(a) participation in atherogenesis. The structure of Lp(a) is similar to plasminogen and tissue plasminogen activator (tPA); it might lead to interference with fibrinolysis cascade since it competes with plasminogen for its binding site, causing reduced fibrinolysis. Lp(a) stimulates secretion of plasminogen activator inhibitor-1 (PAI-1), it leads to thrombogenesis. Lp(a) also carries cholesterol and thus contributes to atherosclerosis[17]. The mechanisms linking thrombogenesis and atherogenesis with plasma lipoproteins via Lp(a) have thrilled the scientific community.

The probable sequence of events is as follows: Lp(a) would interfere with fibrinolytic system thus Lp(a) competes with plasminogen for binding sites of endothelial cells, inhibiting fibrinolysis, and promoting intravascular thrombosis[18]. Additionally, Lp(a) transports the more atherogenic proinflammatory oxidized phospholipids, which attract inflammatory cells to vessel walls[19,20], and leads to smooth muscle cell proliferation[21]. Probably, the major effect of Lp(a) is on advanced plaque development and destabilization rather than thrombosis[1].

An elevated Lp(a) is clearly proatherogenic[22]. The participation of Lp(a) in atherogenesis could be multifaceted. One mechanism of atherogenicity is through the LDL component. However, apo(a) alone and Lp(a) as lipoprotein have additional potential contributions[23], including increasing endothelial cell permeability and expression of adhesion molecules, promoting smooth muscle cell proliferation, enhancing monocyte entry and retention in the vessel wall, macrophage foam cell formation, promoting release of proinflammatory interleukin (IL)-8 levels, and antifibrinolytic effects, as a carrier of proinflammatory and proatherogenic oxidized phospholipids (OxPL)[24]. A study has reported that Lp(a) and OxPL mediate macrophage apoptosis in endoplasmic reticulum. Since, macrophage apoptosis is a key component of plaque vulnerability, these data provide supporting evidence of Lp(a) as a risk factor for the development of advanced, clinically relevant atherosclerotic lesions[1]. Lp(a) levels also predict severity of coronary atherosclerosis in clinically symptomatic patients. A key component of atherogenicity of Lp(a) has been the contribution of OxPL. OxPL are immunogenic and accumulate in atherosclerotic lesions and mediate plaque destabilization. Thus, raised OxPL on apoB are linked with the presence and progression of CAD and peripheral artery disease (PAD) and predict new CVD events in prospective studies[1].

Another proatherogenic mechanism relates to direct deposition of Lp(a) on arterial wall similar to that which happens with LDL and oxidized LDL as Lp(a) is more prone to oxidation than LDL[7]. This might facilitate uptake of macrophages via scavenger receptor[13]. This is the most universal mechanism of atherogenesis. Yet, another proatherogenic mechanism of Lp(a) refers to the inverse correlation between lipoprotein levels and vascular reactivity, wherein increase in Lp(a) plasma levels will induce endothelial dysfunction[25].

A prime feature of atherosclerosis is chronic inflammation and accumulation of proinflammatory substances in the vessel wall, modified and oxidized products of apoB-containing lipoprotein, are key mediators of such proinflammatory responses that contribute to clinical manifestations of CVD. Helgadottir et al[26] has observed the independent residual risk of Lp(a) in mediating CVD is substantial and this can provide an opportunity and a potential target of therapy in reducing the overall risk of CVD even further. Helgadottir et al have suggested that LPA variants rs10455872 and rs3798220, defined as LPA risk score by combining their effects, are associated with angiographically determined earlier onset of CAD ($p = 4.8 \times 10^{12}$), PAD ($p = 2.9 \times 10^{14}$), aortic aneurysm ($p = 6.0 \times 10^{5}$), and ischemic stroke subtype large artery atherosclerosis ($p = 6.7 \times 10^{4}$).

Further, investigators have observed associations between Lp(a) and inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), IL-6, and monocyte chemoattractant protein-1 (MCP-1)[27,28]. In addition to a reduction in fibrinolysis, it may involve platelet aggregation, induction of the expression of adhesion molecules, vascular remodeling via changes in the proliferative and migratory capacity of endothelial cells and resident smooth muscle cells, oxidative modification and formulation of foam cells[7]. In brief, Lp(a) may be atherothrombotic through its LDL moiety, but also through apo(a), including its ability to be retained in vessel well and mediate proinflammatory and proapoptopic effects including those potentiated by its content of OxPL, and antifibrinolytic effects.[1]

Lp(a) as Cardiovascular Risk Factor

A number of cross-sectional studies have confirmed the association between Lp(a) levels and risk of developing CAD, regardless of 2.3 times higher in patients with Lp(a) levels over 50 mg/dL. Riches et al[28] noted risk as twice greater for Lp(a) levels over 20 mg/dL. Rhoads et al[29] and Murai et al[30] confirmed the relationship between Lp(a) and CAD and cerebral infarction. Rhoads et al[29] also noted that with advancing age the risk decreased, and in the age group over 70 years risk became 1.2 times. In the Brazilian population, Maranhao et al[31], have reported a risk of developing CAD 2.3 times greater when Lp(a) levels were over 25 mg/dL. In Korean population with CAD, a raised Lp(a) has been labeled as an independent risk factor[32]. A meta-analysis of 27 prospective studies has clearly identified an independent association between Lp(a) and CAD[5]. A Danish prospective study involving more than 9,000 individuals over 10 years follow-up has observed that very high Lp(a) levels (≥120 mg/dL) increased 3 to 4 times the risk of CAD[33].

Most studies and meta-analyses have shown an increase in CVD risk starting at Lp(a) >25 mg/dL. A majority of prospective studies reported Lp(a) is really an independent risk factor for CVD though conflicting results, ranging from strong positive associations to complete lack of association between Lp(a) and CVD are in the literature. Yet, high Lp(a) levels enhanced the potency as risk factors of both hypercholesterolemia and low HDL cholesterol concentration[34]. High Lp(a) levels predict risk of early atherosclerosis independently of other cardiac risk factors, including LDL. In patients of advanced CVD, Lp(a) indicates a coagulant risk of plaque thrombosis. Elevated Lp(a) levels may augment the CHD risk from increased LDL cholesterol concentrations as has been demonstrated in patients with familial hypercholesterolemia[35]. A consensus paper issued by the European Atherosclerosis Society in 2010 describes Lp(a) as a causal risk factor for CHD and CVD. The possibility that Lp(a) may become functionally altered in patients with CAD has been put forward by Tsironis et al[36] on the basis of mass and specific activity of Lp(a) as mediator of platelet-activating factor acetylhydrolase activity, an enzyme that hydrolyzes oxidized phospholipids. The mean Lp(a) concentrations are markedly high in black individuals, 2 to 3 times greater than in Caucasian and Oriental individuals[14], but these levels are nonpredictive of CVD in black individuals.

Additionally, high Lp(a) is also a risk factor for atherosclerosis in other arterial beds, such as in ischemic cerebral disease where risk gets escalated with Lp(a) levels, over 30 mg/dL. Further, in a 13-year long follow-up in 14,000 participants, a prospective study has shown a higher incidence of ischemic cerebral disease with raised Lp(a) level[37]. Similarly, in another study involving 50,000 individuals, it was also shown that a raised Lp(a) level is associated with ischemic cerebrovascular accidents[5]. In a meta-analysis of 40 prospective studies involving 58,000 individuals, a 2 times increase in the risk for developing CAD and cerebrovascular accident was noted in individuals with smaller apo(a) isoforms, regardless of the Lp(a) concentration, and classical risk factors[38]. In recent years, a number of studies have reported that elevated Lp(a) levels are independently and linearly predictive of future CVD, though the mechanisms linking Lp(a) to atherogenesis are still unclear and that studies proving the therapeutic decrease of Lp(a) reduces the number of events still lack. The influence of Lp(a) levels on carotid intima-media thickness is still controversial. An inverse association in Japanese population has been observed while no relationship between that thickness and Lp(a) levels has been noted in Spaniards.

Regarding implication of gender, it was observed that a raised lipoprotein level leads to more significant risk repercussions in female sex compared to male sex[39]. A more recent Atherosclerosis Risk in Communities (ARIC) study has reported differences in LP(a) concentrations between sexes, which is higher in females[40]. Although most studies have shown no difference between sexes in Lp(a) concentrations. In postmenopausal women, an elevated Lp(a) and triglyceride level are predictive of the presence of CAD. Investigators have observed that predictive utility of Lp(a) is markedly attenuated among women taking hormone replacement therapy and that the relationship of high Lp(a) levels with increased CVD is modified by hormone replacement therapy[41].

Atherogenesis is a common causal factor of abdominal aortic aneurysm and Lp(a) levels are elevated in abdominal aneurysm showing the association between lipoprotein and atherogenesis. Recent events suggest that genetic variation in the LPA locus-mediated by Lp(a) concentration may also predict aortic valve stenosis[42]. This can well explain why heart valve calcification may run in families. A causal relationship between Lp(a) and calcific aortic valve disease has also been demonstrated. Nongenetic risk factors for aortic valve calcification include advanced age, high blood pressure, obesity, high cholesterol levels, and smoking. Development of novel targeted medications in future

might slow the progression of disease. Statins have not been shown to reduce aortic valve calcification.

High Lp(a) levels predict risk of early atherosclerosis independently of other cardiac risk factors, including LDL and that Lp(a) concentrations also associate significantly with the severity of coronary atherosclerosis. In addition, Lp(a) appears to be an independent risk factor in both primary and secondary settings though there is a paucity of information on the predictive value of Lp(a) in patients with stable CVD[43]. The authors observed that Lp(a) represents a significant risk factor for recurrent events. In patients of advanced CVD, Lp(a) indicates a coagulant risk of plaque thrombosis. In the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study, baseline Lp(a) was associated with future CVD and CHD. The authors observed that baseline Lp(a) concentration was associated with total CHD events ($p < 0.001$), total CVD events ($p = 0.002$) and coronary events ($p = 0.03$). For events after 1 year, an increase in Lp(a) at 1 year was associated with adverse outcomes for total CHD events and total CVD events ($p = 0.002$ each). It was demonstrated that a rising Lp(a) level is associated with cardiovascular events[43].

THERAPEUTIC APPROACHES FOR ELEVATED LP(a) LEVELS

The European Atherosclerosis Society currently recommends that patients with a moderate or high risk of cardiovascular risk having one of the following risk factors such as premature CVD, familial hypercholesterolemia, family history of premature CVD, family history of elevated Lp(a), recurrent CVD despite statin treatment, ≥3% 10-year risk of fatal CVD according to the European guidelines, ≥10% 10-year risk of fatal and or nonfatal CVD according to US guidelines should be screened for their Lp(a) levels[2].

If the Lp(a) levels are raised, treatment should be started with a goal of bringing the level below 50 mg/dL. In addition, the patient's other cardiovascular risk factors (including LDL levels) should be optimally managed[2]. Besides Lp(a) plasma concentration, the apo(a) isoforms might be an important risk parameter as well. Moreover, a better understanding of the basic mechanism of production and metabolism of Lp(a) and apo(a) is important to correlate the effect of future therapeutic agents. Major gaps in clinical medicine are: Lowering Lp(a) levels leads to clinical benefit have not been documented; in majority of studies, Lp(a) levels were lowered in conjunction with changes in other lipoprotein thus complexing the outcomes and the underlying mechanisms of Lp(a)-lowering of these agents are not fully clarified[1].

EFFECTS OF DRUGS ON LP(a) CONCENTRATION

There is no specifically targeted definitive therapy to decrease Lp(a) levels and specific and effective agents do not exist without affecting other lipoproteins. Traditional lipid-lowering agents such as statins or fibrates do not consistently decrease Lp(a) concentrations. Statins either have no effect or increase Lp(a) levels, sometimes significantly. The use of atorvastatin at a dose of 20 mg/day for 24 weeks caused no effect on Lp(a) levels. In a double-blind study with placebo, using doses of 10 or 40 mg/day of atorvastatin for 12 weeks, the Lp(a) concentration had significantly decreased[44]. A meta-analysis published in 2012, suggests that atorvastatin may lower Lp(a) levels[45]. In respect to lovastatin, simvastatin, and gemfibrozil, the latter has shown greater efficacy in reducing Lp(a)[46]. Ezetimibe decreases Lp(a) levels approximately 29%[47]; however, ezetimibe is commonly used with simvastatin, which does not have any additive effect to that of ezetimibe in regard to Lp(a) levels.

Presently, more commonly simple treatment which is relatively safe and independent for raised Lp(a) levels is niacin and aspirin.

Niacin

High dose niacin 1-3 g/day generally in an extended-release form is preferred. The Lp(a) levels are reduced by 20%-30%[48], while 4 g/day of niacin leads to 38% reduction in Lp(a) levels though at lower dose 1 g/day niacin has not shown that effectiveness. High dose niacin is widely used in the treatment of dyslipidemia because in addition to reducing LDL cholesterol levels, it increases HDL cholesterol levels and decreases Lp(a) levels[49]. The European Atherosclerosis Society Consensus Panel have suggested use of niacin for Lp(a) and CVD risk reduction. Further, extended-release niacin has also reduced Lp(a) levels in diabetic patients with dyslipidemia. Etofibrate, a hybrid drug combining niacin and clofibrate, at a dose of 1 g/day decreases Lp(a) levels by 26% in type II dyslipidemic patients[50]. Patients with type IIa and IIb hyperlipidemia being treated with neomycin alone have seen a decrease in Lp(a) concentration by 24%, while the neomycin-niacin association in high doses has resulted in a 45% reduction[51].

It may be mentioned that high doses of niacin are associated with adverse effects, such as migraine, flushing, diarrhea, vomiting, tachycardia, and liver toxicity, though, administration of aspirin 30 minutes prior to niacin can relieve some of these adverse effects.

Aspirin

Another commonly used cheap drug, aspirin may be beneficial. Japanese patients with elevated Lp(a) levels (>300 mg/dL) have shown a 20% reduction in Lp(a) levels even with low doses of aspirin (81 mg/day)[52]. Women with high Lp(a) levels and an apo(a) polymorphic allele seem to have benefited more from treatment with aspirin than those who lack that allele[53]. Thus, aspirin has been found useful only in patients that carry the apolipoprotein(a) gene minor allele variant (rs3798220)[53].

Estrogen Replacement

Estrogens lower Lp(a) up to 30%; although estrogen replacement therapy in postmenopausal women has beneficial effects on Lp(a) and other plasma lipids, yet it is studded with controversies regarding increased risk of certain malignant neoplasias and thromboembolic accidents. At present, estrogen is not indicated for treatment of elevated Lp(a). Tamoxifene and raloxifene have not been shown to reduce levels. The precise underlying mechanisms of Lp(a)-lowering of these agents are not fully defined. A variety of agents belonging to different chemical groups are in various stages of development or undergoing clinical trials that may reduce Lp(a) concentrations and in future may open the doors to new avenues of therapy include:

L-carnitine

It is a combination of L-lysine and ascorbate; it may also reduce LPA levels[54]. A more effective treatment is the Linus Pauling protocol, 6-18 g/day ascorbic acid, 6 g/day L-lysine and 2 g/day L-proline. This protocol may reduce Lp(a) two- to fivefold over a few months.

Thyromimetics

The development of selective thyromimetics having specific liver selectivity (affinity to THRβ isoforms) provide an opportunity for the treatment of dyslipidemia, obesity or for weight loss, nonalcoholic fatty liver disease and may play a role in decreasing Lp(a) levels[55].

- *Sobetirome,* a selective thyromimetic compound reduced LDL cholesterol by 41% at 100 μg/day and in primates caused increase in oxygen consumption, reduction in body weight and minimal effects on skeletal mass. The agent reduces fat mass without increasing food intake and controls dyslipidemia, without causing deleterious effects on heart or bone mass[55].
- *KB-141* is another THRβ agonist, which is 10 times more selective for stimulating metabolic rate and 30 times more selective for cholesterol-lowering than for increase in heart rate[55]. KB-141 has been shown to cause weight reduction as well as reduction of cholesterol and Lp(a)[56].
- *Eprotirome:* It is also a THRβ selective compound, causes 40% reduction in total and LDL cholesterol after 14 days treatment probably owing to an increase in bile acid synthesis[55]. In humans, data from a clinical trial of 98 hyperlipidemic patients revealed eprotirome to cause 25% reduction in LDL, apoB, along with 37% decrease in Lp(a) at 100 μg/day after 16 weeks. At 200 μg/day, there was 45% decrease in Lp(a). Triglycerides also decreased significantly. No cardiac, bone or muscle effects were observed, though mild transient elevation in liver enzymes was seen. Moreover, selective thyromimetics may have additive LDL cholesterol-lowering when used in combination with statins in animal models.

Cholesteryl Ester Transfer Protein Inhibitors

These agents reduce risk of atherosclerosis by improving plasma lipid levels. They substantially increase HDL, lower LDL and reverse the transport of cholesterol. A few of these agents namely torcetrapib, dalcetrapib, evacetrapib have failed in clinical trials. However, anacetrapib and TA-8995 had shown encouraging phase II clinical trials results[57]. Cholesteryl ester transfer protein (CETP) inhibitors inhibit CETP, which normally transfer cholesterol from HDL cholesterol to very LDL (VLDL) or LDL. Inhibition of this process results in higher HDL levels and reduces LDL levels. CETP inhibitors do not reduce rates of mortality, heart attack or stroke in patients already taking statins.

Antisense Oligonucleotides to ApoB

Mipomersen, a second-generation antisense oligonucleotide injectable drug approved by the Food and Drug Administration (FDA) to be used in homozygous familial hypercholesterolemia in January 2013, might be a promise to decrease Lp(a) levels[58]. Mipomersen is a polynucleotide of 20 bases that is complementary in sequence to a segment of human apoB-100 mRNA. It specifically binds to apoB-100 mRNA, blocking the translation of the gene product[58]. A reduction in the synthesis of apoB-100 decreases the hepatic production of VLDL, consequently decreasing circulating levels of atherogenic VLDL remnants, intermediate-density lipoprotein (IDL), LDL, and Lp(a) particles[58]. Thus,

mipomersen reduces all apoB-containing atherogenic lipoproteins and that it consistently and effectively reduces Lp(a) levels in patients with a variety of lipid abnormalities and cardiovascular risk. It has been demonstrated that a specific antisense oligonucleotide directed to KIV-11 repeats lowers apo(a) mRNA and apo(a) plasma levels by 85% in apo(a) transgenic mice, with minor effects on other lipoproteins. Mipomersen's mode of action differs from traditional enzymes or protein-targeting drugs such as statins. It has no dependency on cytochrome P450 metabolism, hence minimal interaction with statins, ezetimibe, bile acids binding resins or other lipid-lowering medications with which it might be combined. Lp(a) levels are decreased in conjunction with changes in other lipoproteins. However, the safety of its use has not been well-established.

Farnesoid X Receptor Agonists

Farnesoid X receptor (FXR, also referred to as NR1H4) is a member of the nuclear receptor superfamily of ligand-regulated transcription factors that plays critical role in the regulation of bile acid, triglyceride, and cholesterol homeostasis. However, its impact on cholesterol homeostasis is less clear. Bile acids, the end-product of cholesterol catabolism, are physiological ligand for FXR. Activation of FXR leads to down-regulation of CYP7A1, the rate limiting enzyme in bile acid synthesis, resulting in reduced cholesterol catabolism. WAY-362450 is a potent synthetic FXR agonist, which decreases serum triglyceride levels with efficacy comparable to fenofibrate. It also reduced serum cholesterol levels via reductions in LDL cholesterol, VLDL cholesterol and HDL cholesterol lipoprotein fractions, and may be of clinical utility in the treatment of mixed dyslipidemia. Synthetic FXR ligands have been demonstrated to regulate apolipoprotein CII (apoCII) and apolipoprotein CIII (apoCIII), cofactors involved in lipoprotein lipase (LPL)-mediated lipolysis and down modulate sterol regulatory element-binding protein 1c (SREBP-1c), the master regulator of the triglyceride synthetic pathway. Evans et al[59] demonstrated that orally active FXR ligand WAY-362450 potently lowers serum triglyceride levels and VLDL cholesterol in multiple rodent models of dyslipidemia along with consistent-lowering of circulating serum cholesterol levels. The mechanism of action of WAY-362450 is probably through modulation of genes involved in both lipolysis and lipogenesis.

Anti-proprotein convertase, subtilisin/Kexin type 9 (anti-PCSK-9) inhibitors, monoclonal antibodies, protein responsible for degrading LDL receptor; and anti-tocilizumab antibody, that can block IL-6-signaling are still in experimental phase. In severe cases, such as familial hypercholesterolemia or treatment-resistant hypercholesterolemia lipid apheresis may lead to dramatic reductions in Lp(a) levels in more than 50% of patients.

Miscellaneous Agents

- **Methotrexate:** An immunosuppressive and anti-inflammatory drug used in the treatment of rheumatoid arthritis, may also reduce Lp(a) levels[60].
- ***Gingko biloba*** may be beneficial, but has not been clinically verified. Coenzyme Q-10, pine-bark extract and pharmacological amounts of fish oil supplements may be helpful to lower the levels of Lp(a) but none of these are clinically proven.

Interactions

Lp(a) has been shown to interact with calnexin, fibronectin, and fibrinogen beta chain.

CONCLUSION

New novel, targeted therapeutic agents that can specifically and definitely reduce Lp(a) plasma concentrations are still being sought. In general, in the absence of well-tolerated drugs that effectively decrease Lp(a) concentrations, levels over 25-30 mg/dL should lead to a more strict control of other risk factors for CAD. However, the presumption that lowering Lp(a) levels leads to clinical benefits such as decreased risk of CVD needs confirmation.

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■■■■

CLINICAL STUDY

Comparison of 3-Port versus 4-Port Laparoscopic Cholecystectomy – A Prospective Comparative Study

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ABSTRACT

Laparoscopic cholecystectomy (LC) is the gold standard treatment for gallstones. Since its inception in 1987, it has undergone various changes, with reduced number of ports from standard 4-port LC to 3-port LC being one of them. Three-port LC has been shown to be equal to standard 4-port LC in terms of safety, complications, pain and hospital stay. We conducted a prospective comparative study amongst these two techniques. Three-port LC was found to be superior in terms of less postoperative pain, less need of analgesia, shorter hospital stay and ease of dissection. We concluded that 3-port LC is a better operative technique than 4-port LC.

Keywords: Three-port laparoscopic cholecystectomy, benefits, safety

Standard laparoscopic cholecystectomy (LC) is done by using 4 trocars. Exposing Calot's triangle for satisfactory anatomical details is of paramount importance in safe and proper surgery. The fourth (lateral) trocar is used to grasp the fundus of the gallbladder so as to expose Calot's triangle. The use of the fourth trocar, which is generally used for retraction of the fundus in the American technique, was found unnecessary by some surgeons[1] and LC can be performed safely without using it. With widespread advent of LC, comes the advent of reduction in port size[2]. Most of these studies have demonstrated the advantages of 3-port LC including less postoperative pain, early hospital discharge and less analgesic requirement. We did a prospective comparative clinical study to investigate the safety, and benefit of 3-port LC versus standard 4-port LC in our setup. Benefits associated with 3-port LC were compared in terms of pain on visual analog scale (VAS), requirement of analgesia and hospital discharge.

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MATERIAL AND METHODS

This was a comparative prospective study performed in the Dept. of Surgery, from January 2014 to January 2015. A total of 50 patients, diagnosed to have gallstone disease and confirmed on ultrasound examination, who were willing to participate in the study and gave valid consent, were included in the study. They were allocated into two groups of 3-port LC and 4-port LC with 25 patients in each group.

Exclusion Criteria

Patients with suspected common bile duct stones, history of obstructive jaundice, gallstone pancreatitis, acute cholecystitis.

Preoperative work-up was carried out, which included complete history, clinical examination, and standard laboratory investigations for the fitness for surgery, including ultrasonography of abdomen and liver function tests.

In standard 4-port technique, one 10 mm umbilical port for camera was made after creating capnopneumoperitoneum with closed technique, another 10 mm epigastric port 5 cm below the xiphisternum (main working port), one 5 mm port in the right midclavicular line 5 cm below the right costal margin (accessory working port) and another 5 mm port, i.e., the fourth port in the right anterior axillary line at the level of

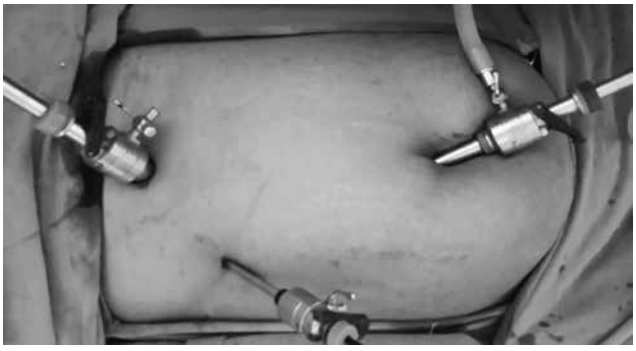

Figure 1. Three-port positions.

umbilicus were used. In 3-port technique, the 4th port (which was put at right anterior axillary line at the level of umbilicus) was not used (Fig. 1).

The outcomes were measured in terms of operating time, conversion rate, intraoperative complications, pain score, analgesic requirement, and hospital stay. Intraoperative complications include gallbladder wall perforation, bile leak, bleeding from liver bed, iatrogenic liver injury, and bile duct injury. In all patients, the same analgesics were used. Pain score was measured using VAS every 12 and 24 hourly. A VAS score 1-3 is called as low pain score (mild) and 4-10 as high pain score (severe).

Statistical Analysis

The Student's *t*-test was used to evaluate the difference in each parameter. A p value <0.05 was considered statistically significant. Statistical package for Social Science version 19.0 for Windows (SPSS, Chicago, Illinois) was used for statistical analysis.

OBSERVATIONS

On comparing the two groups, we made the following observations (Table 1):

- Operating time: Mean operating time was 38.3 minutes in 3-port group while it was 41.0 minutes in the 4-port group. There was no significant difference in operating time in our study (p = 0.06).
- Conversion rate: Both the groups were equal in terms of conversion rate as it was zero in both of them.
- Intraoperative complications: There were two gallbladder wall perforations in 4-port group and no perforation in 3-port group; this was statistically significant (p = 0.02). There was no bleeding from liver bed on comparing both groups, no iatrogenic liver injury in both the groups and fortunately no bile duct injury was found.

Table 1. The Overall Endpoints of the Study

Findings	3-Port group	4-Port group	P value
Operating time (minutes)	38.3	41.0	0.06 (not significant)
Conversion rate	Nil	Nil	NA
Intraoperative complications			
Perforation of gallbladder only	0	2	0.02 (significant)
Bleeding	0	0	NA
Hepatobiliary injuries	0	0	NA
Pain score	1.8	2.9	0.01 (significant)
Analgesic requirement (number)	3.6	5.2	0.001 (significant)
Hospital stay (days)	1.3	2.4	0.02 (significant)

- Pain score: VAS on the scale of 1-10 was used. Mean score in 3-port group was 1.8, while it was 2.9 in 4-port group. This was statistically significant (p = 0.01). Three-port group had better outcome in terms of 4-port group when compared on the basis of VAS. The more pain experienced in 4-port group was probably due to more tissue trauma while putting the 4th port and putting the visceral peritoneum on more stretch.
- Analgesic requirement: Analgesic requirement was high in 4-port group. Patients in 4-port group required 5.2 injection of IV diclofenac 75 mg/2 mL/patient, while the mean requirement in 3-port group was of 3.6 injections/patient. This was statistically significant (p = 0.001), hence the analgesic requirement was significantly less in 3-port group.
- Hospital stay: Mean hospital stay was 1.3 days in 3-port group as most of the patients were discharged on the next day of surgery and it was 2.4 days in 4-port group.

DISCUSSION

At present, LC is the treatment of choice for gallbladder stones[3]. Less postoperative pain and early recovery are major goals to achieve better patient care and cost-effectiveness. These goals; however, cannot be compromised for patient safety. Since Slim et al reported that 4th port is not necessary in their 710 cases of LC, several studies have shown the technical feasibility,

Figure 2. Cystic duct completely dissected in Calot's triangle.

Figure 3. Cystic duct clipped and ready to be cut; cystic artery seen at the back of scissor.

safety, less pain, and early hospital discharge with the 3-port LC[4,5]. In our study, we demonstrated that the advantages of 3-port LC were less intraoperative complications (perforation of gallbladder only), less pain, significantly reduced need for analgesia, and shorter hospital stay. Operating time was not significantly different in the two groups in our study.

In our experience, perforations of gallbladder while dissection occurred in 4-port group because of undue and strong traction on fundus of gallbladder by assistant; there is more stretch on the tissues of gallbladder making them prone to perforation. Most of the studies comparing these two techniques conclude that there are either no or equal intraoperative complications, but we could prove that gallbladder perforation and subsequently bile spillage was more in 4-port group. Another surgical aspect that we observed is that the operating surgeon has full control while doing dissection of Calot's triangle and posterior and anterior peritoneal folds were dissected easily. So, skeletonization of cystic duct and artery becomes very easy, because there is no stretch on gallbladder and it is more mobile for dissection (Figs. 2 and 3).

Less pain and significant reduction of analgesia has been a strong push for reduced port surgery. Our study is in accordance with most of the other studies[2,5-7]. Less tissue dissection in abdominal wall, low stretch on visceral peritoneum significantly reduce the postoperative pain and shorten the hospital stay.

Significant reduction in pain and requirement of analgesia translates into shorter hospital stay in 3-port LC group. The reduction in hospital stay has been proved by many of the studies[5,7]. Three-port LC technique is easy to perform as compared to 4-port LC and can be safely performed after good training in LC.

CONCLUSION

We conclude that the 3-port LC technique is feasible, safe and has better outcomes as compared to those of the standard 4-port LC in terms of postoperative pain, need for analgesia, and shorter hospital stay. The surgical technique is easy and dissection much easier. It is a better technique over 4-port LC.

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CASE REPORT

Tubercular Osteomyelitis of Talus in a Child: A Case Report and Review of Literature

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ABSTRACT

Introduction: Talar tuberculosis is very rare presentation of osteoarticular tuberculosis. Affection of foot is less than 10% in osteoarticular tuberculosis. Presentation of this disease in peripheral bones is highly unusual posing diagnostic dilemma and missed diagnosis. Delayed diagnosis may lead to complications. **Case report:** A 19-month-old male child presented with painful swelling over left foot and inability to bear weight. Hemogram was inconclusive. Radiograph showed lytic lesion in talus with cortical breach in the superior cortex. Aspiration biopsy was inconclusive and open curettage was done under anesthesia. Culture reports were negative but histopathological examination proved tuberculosis. Patient was given antitubercular therapy for 9 months and improved. **Conclusion:** Tuberculosis can affect any part of skeleton and high level of suspicion is essential. Culture negative lesion should be investigated and histopathological examination is essential for any lytic or infective lesion.

Keywords: Tuberculosis, talus, osteomyelitis, osteolytic

Tubercular talar osteomyelitis is an uncommon entity in children. Although tuberculosis of foot is well reported but talar tuberculosis is rare[1,2]. Involvement of talus due to subacute hematogenous osteomyelitis in children has been reported by several authors[3-8]. But, tubercular involvement of talus in children less than 2 years is rare[1,2,9-17]. Moreover, the mimicking radiological features with aneurysmal bone cyst, giant cell tumor and other infections poses diagnostic dilemma[18-20]. Here, we report a rare case of tubercular talar osteomyelitis in a 19-month-old male child who presented with pain and inability to bear weight on left lower limb.

CASE REPORT

A 19-month-old baby presented to our OPD with pain and intermittent low-grade fever for 5 months. Repeated consultation was done for fever with poor response. Limp was not noticed earlier, since child started walking at 14 months and repeated falls were taken as normal. The child had no history of cough, night sweating, loss of weight and appetite. Birth history and perinatal history were insignificant. Immunization schedule was followed as per guidelines including BCG vaccination at birth.

On examination, the general condition was fine. Vitals were stable and child was afebrile. On examination of left foot, it was swollen, tender and warm below the medial malleolus (Fig. 1). There was a boggy swelling over the talonavicular area medially. Ankle range of motion was normal. Foot pronation and supination was restricted. Distal neurovascular assessment was unremarkable. On investigation, hemoglobin (Hb) - 9.90 g/dL, total leukocyte count (TLC) - 14,680/mm^3, differential leukocyte count (DLC) showed neutrophils - 30%, lymphocytes = 56%, blood urea - 7.3 mg/dL, serum creatinine - 0.6%, erythrocyte sedimentation rate (ESR) - 55 mm and C-reactive protein (CRP) titer was raised. Test for viral markers was unreactive. X-ray showed osteolytic lesion in talus with breach in dorsal cortex (Fig. 2). On needle aspiration from talus, we found sanguineous fluid. It was sent for culture sensitivity, which was found sterile. On histopathological examination, only blood cell was found. The patient was kept on below knee pop slab, antibiotics and analgesics with no improvement.

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After a week, the patient was operated with differential diagnosis of chronic osteomyelitis of talus and aneurysmal bone cyst. Through anteromedial incision along tibialis anterior, the talus was approached. Talonavicular joint was exposed to confirm the talus. The talus was drilled over the neck proximal to talonavicular joint and it was thoroughly curetted. Material obtained was sent for Gram staining and Ziehl-Neelsen (ZN) staining, aerobic culture and sensitivity and histopathological examination. Once the normal endosteum was found then the wound was thoroughly lavaged and closure done. Postoperatively, the patient was kept on intravenous antibiotics and below knee plaster-of-Paris (POP) cast in equinus. ZN staining was positive for acid-fast bacilli. The culture and sensitivity report showed no growth, after 10 days; histopathological report confirmed tuberculosis. At 12th day, the stitches were removed and antitubercular therapy was started. After consultation with pediatric department. The patient was discharged on below knee POP cast in equinus. Total 9 months of antitubercular therapy was given with 3 months each for intensive, continuation and maintenance phase. At 1-year follow-up, the patient is doing well with complete healing of the lesion.

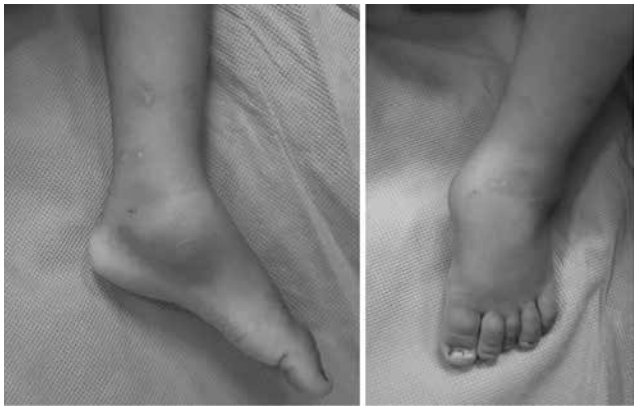

Figure 1. Clinical picture of the patient showing swelling and signs of inflammation.

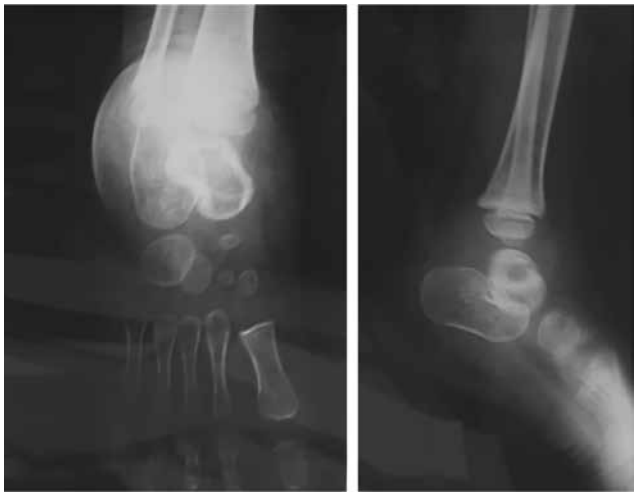

Figure 2. X-ray anteroposterior and lateral view showing a lytic lesion involving the talus.

DISCUSSION

Tuberculous involvement of skeleton is 1%-3% of extrapulmonary tuberculosis[1]. Involvement of foot among osteoarticular tuberculosis is less than 10%[1]. Among all bones of foot, osteomyelitis of talus is rare[1-8]. Our search in electronic and print media revealed cases mostly about subacute hematogenous osteomyelitis of talus and foot bones[3-8]. Dhillon[1] and Mittal[2] have reported exclusively on tuberculosis of foot bones. Only one case of talar osteomyelitis out of 24 cases was reported by Dhillon et al[1] and none out of 44 cases in a series by Mittal et al[2]. Isolated case reports on talus have been reported in recent years and are given chronologically in Table 1[9-17]. Our patient is the youngest case to be reported.

The diagnosis is usually difficult since presentation is vague and nonspecific[4,7]. Flexion at hip and knee with limb in external rotation may be present[4]. Swelling and redness in the foot may be delayed feature[4]. Location of swelling is variable. Verbeek[4] reported swelling on the lateral aspect while Ganaisan[5] reported swelling over the ankle area. We noticed swelling on the medial aspect of mid-foot. Constitutional symptoms are usually nil[1,2,6,7]. In our case, low-grade fever and inability to bear weight for 5 months was the only complaint.

Delayed diagnosis is usually due to lack of constitutional symptoms, poor localizing signs, low level of suspicion and simulating radiological features[1-8,18,19]. Symptoms

Table 1. Isolated Cases of TB Talus as Reported in Chronological Order

Author	Year of reporting	Age of patient (years)
Anand et al[9]	2002	8
Teklali et al[10]	2003	20 months
Ebrahimzadeh et al[11]	2006	7
Mardanpour et al[12]	2010	52
Arora et al[13]	2014	45
Dahuja et al[14]	2014	14
Mohammad et al[15]	2015	42
Sekhon et al[16]	2015	14
Khan et al[17]	1999	5

to admission was 5 months average (Dhillon[1]), 1 month (Ganaisan[5]), 2-12 weeks (Ezra[6]), 5 days to 4 weeks (Grattan-Smith[7]) and 1-5 months (Skevis[8]). In our case it was 5 months.

Hemogram shows signs of infection with raised ESR[1,4-8], but CRP is rarely raised[4,6]. In our case, the ESR and CRP were raised along with lymphocytosis.

Conventional radiography is the primary tool for diagnosis. Phemister's triad of periarticular osteoporosis, marginal erosions and narrowing of joint space is usually seen in osteoarticular tuberculosis. But, this feature is not evident in foot bones always[2]. Mittal et al[2] observed five patterns of foot bone lesions in tuberculosis: cystic, rheumatoid, subperiosteal, kissing, and spina ventosa. In our case, it was cystic type of lesion, which has central osteolytic lesion with no sequestrum and no periosteal reaction.

The lesion in foot usually mimics other conditions as well[18-20]. Aneurysmal bone cyst, giant cell tumors, and infections of foot bones mimics cystic type of tuberculosis. Shirazi et al[20] noted aneurysmal bone cyst was as common as giant cell tumor of small bones of hand and feet. Infections and inflammatory simple cysts were equally prevalent in less than 10 years old children[20]. We found blood on aspiration from talus in our case. Hence, our differential diagnosis was aneurysmal bone cyst and chronic osteomyelitis.

Computed tomography (CT) scan, magnetic resonance scan and bone scan of foot is usually required to localize the lesion and to see the soft tissue condition[1,2,4-7,18]. Magnetic resonance imaging (MRI) shows changes consistent with chronic osteomyelitis[5]. Bone scan with gallium-67 (Ga-67) and technetium-99 (Tc-99) shows increased tracer uptake in the tarsal bones[6,7]. On getting negative report on aspiration cytology and culture sensitivity we directly opted for curettage exploration of the lesion as suggested by Dhillon et al[1]. The same has been done by other authors[1,7,18,20]. The culture report is usually negative since osteoarticular tuberculosis is a paucibacillary condition[1,2,7]. Open curettage and biopsy is usually required for diagnosis[1,2,7,8,18-20].

Minimal pus and granulation tissue is found with evidence of necrotic bone and polymorphonuclear infiltrate[7]. As a rule, we send sample for culture in every case of suspected tumor and we do histopathological examination of every abscess.

Following the rule, we found granuloma in our case. Culture negative and lack of conclusive diagnosis can be curtailed by early biopsy. Delay in diagnosis may lead to complete destruction of bone and joints. Hence, early diagnosis is the priority.

CONCLUSION

Age is no bar for osteoarticular tuberculosis. Any osteolytic lesion in talus or foot bones should be investigated and high level of suspicion is essential to rule out tuberculosis. All the abscesses should be biopsied to prevent missed diagnosis. Early diagnosis and complete treatment of tuberculosis should be the aim.

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■■■■

BRIEF COMMUNICATION

Utility of the National Early Warning Score (NEWS) in the Management of Patients in a Primary Care Setting in Ghana

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ABSTRACT

The National Early Warning Score (NEWS) was developed to assist in the early identification of critically ill patients by monitoring key physiological parameters. This brief communication highlights the utility of the NEWS system in the management of patients at Manna Mission Hospital, an urban primary care facility in Ghana. The article discusses the events leading to the adoption of NEWS at the facility and examines its application in in-patient care to ensure early intervention. Additionally, it addresses the use of the tool to support referral decisions to higher levels of care, which is particularly relevant to health services delivery in Ghana and other low- to middle-income countries.

Keywords: Clinical decision-making, practice improvement, primary care

The National Early Warning Score (NEWS) was created as a systematic method of identifying seriously unwell patients while they are being treated in hospitals[1]. Its use has been recommended in acute care settings, with proven effectiveness for predicting the severe outcomes of in-patients[2,3]. The NEWS system consists of seven physiological parameters evaluated by the user: respiratory rate, oxygen saturation, need for supplemental oxygen, heart rate, systolic blood pressure, body temperature, and level of consciousness[3]. Based on these physiological measures, patients can be grouped into three risk categories, namely low, medium, and high risk[3]. The NEWS is a tool for clinical decision-making, furnishing clinically useful patient assessment information in a succinct and abbreviated format[4]. It provides decision support for health care providers and is neither a hindrance nor a replacement for expert clinical judgment[4].

A revised form of NEWS (NEWS2) was released by the Royal College of Physicians in the year 2017[5]. NEWS2 is a revised version that emphasizes new-onset confusion and recognizes various oxygen saturation levels for individuals with respiratory disease as part of their typical calculated score[6]. According to the National Early Warning Score Development and Implementation Group (NEWSDIG) report, NEWS should be used in conjunction with tried-and-true existing procedures rather than as a replacement for all other assessment systems[1]. Based on NEWS2, the Royal College of Physicians recommends four clinical alert thresholds that must be met for a clinician to assess the situation and decide how quickly a clinical response is needed[4]. An aggregated score of 1-4 is low and should trigger an evaluation by a qualified registered nurse, who should determine whether an intensification of clinical treatment is necessary. If a single red score of 3 is recorded in any of the parameters on the NEWS2 chart, a clinician with expertise in the assessment of acute illness should review the patient immediately[4]. A score of 5-6 is medium and should necessitate a physician doing an urgent review to determine whether care must be escalated to a team with critical care expertise. A high score of 7 or more should result in a patient receiving an emergency assessment by a critical care team and being transferred to a facility with greater levels of care[4]. Due to its usability and its validity, which has been supported by research, the NEWS is a standard early warning system in the United Kingdom and is being used increasingly more internationally[7].

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UTILITY OF THE NEWS IN A RESOURCE-LIMITED PRIMARY CARE SETTING

The NEWS system is currently being utilized at a primary care hospital in Accra, Ghana, as part of patient management. The hospital is a 49-bed medical hospital that provides general practice and family medicine, general surgery, obstetrics and gynecology, and pediatric services at the primary and secondary levels of care. The NEWS was adopted after several educational sessions were presented by a Doctor of Nursing Practice (DNP) graduate student from Oklahoma Wesleyan University as part of her quality improvement project. The project aimed to help improve health care providers' ability to identify imminent signs of a clinically deteriorating patient and provide prompt intervention. Training in the use of the NEWS helped to improve their ability to rapidly identify a declining patient. In addition to training on the use of NEWS, the health care providers were educated on how to implement a rapid response system at the facility. Over 30 health care providers were trained as members of the rapid response team who would be available to swiftly respond to the bedside of patients needing urgent care based on the score of the NEWS system.

The NEWS is calculated for patients on admission to the male ward, female ward, and recovery ward. Following the recommendations of the Royal College of Physicians, the NEWS is not to be used in children <16 years of age or in pregnant women, because they can have alterations in their physiological response to acute illness[4]. A single score is calculated by nurses on duty for every patient during each working shift. The score is recorded on an observation sheet which allows for various actions to be taken as recommended by the Royal College of Physicians, based on the score. Currently, the aggregation of the score is done manually. Plans to integrate the NEWS into the existing electronic health record and to automate the aggregation are being pursued. Digital measurement and application of artificial intelligence (AI) creates prospects for more precise measurement and triggering of response[7]. The main limitations of the use of the NEWS are that the measurement is time-consuming, labor-intensive, and prone to error on calculation, especially when done manually[8]. These are the main drawbacks that have been observed in this primary care facility since the NEWS2 chart was adopted. Since the measurement also requires trained professionals, periodic training is required for new employees (nurses and clinicians) who join the health care facility.

In-Patient Care and Early Intervention

The use of the NEWS in hospitalized patients at this primary care hospital has been able to assist health care providers in triggering early interventions. The NEWS provides the evaluation of clinical severity that can be used to both initiate therapeutic interventions and evaluate how well the intervention works. Furthermore, the NEWS allows for a thorough clinical evaluation that can establish an appropriate course of action in response to a trigger. It is recommended in the literature that NEWS should not be the only metric used for risk stratification because its accuracy in predicting mortality beyond 24 hours may not be reliable and is heavily impacted by other factors[8]. Hence, other factors are also taken into consideration such as comorbidities of the patient, acute complications, medications, etc. Other indicators that have been suggested to be used in conjunction with the NEWS2 are capillary blood glucose and ketones, fluid balance, pain, and acute limb weakness[7]. In a study comparing the performance of Early Warning Scores (EWS) used in the developed world with those generated in low-resource settings, the NEWS2 with additional points for mobility impairment exhibited the highest discrimination and sensitivity[9].

Referral to Higher Levels of Care

Generally, the decision to refer a patient from primary care to higher levels of care is often not straightforward and may involve a complex process. When referring patients to acute care in primary care, the use of NEWS appears to be correlated with clinical acuity[6]. The danger of reducing clinical observations to a single score is that it might be used as a cognitive shortcut when making decisions[6]. Therefore, along with NEWS2, which may potentially result in escalation, condition-specific observations should be used[7]. In addition, the concerns of the patient, family, and physician are taken into consideration to enhance the assessment for appropriate referral decisions and facility placement.

When NEWS was determined at the point of referral, higher scores were associated with prompt clinician reviews and rapid ambulance transport[6]. The utility of the NEWS in this low-resource primary care setting has supported clinical decision-making at the point of referral to a secondary or tertiary facility when the score was higher than 7. According to Pullyblank et al, the use of NEWS2 in the community contributed to reductions in mortality among patients admitted with suspicion of sepsis without increasing admissions[10]. It is hoped that with the continuous use of the NEWS, prompt intervention, and appropriate referrals, patients

admitted to this primary care facility will achieve positive outcomes reflected by a reduction in morbidity and mortality.

CONCLUSION

The NEWS system is a valuable tool that provides monitoring support for in-patients. It will help achieve improvements in patient care and promote a culture of safety in low-resource settings at the primary care level. It is recommended that more future research could be conducted to evaluate the performance of NEWS within resource-limited settings.

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Disclosure of Interest

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Protein Diet and Menstrual Cycle

SHAILY DUNGARWAL

FOOD INTAKE DURING MENSTRUAL CYCLE[1]

- Food intake is affected due to neurochemical hormonal, physiological and psychological factors.
- Significant variations observed in appetite and energy intake in women during their menstrual cycle.
- Variations are due to: The effect of estrogen and progesterone on gastric emptying. The effect on secretion of some gastrointestinal hormones (glucagon-like peptide-1, cholecystokinin) important for appetite regulation and energy intake.

EFFECT ON PROTEIN INTAKE DURING MENSTRUAL CYCLE

Various studies have revealed: A significant decrease in protein intake during the ovulatory phase. A decrease in protein intake in the luteal phase. An increase in protein intake during the premenstrual phase[1].

PROTEIN REQUIREMENTS OF YOUNG WOMEN

Urinary nitrogen cycle in women uniquely implies a hormonal regulation of nitrogen utilization[2].

- Based on the short-term nitrogen balance method, average requirement to maintain crude balance (I-F-U) is about 75 mg egg or about 100 mg of mixed dietary proteins[3].
- Balance must be positive to the extent of about 8 mg/kg body weight to allow for various losses under temperate conditions with light activity[3].
- The average dietary protein requirement is 0.8 g/kg[3].
- However, recently it has been suggested that females may require higher protein intakes owing to the increased protein oxidation, ~1.6 g/kg/day[4].

DIETARY PROTEIN[4]

- Dietary protein has many functions in the body with regulation of skeletal muscle mass being a primary role.
- Maintaining sufficient quantity of protein intake is extremely important to ensure that the rate of muscle protein synthesis is at least equal to the rate of muscle protein breakdown, and the muscle mass is maintained.
- Intake of adequate amino acids through food is important as the amino acids are the building blocks for new proteins in the body such as actin in skeletal muscle.

During the mid-luteal phase, estrogen and progesterone peak corresponding to an increase in protein oxidation at rest. It has been shown that females need more lysine during the luteal phase than the follicular phase. This is attributed to the various factors affecting progesterone up-regulation of amino acid use[4].

- Rise in progesterone during the mid-luteal phase leading to reduction in amino acid plasma levels due to increased protein biosynthesis from endometrial thickening[4].
- Besides, protein use during exercise appears to be higher during the mid-luteal phase[4].

Hence, it is warranted to increase the protein consumption during the mid-luteal phase to meet the anabolic demands of the body[4].

In a study on women during the mid-follicular phase of the menstrual cycle, it was seen that the protein needs were further increased. Hence, it is important to consider the menstrual cycle phase of women when assessing them for dietary protein needs[4].

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PICTURE QUIZ

What is the Diagnosis?

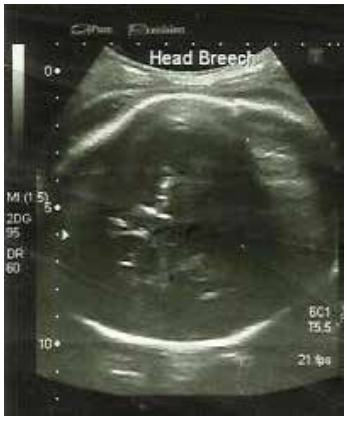
A 21-year-old woman with 37 weeks 2 days pregnancy presents with loss of fetal movement and pain in abdomen since 3 days. On general examination: patient was of average built with marked pallor, pulse 120/min, and blood pressure 100/60 mmHg. Respiratory and cardiovascular system did not reveal any abnormality. Per abdominal examination: heights of uterus 34 weeks, tenderness present, lower pole empty, fetal heart sound were absent. Per vaginum examination: OS closed, cervix long uneffaced. Investigation: hemoglobin 5 g/dL, blood group AB –ve, bleeding time 2 minutes 15 seconds, and clotting time 3 minutes.

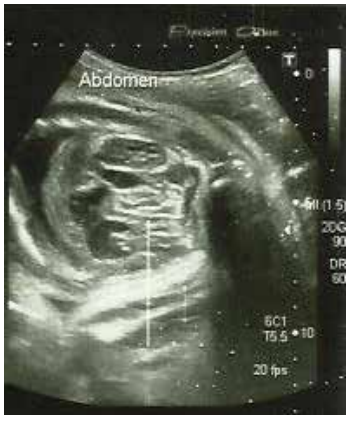
a) Abruptio placentae

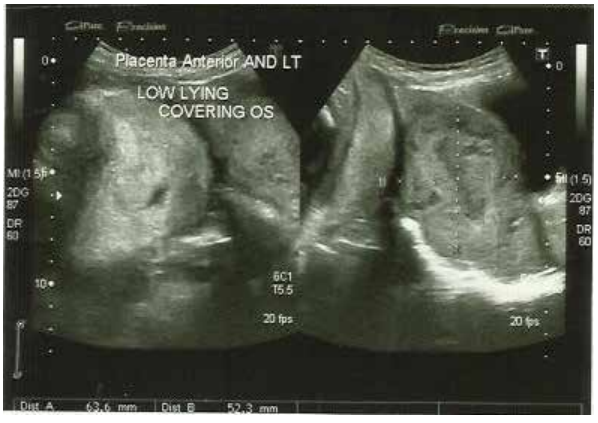
b) Ruptured uterus

c) Fetal death

d) Both (b) and (c)







See Answer in the Next Month's Issue!

LETTER TO EDITOR

Clues in the Drain

ANKUR VERMA*, POOJA SINGH†, SHUBHASHISH BISWAS*, TARUN TYAGI†, ANKIT SHARMA‡, ABINASH PANIGRAHI‡, SURENDER KUMAR DABAS#

Dear Sir,

A 64-year-old male presented with hoarseness of voice for past 9 months. Direct laryngoscopy showed that the left vocal cord had a proliferative growth was extending into the subglottis. The left vocal cord was fixed. The biopsy of this lesion was suggestive of carcinoma larynx. He was planned for total laryngectomy and bilateral neck dissection under general anesthesia. His past history was notable for coronary artery diseases for which he had undergone coronary angioplasty. He had a stent in left anterior descending artery, an ejection fraction of 35%-40% and a pacemaker was *in situ*. Prior to the surgery, central venous access was established by inserting a right subclavian line by infraclavicular approach as per standard protocol[1]. The subclavian venous access had been confirmed by a flash of blood and a nonpulsatile drip of blood upon removing the needle, prior to inserting the catheter. A check radiograph was done after the procedure which confirmed the correct position of the line (Fig. 1).

The surgery was uneventful and after surgery, the anesthesia was reversed and the patient was breathing spontaneously from the tracheostomy tube. On postoperative day 1, the patient complained of swelling in the neck which was present diffusely around the surgical site and extending towards the chest. The surgeons noted serosanguineous discharge from the drain placed at the surgical site in the neck. The discharge continued till the next day and the surgeons were not sure of the cause. Accordingly, a surgical re-exploration was planned. The patient was shifted to the operating room and general anesthesia was being induced. The anesthetist who was administering the anesthesia, noted that immediately after injecting propofol, a milky white fluid was observed in the drain. Suspecting the obvious, the surgery was put on hold and a neck radiograph was ordered immediately. The radiograph revealed that the central line had malpositioned and its tip was seen at the level of clavicle in the radiograph, probably lying in the subcutaneous space (Fig. 2). As a consequence of this, intravenous fluid being given to the patient had been leaking into surrounding tissues – the same was appearing in the surgical drain as well as causing local edema. There was no evidence of any mediastinal collection or pneumothorax or hydrothorax. The central line was promptly removed and the surgery was canceled. By the next day, the swelling had subsided and the drain showed minimal output. The patient was discharged after 2 days.

Figure 1. Initial check radiograph showing appropriately positioned subclavian venous catheter (*white arrow*).

Subclavian vein catheterization is a common procedure performed often for perioperative fluid management, giving chemotherapy, total parenteral nutrition or long-term antibiotics. Complications in subclavian vein catheterization are not uncommon and around 10% cases can have complications[2]. The complications can be immediate such as catheter misplacement, cardiac arrhythmia, arterial puncture, pneumothorax, pneumomediastinum, bleeding, mediastinal hematoma,

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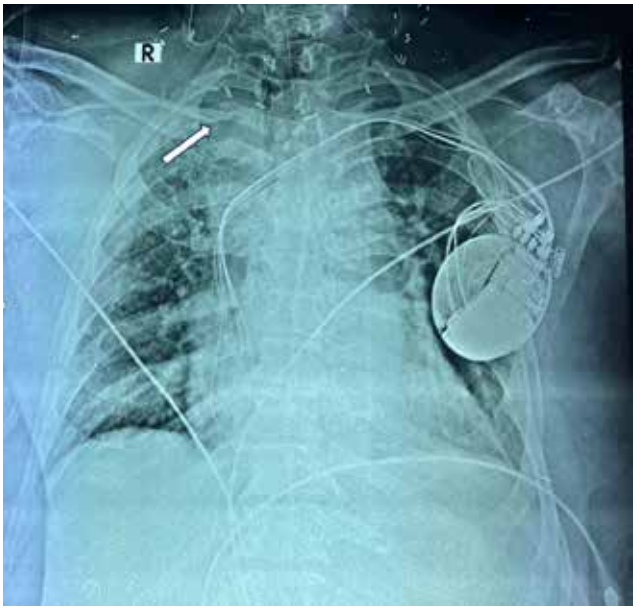

Figure 2. Radiograph taken on postoperative day 2 after noting intravenous propofol appearing in surgical drain showing catheter malposition (*white arrow*).

guidewire or catheter entanglement or entrapment apart from several others[3,4]. Delayed complications include infections and catheter blockade due to fibrin sheath, thrombosis or catheter fracture. Misplacement was the most common complication in one study, seen in 6% of cases[2].

The misplacement related complications are usually noted immediately and are almost always detectable by performing a check radiograph. In our case, there does not appear to be an immediate misplacement as the catheter was working normally and the radiograph was also showing appropriate placement. The malposition of the catheter appears to have occurred after surgery. Under normal circumstances, swelling around the catheter insertion site would have been a dead giveaway of leakage but in our case since the surgical site was nearby and the surgical drain was showing a collection, a surgical complication was suspected. The chance noting of the propofol appearing in the drain by the anesthetist averted an unnecessary surgery. Delayed malposition of subclavian vein catheter appears to a rare complication about which the anesthetists should be aware.

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Insights on Medicolegal Issues

Question: Whether consent given for diagnostic surgery, can be construed as consent for performing additional or further surgical procedure?

Answer: If in the course of one operation, there is a medical emergency requiring a medical procedure, the doctor can operate on the patient without his or her consent and is protected by the defense of medical necessity.

The 3 Judges Constitution Bench of Hon'ble Supreme Court of India in the landmark judgment titled as "Samira Kohli versus Prabha Manchanda, AIR 2008 SC 1385" has held that the doctor can act without the consent of the patient where it is necessary to save the life or preserve the health of the patient. However, the principle of necessity by which the doctor is permitted to perform further or additional procedure (unauthorized) is restricted to cases where the patient is temporarily incompetent (being unconscious), to permit the procedure delaying of which would be unreasonable because of the imminent danger to the life or health of the patient. Thus, unless the unauthorized additional or further procedure is necessary in order to save the life or preserve the health of the patient and it would be unreasonable (as contrasted from being merely inconvenient) to delay the further procedure until the patient regains consciousness and takes a decision, a doctor cannot perform such procedure without the consent of the patient. The relevant paragraphs of the judgment are reproduced hereunder:

> *"16. The next question is whether in an action for negligence/battery for performance of an unauthorized surgical procedure, the Doctor can put forth as defense the consent given for a particular operative procedure, as consent for any additional or further operative procedures performed in the interests of the patient. In Murray vs. McMurchy - 1949 (2) DLR 442, the Supreme Court of BC, Canada, was considering a claim for battery by a patient who underwent a cesarean section. During the course of cesarean section, the doctor found fibroid tumors in the patient's uterus. Being of the view that such tumors would be a danger in case of future pregnancy, he performed a sterilization operation. The court upheld the claim for damages for battery. It held that sterilization could not be justified under the principle of necessity, as there was no immediate threat or danger to the patient's health or life and it would not have been unreasonable to postpone the operation to secure the patient's consent. The fact that the doctor found it convenient to perform the sterilization operation without consent as the patient was already under general anesthetic, was held to be not a valid defense. A somewhat similar view was expressed by Courts of Appeal in England in Re: F. (supra). It was held that the additional or further treatment which can be given (outside the consented procedure) should be confined to only such treatment as is necessary to meet the emergency, and as such needs to be carried out at once and before the patient is likely to be in a position to make a decision for himself. Lord Goff observed:*
>
> > *'Where, for example, a surgeon performs an operation without his consent on a patient temporarily rendered unconscious in an accident, he should do no more than is reasonably required, in the best interests of the patient, before he recovers consciousness. I can see no practical difficulty arising from this requirement, which derives from the fact that the patient is expected before long to regain consciousness and can then be consulted about longer term measures.'*
>
> *The decision in Marshell vs. Curry - 1933 (3) DLR 260 decided by the Supreme Court of NS, Canada, illustrates the exception to the rule, that an unauthorized procedure may be justified if the patient's medical condition brooks no delay and warrants immediate action without waiting for the patient to regain consciousness and take a decision for himself. In that case the doctor discovered a grossly diseased testicle while performing a hernia operation. As the doctor considered it to be gangrenous, posing a threat to patient's life and health, the doctor removed it without consent, as a part of the hernia operation. An action for battery was brought on the ground that the consent was for a hernia operation and removal of testicle was not consent. The claim was dismissed. The court was of the view that the doctor can act without the consent of the patient where it is necessary to save the life or preserve the health of the patient. Thus, the principle of necessity by which the doctor is permitted to perform further or additional procedure (unauthorized) is restricted to cases where the patient is temporarily incompetent (being unconscious), to permit the procedure delaying of which would be unreasonable because of the imminent danger to the life or health of the patient."*

"17. It is quite possible that if the patient been conscious, and informed about the need for the additional procedure, the patient might have agreed to it. It may be that the additional procedure is beneficial and in the interests of the patient. It may be that postponement of the additional procedure (say removal of an organ) may require another surgery, whereas removal of the affected organ during the initial diagnostic or exploratory surgery, would save the patient from the pain and cost of a second operation. Howsoever, practical or convenient the reasons may be, they are not relevant. What is relevant and of importance is the inviolable nature of the patient's right in regard to his body and his right to decide whether he should undergo the particular treatment or surgery or not. Therefore at the risk of repetition, we may add that unless the unauthorized additional or further procedure is necessary in order to save the life or preserve the health of the patient and it would be unreasonable (as contrasted from being merely inconvenient) to delay the further procedure until the patient regains consciousness and takes a decision, a doctor cannot perform such procedure without the consent of the patient."

The Hon'ble National Consumer Disputes Redressal Commission in the matter titled as "Saroj Chandhoke versus Ganag Ram Hospital, 2007 (3) CPJ 189 (NCDRC)" has held that:

"VI. Conclusion:

In conclusion it is held that:

(i) In a simple Hysterectomy operation, the Complainant lost her ovaries and left kidney. She was required to undergo other operations for control of fecal discharge from vagina. She was required to stay in the hospital for complete cure for months.

(ii) Informed consent was obtained only for total abdominal hysterectomy (TAH). There was no necessity of trying to operate via vaginal route.

(iii) No consent was obtained for removal of ovaries in advance planned surgery.

(iv) In the present case, the question is not whether TAH is preferable to vaginal hysterectomy (VH). The patient was prepared for TAH and had given written consent for TAH and no consent was obtained or no information was given to the patient that her ovaries would be removed. In such set of circumstances, it cannot be said that because a surgeon is expert in the field he/she can carry out the surgery of his choice. If he/she does so, he/she does it at his/her risk in case of mishap.

No doubt, in case of emergency there can be deviation in mode of surgery, but not in a planned surgery where express consent for a particular mode is taken from the patient, particularly, when there is no emergency.

(v) Before performing surgery, properly informed written consent is must. No doubt, while operating, to control adverse situation or to save the life of the patient or for benefit of the patient, other procedure could be followed or other part of the body could be operated.

(vi) As held in Spring Meadows Hospital (supra) it is to be seen that superiority of the Doctor is not abused in any manner. Further, if during the operation any mishap occurs because of error of judgment, it would be deficiency in service or negligence, if that would not have been committed by a reasonably competent professional man professing the standard and type of skill that a surgeon held out as having. The Opposite Party No. 2 is an expert Gynecologist who has performed many such operations as contended by her and Opposite Party No. 1 is a known big Hospital. In such a case, it is difficult to accept that for no fault there was avulsion of vein to such an extent that left kidney was required to be removed. Inference could be that there was some error which resulted in cut of a vein."

Question: Whether the doctor is required to obtain consent of the patient in case of accident?

Answer: In Re F (Mental Patient: Sterilization), 1990 (2) AC 1, Lord Bridge has observed that doctors and other health care professionals would otherwise face on intolerable dilemma, if they administer the treatment which they believe to be in the interest of the patient, they might face an action for trespass to the person, but if they withhold that treatment they could be in breach of duty of care in negligence.

The Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002 casts a duty on all medical practitioners, i.e., all medical practitioners must attend to sick and injured immediately and it is the duty of the medical practitioners to make immediate and timely medical care available to every injured person whether he is injured in accident or otherwise. The relevant provisions of Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002 is reproduced hereunder:

"2. Duties of physicians to their patients

2.1 Obligations to the sick

2.1.1 Though a physician is not bound to treat each and every person asking his services, he should not only be

ever ready to respond to the calls of the sick and the injured, but should be mindful of the high character of his mission and the responsibility he discharges in the course of his professional duties. In his treatment, he should never forget that the health and the lives of those entrusted to his care depend on his skill and attention. A physician should endeavor to add to the comfort of the sick by making his visits at the hour indicated to the patients. A physician advising a patient to seek service of another physician is acceptable, however, in case of emergency a physician must treat the patient. No physician shall arbitrarily refuse treatment to a patient. However for good reason, when a patient is suffering from an ailment which is not within the range of experience of the treating physician, the physician may refuse treatment and refer the patient to another physician.

2.1.2 Medical practitioner having any incapacity detrimental to the patient or which can affect his performance vis-à-vis the patient is not permitted to practice his profession.

2.4 The Patient must not be neglected

A physician is free to choose whom he will serve. He should, however, respond to any request for his assistance in an emergency. Once having undertaken a case, the physician should not neglect the patient, nor should he withdraw from the case without giving adequate notice to the patient and his family. Provisionally or fully registered medical practitioner shall not willfully commit an act of negligence that may deprive his patient or patients from necessary medical care.

3.5 Treatment after Consultation

No decision should restrain the attending physician from making such subsequent variations in the treatment if any unexpected change occurs, but at the next consultation, reasons for the variations should be discussed/explained. The same privilege, with its obligations, belongs to the consultant when sent for in an emergency during the absence of attending physician. The attending physician may prescribe medicine at any time for the patient, whereas the consultant may prescribe only in case of emergency or as an expert when called for."

The Hon'ble Supreme Court of India in the matter titled as "Parmanand Katara versus Union of India, AIR 1989 SC 2039" has held that:

"*There can be no second opinion that preservation of human life is of paramount importance. That is so on account of the fact that once life is lost, the status quo ante cannot be restored as resurrection is beyond the capacity of man. The patient whether he be an innocent person or be a criminal liable to punishment under the laws of the society, it is the obligation of those who are in-charge of the health of the community to preserve life so that the innocent may be protected and the guilty may be punished. Social laws do not contemplate death by negligence to tantamount to legal punishment.*"

"*Article 21 of the Constitution casts the obligation on the State to preserve life. The provision as explained by this Court in scores of decisions has emphasized and reiterated with gradually increasing emphasis that position. A doctor at the Government hospital positioned to meet this State obligation is, therefore, duty-bound to extend medical assistance for preserving life. Every doctor whether at a Government hospital or otherwise has the professional obligation to extend his services with due expertise for protecting life. No law or State action can intervene to avoid/delay the discharge of the paramount obligation cast upon members of the medical profession. The obligation being total, absolute and paramount, laws of procedure whether in statutes or otherwise which would interfere with the discharge of this obligation cannot be sustained and must, therefore, give way. On this basis, we have not issued notices to the States and Union Territories for affording them an opportunity of being heard before we accepted the statement made in the affidavit of the Union of India that there is no impediment in the law. The matter is extremely urgent and in our view, brooks no delay to remind every doctor of his total obligation and assure him of the position that he does not contravene the law of the land by proceeding to treat the injured victim on his appearance before him either by himself or being carried by others. We must make it clear that zonal regulations and classifications cannot also operate as fetters in the process of discharge of the obligation and irrespective of the fact whether under instructions or rules, the victim has to be sent elsewhere or how the police shall be contacted, the guideline indicated in the 1985 decision of the Committee, as extracted above, is to become operative. We order accordingly.*"

The Hon'ble National Consumer Dispute Redressal Commission in the matter titled as "Pravat Kumar Mukherjee versus Ruby General Hospital & Ors., 2005 (2) CPJ 35" has held that:

"*Considering the aforesaid law, it is apparent that: emergency treatment was required to be given to the deceased who was brought in a seriously injured condition; there was no question of waiting for the consent of the patient or a passer by who brought the patient to the hospital, and was not necessary to wait for consent to be given for treatment;*

There is nothing on record to suggest that the Doctor has informed the patient or the relatives or the person who has brought him to the hospital with regard to dangers ahead or the risk involved by going without the operation/treatment at the earliest.

Consent is implicit in such cases when patient is brought to the hospital for treatment, and a surgeon who fails to perform an emergency operation must prove that the patient refused to undergo the operation not only at the initial stage but even after the patient was informed about the dangerous consequences of not undergoing the operation."

Thus, the patient's consent is not necessary in case of accident/emergency as in such cases, the consent is implied when the patient is brought to the hospital.

Further, it is an obligation on the doctor to treat his patient without any delay.

■■■■

CSI NIC Mid Term Meet: NIC 2024

NOVEL STENT DESIGN AND TECHNIQUE FOR SINUS VENOSUS DEFECT WITH SHORT ANCHOR

Dr Pramod Sagar, Chennai

- Transcatheter sinus venosus defect closure is a well-accepted procedure now.
- Shorter anchor due to additional PV and short superior vena cava (SVC) had relatively higher complication rates with the old technique.
- New hybrid stents with distal uncovered portions can avoid the need for two overlapping stents. A novel technique involves use of additional wire in additional PV or left innominate vein.
- Mounting the stent on a guide and balloon allows precise deployment of stent.
- The risk of caudal migration will be completely eliminated by this strategy.

A 'RIGHT' WAY TO DO CRT

Dr Priya Shanmukhan, Thiruvananthapuram

- The left SVC usually drains to the coronary sinus.
- The prevalence of left SVC is 0.1%-0.5%. In left SVC patients, it is better to proceed via the right subclavian vein.
- Cannulation of coronary sinus and lateral vein (due to unfavorable angulation) may be cumbersome. Prevalence is the key.
- Proper pre-cath evaluation is very important in picking up small anatomical variations prior to the actual procedure.

A CASE OF LAD OSTIAL CTO

Dr Anand Manjunath, Chennai

Chronic total occlusion (CTO) is a challenging condition that can be particularly difficult for interventional cardiologists to manage. In some cases, CTO lesions and bifurcation lesions with severe curvature and stenosis prevent the introduction of wires into the main artery, though wiring into the side branch (SB) remains possible. Ostial left anterior descending (LAD) artery lesions are crucial for coronary stenting due to their location, which affects a large area of the myocardium and presents additional technical challenges.

Despite advancements in percutaneous coronary intervention (PCI) devices and operator expertise, CTO remains a significant challenge. This case underscores the importance of effectively addressing CTO in coronary stenting.

Here a case study was discussed, which involved a 44-year-old male with type 2 diabetes mellitus, chronic stable angina class III, a positive treadmill test, and obesity, but with normal liver function, presented with complex coronary artery disease. His CT coronary angiography (conducted on 14/7/2023) showed 70%-90% stenosis in the proximal LAD, 50%-70% in the diagonal branch, and 50%-70% in the mid RCA. Additionally, the coronary angiography revealed 99% stenosis in the distal right coronary artery (RCA), 70% in the left circumflex artery (LCx), and 80% in the RAMUS, with a CTO in the ostial LAD.

The patient was advised to undergo coronary artery bypass grafting (CABG) but declined. Consequently, a multivessel PCI was planned in two stages, utilizing an antegrade approach. The study concluded the following:

- Addressing all non-CTO lesions before attempting CTO PCI is crucial.
- If the initial strategy fails, promptly transitioning to an alternative crossing technique enhances the chances of success.
- In this case, the approach involved IVUS-guided antegrade wire escalation, along with retrograde wire escalation, antegrade wire escalation, and antegrade dissection and re-entry.
- Pre-stenting imaging proved to be essential.

CTO PCI TOOLBOX 2024: 7 STEPS TO LEARNING CTO PCI SKILLS

Dr Arun Kalyanasundaram, Chennai

- Become familiar with the basics.
- Start watching CTO cases, liver or otherwise.
- Connect with teachers through colleagues, vendors, etc.
- Connect with fellow learners.
- Start using your new found skills in non-CTO settings.

- Travel to labs that do CTOs and do them.
- Start doing CTOs in your lab or labs that do them.

ACHIEVING OPTIMAL LDL-C LEVELS IN ASCVD: THE SYNERGY OF INCLISIRAN AND STATINS

Dr Amit B Kinare, Madhya Pradesh

From the decades, statins are the gold standard for lipid management but their underutilization in real-world practice poses significant challenges. Many patients discontinue or avoid statin therapy due to concerns about side effects, lack of understanding of their benefits, or insufficient guidance from health care providers. This underutilization hampers the ability to achieve guideline-directed lipid targets, particularly the low-density lipoprotein cholesterol (LDL-C) level of <70 mg/dL, which is critical for reducing the risk of recurrent cardiovascular events in patients with established atherosclerotic cardiovascular disease (ASCVD).

Inclisiran emerges as a highly effective add-on therapy in cases where statins alone fail to achieve the desired LDL-C reduction. Its novel mechanism, utilizing RNA interference to inhibit PCSK9, enables a substantial and sustained lowering of LDL-C. About 60% reduction in LDL-C from baseline were reported in VICTORION-INITIATE Study with only biannual dosing.

For patients struggling to meet their lipid targets with statins alone, Inclisiran provides a promising solution to achieve and maintain the recommended LDL-C levels, thereby enhancing cardiovascular outcomes and reducing the burden of ASCVD.

NIGHTMARES IN CATH LAB: ALL-IN-ONE

Dr SK Malani, Pune

- Complex PCI requires anticipation of possible complications.
- Acute complications like abrupt vessel closure should be identified at the earliest and addressed immediately. Imaging should be done whenever available. Help from colleagues and cardiothoracic and vascular surgery should be sought immediately.
- A sustained effort and teamwork is required to salvage the situation.

ZERO CONTRAST PCI IN A CASE OF ACS WITH CKD

Dr Ashwin Tumkur, Hyderabad

Contrast-induced nephropathy is a common complication after diagnostic and therapeutic coronary procedure especially when the patient has chronic kidney disease/acute kidney injury, left ventricular (LV) dysfunction. The only potent preventative strategy involves aggressive fluid administration and reduction of contrast volume.

Contrast limiting techniques: First, during both angiography and PCI, we need to seek anatomical landmarks (particularly calcifications) to navigate our interventions without contrast usage. Second, small injections with small syringes as well as evacuation of unused contrast from catheters must be standard. Finally, wider use of intravascular imaging techniques, especially intravascular ultrasound (IVUS), should decrease contrast volume and improve PCI results.

THE POWER OF INCLISIRAN IN FAMILIAL HYPERCHOLESTEROLEMIA MANAGEMENT

Dr Praveen Chandra, Gurugram

Lowering LDL-C levels is pivotal in reducing cardiovascular (CV) risk, a fact underscored by extensive evidence supporting the efficacy of lipid-lowering therapies (LLT) over the long-term. Despite these advancements, a significant number of patients still need to achieve and maintain target LDL-C levels with existing treatments, highlighting the need for innovative approaches in lipid management.

Administered twice yearly via subcutaneous injection, inclisiran has emerged as a game-changer in LDL-C reduction strategies. Clinical trials, including the ORION-3 study, have demonstrated that inclisiran can achieve approximately 50% reduction in LDL-C levels when combined with maximal oral LLT across diverse patient populations, including those with familial hypercholesterolemia and high CV-risk individuals.

Approved as the first small interfering RNA therapy for hypercholesterolemia, inclisiran's safety and tolerability profile has also been extensively studied. Pooled data from pivotal Phase 3 trials (ORION-9, -10, and -11) involving over 1,800 patients showed that inclisiran was well-tolerated over 18 months, with adverse events comparable to placebo. Injection site reactions, the most common side effect, were typically mild and transient, underscoring inclisiran's favorable safety profile in clinical use.

Long-term safety assessments are ongoing, evaluating Inclisiran's safety beyond the initial trials with the aim of providing clinicians and patients with comprehensive insights into Inclisiran's durability and safety over extended treatment periods.

As research continues, inclisiran stands poised to redefine standards in lipid management, potentially reducing the burden of cardiovascular disease worldwide. This potential impact of inclisiran serves as a powerful motivator, inspiring health care professionals to continue their efforts in the fight against cardiovascular disease.

Wright RS, Koenig W, Landmesser U, et al. Safety and tolerability of inclisiran for treatment of hypercholesterolemia in 7 clinical trials. J Am Coll Cardiol. 2023;82(24):2251-61.

THE FUTURE OF ADULT CONGENITAL HEART INTERVENTIONS IN INDIA

Dr Bharat Dalvi, Mumbai

Congenital heart disease (CHD) is the most common disorder and the leading cause of mortality in India. Interestingly, more adults live with CHD than children.

In India, the cardiovascular disease epidemic is marked by a higher relative risk, earlier onset, greater case fatality, and higher rates of premature death.

Key Points

- Fewer cases of de novo CHDs in adulthood.
- An increase in patients with postoperative or post-interventional issues.
- Valve repair and replacement are primarily handled by interventionalists.
- Procedures such as sinus venosus atrial septal defect repairs and Fontan completions are increasingly performed in the catheterization lab rather than the operating room.

OPTICAL COHERENCE TOMOGRAPHY: FUTURE PROSPECTS

Dr Takashi Akasaka, Japan

- Artificial intelligence for optical coherence tomography (OCT) might be focused on the automated analysis of the images to assess coronary artery structure, plaques, stents, and so on, including measurements of lumen and vessel diameter, plaque volume, stent apposition and expansion with 3D reconstruction, etc.
- Development of automated analysis of the OCT images allows us to assess plaque characteristics and coronary structures, including stents, for improving the patient's prognosis by accurate diagnosis, better PCI results, and predicting future events.
- Hybrid intracoronary imaging systems with OCT may develop rapidly to demonstrate much more precise information to predict future events and to improve patient prognosis.
- Further development could be expected in the field of coronary imaging, especially in OCT.

SEEING IS BELIEVING

Dr Pankaj Manoria, Bhopal

- In cases of in-stent restenosis, imaging helps in doing precision angioplasty without any guess work.
- It helps identify the mechanism of restenosis, planning the strategy and optimizing the result post-procedure.

CURRENT IVUS TRIALS

Dr Sajan Narayanan, Kochi

Clinical trials validate IVUS's efficacy and safety, providing evidence on improved patient outcomes, guiding best practices, and supporting advanced IVUS technologies in interventional cardiology.

Learning from the IVUS Trials

- IVUS-guided PCI improves major adverse cardiac events in complex lesion interventions.
- IVUS guidance has compelling evidence supporting its use in left main coronary artery (LMCA) interventions.
- Target minimal stent areas for crush stenting are recommended to be: 7(LCx)-9(LAD)-12(LM).
- IVUS-optimized PCI is feasible in acute coronary syndrome (ACS) and significantly improves outcomes.

NIGHTMARE WITH A RAY OF HOPE

Dr P Krishnananth, Tirunelveli

Coronary angiography (CAG) and PCI constitute effective treatments for coronary heart disease. CAG enables percutaneous transluminal coronary angioplasty (PTCA) by offering detailed images of coronary arteries, aiding interventional cardiologists in identifying blockages and evaluating disease severity.

This diagnostic capability guides treatment decisions during PTCA, determining the optimal balloon angioplasty, and stent placement strategy. Real-time visualization provided by CAG enhances blood flow and contributes to potentially life-saving outcomes.

A case study exemplified successful treatment using CAG and PCI in a 38-year-old male with a history of chronic smoking, alcohol use, and angina chest pain.

The study also stated that the Wait and Watch Approach can be beneficial in some cases, provided the patient's vitals remain stable.

OSTIAL LCx ACUTE THROMBOSIS HANGING STENT STRUTS ACROSS LCx OSTIUM

Dr Mohajit Arneja, Nagpur

- Ostial left LCx is the Achilles heel; always tricky and difficult to treat.
- Crowded hanging stent struts across LCx ostium can act as the nidus for acute thrombus formation leading to acute coronary syndrome-ST-elevation myocardial infarction (ACS-STEMI).
- After understanding the mechanism and imaging the vessels, we can consider tackling it without the use of more metal.
- Combining physiology along with imaging can give us more confidence in dealing with these situations without putting additional stents.
- Although data is neutral, opening of LCx struts in LM bifurcation provisional stentings will help prevent the restenosis.

IVUS-GUIDED LEFT MAIN BIFURCATION STENTING WITH COMPLEX MULTIVESSEL PCI

Dr Arpita Katheria, Lucknow

Intravascular ultrasound (IVUS) aids in PCI. A case study of a 69-year-old male diabetic patient with a recent anterior wall myocardial infarction (nonthrombolysed) followed by acute onset of heart failure (AOE II) emphasized that:

- Imaging should be done routinely during complex PCI, particularly for lesions involving the LM. In this case, IVUS helped in: Assessing the severity of LM ostial disease; selecting the size of balloons and stents; identifying and treating distal stent edge dissection.
- Although all guidelines recommend CABG over PCI for LM bifurcation lesions, PCI can still yield good results in selected patients.
- PCI outcomes can be comparable with CABG nowadays in LM diseases with the advent of newer-generation drug-eluting stents and the use of intracoronary imaging.
- The STEP-CRUSH technique can be a simple yet effective way of performing LMCA bifurcation.

FROM INNOVATION TO IMPLEMENTATION: THE JOURNEY TO THE PROMISED LAND OF LEAVING NOTHING BEHIND WITH THIN STRUTS BIORESORBABLE SCAFFOLDS

Col Dr Ajay Joshi, New Delhi

Scaffold thrombosis is a severe complication of PCI, causing adverse cardiovascular events. Bioresorbable scaffolds (BRS) have emerged as a potential solution to avoid adverse reactions caused by permanent metallic implants, allowing a "leave nothing behind" approach. Understanding the constrains is important.

Key Points

- Understand the limitations of the tool and the technology as it is still evolving.
- Select your patients carefully.
- Success depends on thorough planning and assessment.
- Imaging, particularly OCT, aids in evaluating plaque severity and planning the best strategy for PCI.
- Bed preparation is crucial.
- Post-bed preparation imaging is essential before BRS deployment.
- If adequate bed preparation is achieved, even calcified vessels are not an absolute contraindication for BRS, but imaging is necessary before deployment.
- BRS can be easily overlapped in long lesions.
- Post-dilatation is crucial; avoid leaving much for post-dilatation.
- Be prepared to anticipate and manage complications.

THROUGH THE LOOP: UNDERSTANDING THE WIRE EXIT PERFORATION AND SALVAGE TECHNIQUES

Dr Krishna Prasad

- Hydrophilic wires are notorious to cause wire exit perforations.
- First step is to tamponade the feeding vessel.
- Various other ways include cut balloons, autologous fat particles and coils, etc.
- Sometimes multimodality techniques may have to be used.

■■■■

News and Views

Benefits of Finerenone in Heart Failure with Preserved or Mildly Reduced Ejection Fraction

Treating patients who have heart failure with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) with finerenone reduces their risk of worsening HF events and cardiovascular mortality, according to the results of the FINEARTS-HF study published in the *New England Journal of Medicine*[1,2].

To study the impact of finerenone on symptomatic HFmrEF or HFpEF, researchers selected 6,001 patients with HF and a left ventricular ejection fraction (LVEF) of ≥40%. Most patients were in New York Heart Association (NYHA) class II. A total of 3,003 patients were randomized to receive finerenone (20 mg or 40 mg once daily) and 2,998 patients received placebo, in a 1:1 ratio, along with standard care. The primary study outcome was a composite of total worsening HF events and cardiovascular mortality. An urgent visit for HF or the first or recurrent unplanned hospital admission was defined as an event.

There were 1,083 primary-outcome events in 624 patients in the finerenone group over a median follow-up of 32 months, while 1,283 primary-outcome events occurred in 719 patients receiving placebo. "First worsening HF events or death from cardiovascular causes was similarly reduced with finerenone". The rate ratio was 0.84. Overall, total worsening HF events were reduced by 18% with finerenone. The total number of worsening HF events was 842 in the finerenone group and 1,024 in the placebo group with rate ratio of 0.82. Cardiovascular mortality was comparable between the two groups, 8.1% and 8.7%, respectively, with hazard ratio (HR) of 0.93. However, the risk of hyperkalemia (>5.5 mmol/L) was increased in the finerenone group (14.3%) compared to placebo group 6.9%). The rate of hypokalemia was lower in patients treated with finerenone.

Finerenone was FDA approved in 2021 for patients with chronic kidney disease associated with type 2 diabetes.

The findings of this study support the use of finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist (MRA), in this patient group. However, sounding a note of caution, the authors state that despite fewer side effects than other MRAs, finerenone is associated with risk of hyperkalemia. Hence, patients, especially those with impaired kidney function, should be closely monitored for this adverse effect. This study also demonstrated the lower risk of hypokalemia with finerenone, which is also associated with worse outcomes.

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Anticancer Drugs may Lower Alzheimer's Risk: Study

A study in Scientific Reports found that certain anticancer drugs, specifically molecular targeted therapies and antimetabolites, may reduce the risk of Alzheimer's dementia in older adults. However, these drugs showed no significant impact on vascular dementia risk.

In a recent study published in *Scientific Reports*, researchers observed that specific anticancer drugs may reduce the risk of Alzheimer's dementia (DAT) in older adults. The study, which analyzed data from the Korea National Health Insurance Service database, focused on more than 1,00,000 cancer patients aged 65 and above who were prescribed anticancer medication between January 2008 and December 2018.

The researchers found that two classes of anticancer drugs—molecular targeted therapies and antimetabolites—were associated with a reduced risk of DAT. Specifically; the study reported HR of 0.91 for antimetabolites and 0.60 for molecular targeted therapies in reducing the risk of DAT. However, these drugs showed no significant impact on the risk of vascular dementia, the second most common type of dementia.

The average age of patients receiving anticancer treatments was 71.64 years, with a majority of the patients (64.4%) female. The most frequently used classes of anticancer drugs were platinum (39.0%), antimetabolites (30.5%), and antibiotics (21.3%). Among molecular targeted therapies, epidermal growth factor receptor (EGFR) inhibitors were the most common, accounting for nearly half of the usage.

Further analysis using the Cox proportional HR revealed that antimetabolites (HR = 0.93) and molecular-targeted therapies (HR = 0.67) significantly reduced the DAT risk. When examining molecular-targeted therapies more closely, the study found multikinase inhibitors had the most substantial protective effect (HR = 0.50), followed by EGFR inhibitors (HR = 0.66).

Specialized Medication Management Reduces Hospital Stays and Mortality in Older Patients

A study in JAMDA found that specialized medication management for older patients reduces their hospital stays and mortality risk. One in 10 older patients experienced adverse drug reactions, which significantly impacted their outcomes.

New research published in the *Journal of the American Medical Directors Association (JAMDA)* suggested that specialized medication management for older hospital patients can shorten their hospital stays and lower their risk of death. The study found that 1 in 10 older patients experienced adverse drug reactions (ADRs) during hospitalization, significantly affecting their outcomes.

Examining over 700 patients aged 65 and older, the study revealed that ADRs from medications such as those for high blood pressure, strong painkillers, and antibiotics significantly increased the likelihood of prolonged hospital stays and mortality. Each ADR was associated with a higher risk of extended hospitalization and death, underscoring the importance of careful medication management in this vulnerable population.

Study Links High Diastolic Blood Pressure to Increased Migraine Risk in Women

A study in Neurology found that high diastolic blood pressure slightly increases the risk of migraines in women. No similar associations were found with other cardiovascular risk factors or in men.

A new study published in *Neurology* showed that high diastolic blood pressure—the blood pressure measurement when the heart is resting between beats—is linked to a slightly higher likelihood of having migraines in women. The study, however, did not find any increased migraine risk associated with other cardiovascular factors.

The research involved 7,266 male and female participants with a median age of 67 years, of whom 15% reported having experienced migraines at some point. All participants underwent physical exams, provided blood samples, and answered questions about their migraine history, including whether they had ever had a headache with severe pain that impacted daily activities.

After adjusting for various cardiovascular risk factors and education levels, researchers discovered that female participants with higher diastolic blood pressure had a 16% increased odds of experiencing migraines for each standard deviation increase in diastolic blood pressure. This finding suggested that migraines may be linked to a slightly reduced function of small blood vessels rather than large ones.

No associations were found between migraines and systolic blood pressure, high cholesterol, or obesity in women. Interestingly, current smoking was associated with 28% lower odds of having migraines, and diabetes was linked to 26% lower odds of migraines. No significant associations between cardiovascular risk factors and migraines were observed in male participants.

Extreme HDL-C Levels Linked to Increased Kidney Disease Risk in Women with Type 2 Diabetes

A study in Scientific Reports found that very high and very low levels of HDL-C are linked to an increased risk of kidney disease in women with type 2 diabetes but not in men. Women with HDL-C levels outside the 0.95-1.54 mmol/L range faced significantly higher risks.

A study published in *Scientific Reports* showed that very high and very low levels of high-density lipoprotein cholesterol (HDL-C) are associated with a higher risk of kidney disease in women with type 2 diabetes but not in men.

Researchers conducted a cross-sectional observational study involving 936 patients with type 2 diabetes (mean age around 60 years; 41% women; 33% with diabetic kidney disease) from the Endocrinology Department at Jinhua Hospital between September 2020 and July 2021.

The study used logistic regression and a restricted cubic spline curve to analyze the relationship between HDL-C levels and the risk of diabetic kidney disease. The researchers identified a U-shaped association between HDL-C levels and kidney disease risk, with significant threshold values at 0.95 and 1.54 mmol/L.

Women with HDL-C levels below 0.95 mmol/L or above 1.54 mmol/L had a 128% and 77% increased risk of diabetic kidney disease, respectively, compared to those with levels within the 0.95-1.54 mmol/L range. After adjusting for confounding factors, this association was significant in women but not men. Continuous HDL-C levels were unrelated to kidney disease risk.

Higher Risk of Autoimmune and Psychiatric Disorders in Alopecia Areata Patients, Study Finds

A JAMA Dermatology study found that alopecia areata patients are at higher risk for autoimmune and psychiatric comorbidities both at diagnosis and afterward. The risk for conditions like systemic lupus erythematosus and anxiety was significantly elevated in these patients.

A study published in *JAMA Dermatology* revealed that patients with alopecia areata face a higher prevalence of autoimmune and psychiatric comorbidities at diagnosis and an increased risk of these conditions developing afterward. Analyzing data from the Merative MarketScan Research Database, the study involved 63,384 patients with alopecia areata and 3,309,107 without. At the time of diagnosis, 30.9% of alopecia areata patients had psychiatric comorbidities, compared to 26.8% of unmatched controls without the condition. Additionally, 16.1% of patients with alopecia areata had autoimmune comorbidities, compared to 8.9% of controls. After matching for sex, age, and geographic region, the incidence of psychiatric diseases within the first year of diagnosis was 10.2% for alopecia areata patients and 6.8% for controls. The incidence of autoimmune or immune-mediated diseases was 6.2% for patients with alopecia areata, compared to 1.5% for the control group.

The study highlighted that patients with alopecia areata have a significantly higher risk of developing psychiatric comorbidities, with an adjusted hazard ratio (aHR) of 1.3, and autoimmune comorbidities, with an aHR of 2.7. Notably, psychiatric disorders with the highest risk included adjustment disorder (aHR 1.5), panic disorder (aHR 1.4), and sexual dysfunction (aHR 1.4). Among autoimmune and immune-mediated disorders, systemic lupus erythematosus had the highest risk (aHR 5.7), followed by atopic dermatitis (aHR 4.3) and vitiligo (aHR 3.8).

Approach to Postpartum Hemorrhage in the Lower Uterine Segment

Pulling down the cervix and packing in the vaginal fornix (PC-PVF) can effectively control postpartum hemorrhage in the lower uterine segment (PPH-LUS), according to a study published online August 4, 2024 in the *Journal of Maternal-Fetal and Neonatal Medicine*[1].

In this study, researchers retrospectively analyzed data of 127 women with PPH-LUS at two tertiary care hospitals. The selected participants had undergone vaginal delivery at these hospitals between 2019 and 2022. Three women underwent laparotomy because of failure of hemostasis. The remaining 124 women who were successfully managed conservatively were further categorized into three subgroups: routine treatment only with uterine massage, uterotonics and tranexamic acid (40 patients), routine treatment + early PC-PVF (simultaneous application of routine treatment and PC-PVF) (33 patients), and routine treatment + late PC-PVF (application of PC-PVF after routine treatment was ineffective) (51 patients). PC-PVF involves continuous external compression of the LUS by pulling down the cervix and packing the posterior and anterior fornices of the vagina with gauze soaked in iodophor. The volume and rate of bleeding within 24 hours after childbirth was compared between the three groups. Data analysis revealed that treatment efficacy rate was 44% in the routine treatment alone group, whereas women who also received PC-PVF along with routine treatment showed treatment efficacy of 100% after excluding PPH due to laceration and patients with incomplete rupture of the LUS. No impact of maternal age, gestational week, Apgar score, and neonatal weight was observed on the outcomes. "All tamponade gauzes remained in place until they were removed, and no tamponade-related complications were observed", note the authors. However, between-group differences were noted for blood loss and bleeding rate with significantly lower total blood loss in the routine treatment + early PC-PVF group. The mean total blood loss was 657.27 mL in patients receiving routine treatment + early PC-PVF versus 847.13 mL in those receiving routine treatment alone and 1040.78 mL in patients receiving routine treatment + late PC-PVF.

Bleeding rate was faster in the routine treatment + early PC-PVF group versus the routine treatment + late PC-PVF treatment group. After tamponade, a significant decrease in bleeding rate was noted in both, but bleeding rate was slower in the routine treatment + early PC-PVF group. This study illustrates the role of PC-PVF as a safe and effective treatment for LUS PPH. Early diagnosis followed by prompt use of this technique may help to reduce blood loss after vaginal delivery. PC-PVF helps to achieve hemostasis by continuously pressing on the LUS from outside to inside. This pressure closes the peripheral blood vessels within the myometrium of the LUS and checks the bleeding. This noninvasive, rapid and simple to perform technique can be easily adopted in routine day-to-day practice as an effective method to control PPH-LUS after vaginal delivery, especially in resource-crunched settings.

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Bleeding Risks after Untreated Respiratory Infections in Patients on Oral Anticoagulants

In patients on oral anticoagulants, the risk of both major and non-major bleeding is more than doubled during the first 2 weeks after an untreated respiratory tract infection, according to a study published in *BMJ*[1].

This study sought to determine the association between untreated, community-acquired, respiratory tract infections and bleeding in patients on oral anticoagulants, warfarin or direct oral anticoagulants (DOAC). A total of 1,208 patients, who had experienced a bleeding event between January 2010 and December 2019 and also had a history of untreated community-acquired respiratory tract infection, i.e., no antibiotics were prescribed were enrolled in the study. Data was obtained from the Clinical Practice Research Datalink GOLD. Men comprised 58% of the study population and the first bleeding episode occurred at the median age of 79 years.

Over the median observation period of 2.4 years, there were 292 major bleeds during unexposed time periods and 41 in the 0 to 14 days following a consultation for a respiratory tract infection. The number of clinically relevant non-major bleeds during unexposed time periods was 1,003 and after consultation for a respiratory tract infection, this number was 81.

The incidence rate ratio (IRR) for major bleeding was 2.68 after controlling for confounders such as age, season, and calendar year. The IRR for clinically relevant non-major bleeding was 2.32. The IRR for both types of bleeding was found to increase in the 0 to 14 days after an untreated respiratory tract infection. This association was not affected by gender or the type of anticoagulant administered.

Patients on oral anticoagulants are at high-risk for bleeding and therefore require close monitoring, especially during acute infections such as those involving the respiratory tract. Early and effective treatment of respiratory infections may reduce the risk of major bleeding in patients taking anticoagulants.

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Assessing Cardiovascular Risk

Measuring low-density lipoprotein "bad" cholesterol (LDL-C) levels along with lipoprotein(a) and high-sensitivity C-reactive protein (hsCRP) levels at middle age is a better predictor of 30-year risk of future cardiovascular events in women, according to a study published in the *New England Journal of Medicine*[1-3]. These findings were also presented at the recently concluded European Society of Cardiology Congress 2024 in London.

Baseline data of LDL-C, hsCRP, and lipoprotein(a) or Lp(a) levels were collected from 27,939 initially healthy participants of the Women's Health Study. They were followed for a duration of 30 years from the time they were recruited for the study between 1992 and 1995 at an average age of ~55 years. Occurrence of the first major adverse cardiovascular event (MACE), a composite of myocardial infarction, stroke, coronary revascularization, or cardiovascular mortality was the primary end point of the study. The objective of the study was how the three biomarkers correlated with these events, alone and all together.

The study subjects were categorized into five groups based on the highest to lowest level of each biomarker. The highest quintile for LDL-C was >150 mg/dL, for hsCRP it was >5 mg/dL and for Lp(a) it was >44 mg/dL. The mean body mass index (BMI) at the time of enrollment was 25.9 kg/m^2. Twenty-five percent were hypertensive, 12% were current smokers, and 2.5% had diabetes.

A total of 3,662 first MACE were recorded over three decades of follow-up. The increasing levels of all the three biomarkers were predictive of the primary endpoint by 30 years. Analysis of data revealed that the risk of cardiovascular events increased by 36% among the participants with the highest levels of LDL-C with covariable-adjusted hazard ratio of 1.36 versus women with the lowest LDL-C levels. Showing a similar trend, the risk of MACE increased by 33% in women with highest levels of Lp(a) (aHR 1.33) and 70% in those with the highest levels of hsCRP (aHR 1.70) compared to those with the lowest levels. Risk was greater as the number of biomarkers increased. The HR for one biomarker in the highest quintile was 1.27, 1.66 for two biomarkers and 2.63 for three biomarkers than those who had none. Collective assessment of LDL-C, Lp(a) and CRP demonstrated more than threefold increased risk for coronary heart disease and 1.5 times heightened risk for stroke vis-a-vis women with the lowest levels of these biomarkers.

Traditionally, the 10-year risk of developing cardiovascular disease is usually estimated. While LDL-C is a routinely ordered test, hsCRP and Lp(a) are usually not advised. But all three are easily available tests.

This study shows that the three biomarkers, when assessed individually, are predictive of cardiovascular risk; the strongest predictor of long-term risk was hsCRP.

Using them in combination enhances their ability to anticipate acute cardiovascular events and therefore is a more comprehensive approach to evaluating long-term cardiovascular risk as shown in this study with over 30 years of follow-up. This allows targeted interventions as they can be "modified either with behavior changes and/or drug therapy". Hence, for primary prevention, risk stratification for atherosclerotic cardiovascular disease should look beyond just measuring cholesterol levels.

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Psychiatric Safety of Semaglutide in Obesity Treatment

The use of semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), in patients with obesity without a known major mental health disorder does not increase the risk of developing depression or suicidal ideation thoughts compared to placebo, as per a study, which analyzed the STEP trials, published September 3, 2024 in *JAMA Internal Medicine*[1,2].

This post hoc analysis of the phase 3a STEP 1, 2, and 3 trials and phase 3b STEP 5 trial was conducted to examine the psychiatric outcomes of subcutaneous semaglutide, 2.4 mg, administered once weekly (vs. placebo) in patients without any known major psychopathology. The participants were overweight or had obesity, while those in the STEP 2 trial also had type 2 diabetes. Depressive symptoms, the main outcomes of the present study, were assessed with the help of Patient Health Questionnaire (PHQ-9). Suicidal ideation/behavior was also a major study outcome and was measured with the Columbia-Suicide Severity Rating Scale.

The study group consisted of 3,377 participants in the STEP 1, 2, and 3 trials and 304 participants in the STEP 5 trial. All the trials had a female preponderance.

Analysis of pooled data showed that the mean PHQ-9 score at baseline for patients in the STEP 1, 2, and 3 trials treated with semaglutide was 2.0 suggesting that the study subjects had no or minimal symptoms of depression. In the placebo group, the mean PHQ-9 score at baseline was 1.8. At week 68, the PHQ-9 scores were 2.0 and 2.4 in the semaglutide and placebo groups, respectively. The estimated between-group treatment was −0.56. Patients receiving semaglutide had a lower probability of progressing to a more severe category of depression on PHQ-9 with odds ratio (OR) of 0.63.

Only ≤1% of participants reported experiencing suicidal ideation or behavior during treatment based on the Columbia-Suicide Severity Rating Scale. There were no significant differences between the two groups. The adverse psychiatric events were generally similar between the two groups.

The STEP 5 trial showed similar results.

Semaglutide injection, 2.4 mg once in a week, is FDA approved for chronic weight management in adults with obesity or overweight with at least one weight-associated condition such as type 2 diabetes, high blood pressure, or high cholesterol as adjunct to lifestyle modification.

Obesity has a significant impact on emotional health due to the weight-related stigma leading to reduced self-esteem, feelings of isolation, depression, or anxiety. Monitoring their mental health is of utmost importance.

An earlier study published in August this year in *JAMA Network Open* had shown 45% higher risk of suicidal ideation with semaglutide[2]. The current study has thrown up opposite results regarding psychiatric effects. Semaglutide was not associated with increased risk of any unintended psychiatric effects such as depression and suicidal ideation or behavior. It was associated with "a small but statistically significant reduction in depressive symptoms (not considered clinically meaningful)", according to the authors.

These findings should alleviate the concerns of both patients and clinicians regarding the psychiatric safety of semaglutide treatment. It can therefore be prescribed for weight management in patients with obesity, who have no significant underlying mental health issues, without major apprehensions about potential psychiatric adverse effects.

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Hypertonic Saline Nasal Drops: A Remedy for Pediatric URTIs?

Use of hypertonic saline nasal drops can shorten the duration of a upper respiratory tract infections (URTI) in children by 2 days, according to the results of ELVIS-Kids randomized controlled trial presented at the ongoing European Respiratory Society (ERS) Congress being held in Vienna, Austria[1,2]. Transmission of infection in the household contacts was also reduced.

The study enrolled 301 children, aged up to 6 years, within 48 hours of development of URTI. They were otherwise healthy. One hundred fifty children in the intervention group were administered hypertonic saline nasal drops (2.6%) by the parents in the dose of 3 drops per nostril, at least 4 times in a day until they recovered, while 151 children in the control group received the usual care (UC) for colds. A daily diary was maintained with a record of side effects, symptoms and compliance as assessed by the Canadian Acute Respiratory Illness and Flu Scale (CARIF). Nasal mid-turbinate swabs were collected daily for 5 days to test for viruses using a respiratory polymerase chain reaction (PCR) panel; 17 URTI viruses were identified. The aim was to study the impact of the nasal drops on the duration of URTI.

The median duration of symptoms decreased by 2 days in children who used the hypertonic saline nasal drops for 5 days (median). Children in the nasal drops group had the symptoms for an average of 6 days (interquartile range [IQR], 5-9 days), whereas children in the UC group remained symptomatic for 8 days (IQR, 5-11 days). The saline nasal drops reduced the duration of symptoms in cases where virus was detected (hypertonic saline drops [n = 102], median 6 days; UC [n = 101], median 8 days), but not where virus was not detected. The most frequently isolated virus was Rhinovirus, detected in 73%. Children who received the drops also had significantly fewer episodes of wheeze; 5% vs. 19%, respectively.

The spread of infection among household contacts of children who received hypertonic saline nasal drops was also reduced compared to the UC group. There were 66 infections (41%) among household members in the hypertonic saline nasal drops group vs. 92 (58%) in the UC group.

"Eighty-two percent of parents said the nose drops helped the child get better quickly and 81% said they would use nose drops in the future"[2].

The side effects were rare and included sneezing, runny nose, and pain. These were mild in nature. No serious adverse effects were observed.

The authors also explained the mechanism by which the hypertonic salt nasal drops exert their beneficial effect. They said, "Salt is made up of sodium and chloride. Chloride is used by the cells lining the nose and windpipes to produce hypochlorous acid within cells, which they use to defend against virus infection. By giving extra chloride to the lining cells this helps the cells produce more hypochlorous acid, which helps suppress viral replication, reducing the length of the virus infection, and therefore the duration of symptoms"[2].

These findings demonstrate the benefits of hypertonic saline nasal drops in children with URTIs as well as in their family members as a simple and cost-effective intervention. Faster recovery of children translates to fewer infections among their household contact with "clear implications for how quickly a household feels better and can return to their usual activities like school and work etc.[2]"

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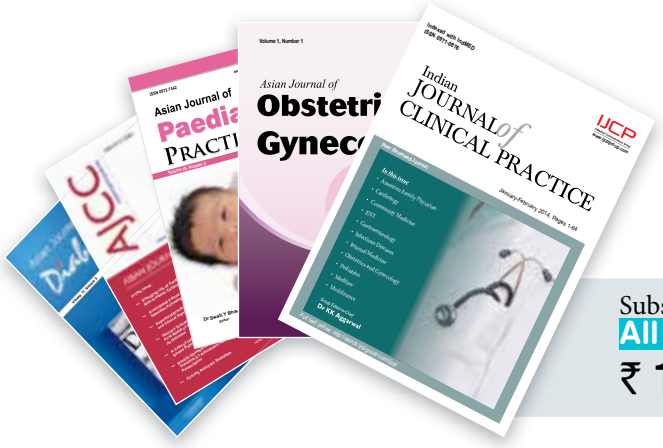

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Inflation: Cutting money in half without damaging the paper…

Tomorrow: One of the greatest labor saving devices of today..

Handkerchief: Cold Storage…

Secret: Something you tell to one person at a time…

Toothache: The pain that drives you to extraction…

Yawn: An honest opinion openly expressed...

Compromise: The art of dividing a cake in such a way that everybody believes he got the biggest piece.

Smile: A curve that can set a lot of things straight.

Opportunist: A person who starts taking bath if he accidentally falls into a river.

Optimist: A person who while falling from Eiffel tower says in midway "See I am not injured yet."

GRADUATE DEGREES IN ACTION

What does a graduate student with a science degree ask?
"Why does it work?"

What does a graduate student with an engineering degree ask?
"How does it work?"

What does a graduate student with an accounting degree ask?
"How much will it cost?"

What does a graduate student with a liberal arts degree ask?
"Do you want fries with that?"

X MARKS THE SPOT

Paul and Jim decided to rent a boat on a lake for their favorite sport. After fishing for 4 hours at various places around the lake with no luck at all they decided to try one more spot before calling it quits.

Suddenly things started to happen, and they caught their limit inside of 20 minutes. Paul said, "Hey, we should mark this spot, so next time we will know where to come." Jim says, "Good idea," and he took out a can of spray paint and made a large X on the floor of the boat to mark the spot.

With that Paul says, "Why did you do that? Now anyone who rents this boat will know where to fish!"

A WALKING ECONOMY

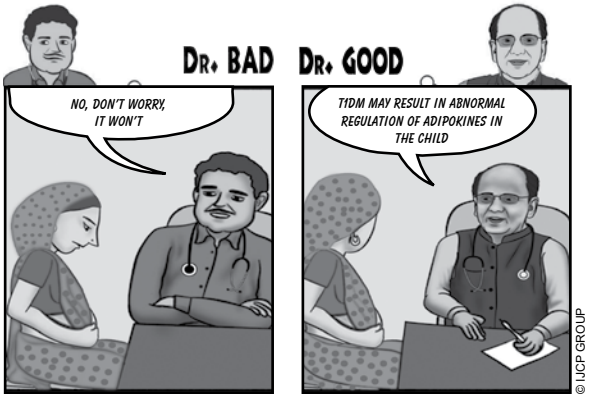
This guy is walking with his friend, who happens to be a psychologist. He says to this friend, "I'm a walking economy."

The friend asks, "How so?"

"My hairline is in recession, my stomach is a victim of inflation, and both of these together are putting me into a deep depression!"

Dr. Good and Dr. Bad

SITUATION: A pregnant woman with T1DM was worried if her diabetes would affect the child.



LESSON: It has been observed that children of women with T1DM usually have increased serum leptin and leptin to adiponectin ratio, with reduced serum adiponectin in females only. The abnormal regulation of adipokines could be attributed to T1DM in mothers during pregnancy.

Metabolism. 2017;72:47-56.

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- These should be concise and include only the tables and figures necessary to enhance the understanding of the text.

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

Books

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

Articles in Books

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

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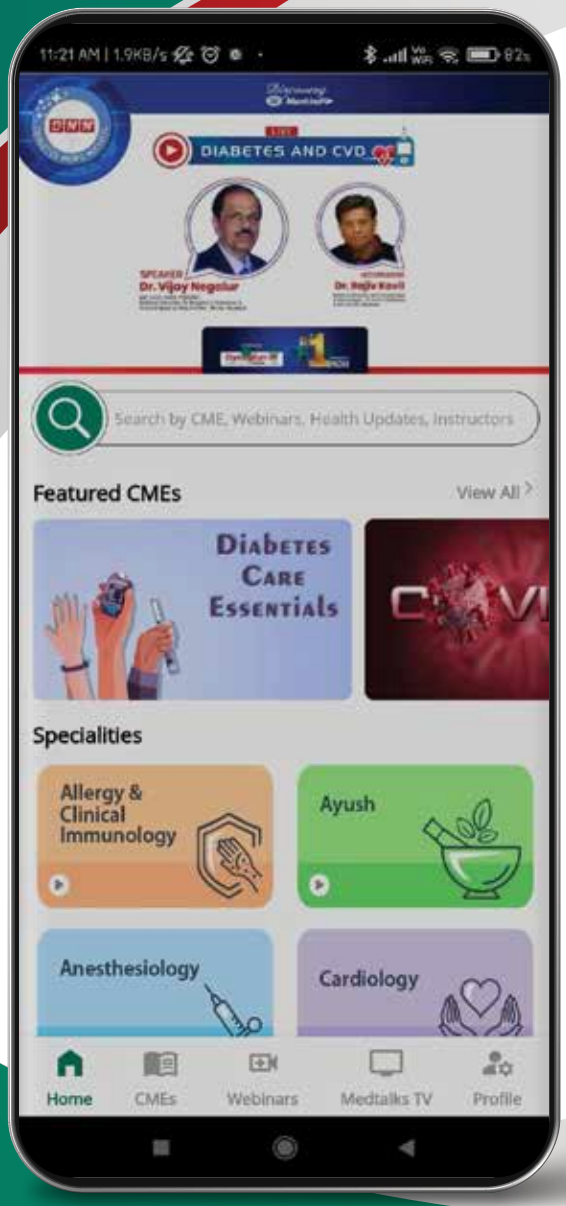

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